

# CODE OF PRACTICE REVIEW

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the ABPI Code of Practice for the Pharmaceutical Industry independently of the Association itself.

## PMCPA COMMUNICATIONS ACTIVITY

The PMCPA has appointed The EarthWorks to create a communications programme, including an app to help increase understanding of the Code.

The programme will be digitally led and will include new content on the PMCPA's website and via social media. It will also involve work with other healthcare organisations. There will be a key focus

on research to assess perception of the PMCPA amongst its key stakeholders.

The goals of this project are two-fold. Firstly, to promote a strong and positive profile for the PMCPA's work in relation to the Code of Practice and secondly, to build awareness and promote the benefits of self-regulation to the industry, health professionals, patients and the public.

## ANNUAL REPORT FOR 2013

The Annual Report of the Prescription Medicines Code of Practice Authority for 2013 will be published on our website ([www.pmcpa.org.uk](http://www.pmcpa.org.uk)) shortly.

## CONSULTATION ON CHANGES TO THE CODE

The consultation on the proposed changes to the 2014 ABPI Code and the Constitution and Procedure for the PMCPA ends on Friday, 5 September.

There were a number of reasons for the proposed changes including the work done by the group established by the ABPI Board to review the Code. Additional changes were also proposed to implement fully the European Federation of Pharmaceutical Industry Associations (EFPIA) Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations. Updates to the EFPIA Disclosure Code and the EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals were agreed at the EFPIA General Assembly on 6 June 2014. The Medicines and Healthcare

Products Regulatory Agency (MHRA) consultation as part of the red tape challenge and the regular update of the Code and its operation also resulted in proposals for change.

Full details of the proposed changes are available on the PMCPA website. A draft of the 2015 Code and Constitution and Procedure is also available.

The consultation responses will be reviewed and the final proposals agreed by the ABPI Board of Management in October 2014. The proposals will then go before the ABPI membership for approval on 20 November 2014 at the ABPI Half-Yearly General Meeting. If approved, the new Code will come into operation on 1 January 2015 with a transition period for newly introduced requirements until 1 May 2015.

## CODE OF PRACTICE TRAINING

Training seminars on the Code of Practice, run by the Prescription Medicines Code of Practice Authority and open to all comers, are held on a regular basis in central London.

These full day seminars offer lectures on the Code and the procedures under which complaints are considered, discussion of case studies in syndicate groups and the opportunity to put questions to the Code of Practice Authority.

The next Code of Practice seminar date on which places remain available is:

Monday, 1 December 2014

Short training sessions on the Code or full day seminars can be arranged for individual companies, including advertising and public relations agencies and member and non member companies of the ABPI. Training sessions can be tailored to the requirements of the individual company.

*For further information regarding any of the above, please contact Nora Alexander for details (020 7747 1443 or [nalexander@pmcpa.org.uk](mailto:nalexander@pmcpa.org.uk)).*

## HOW TO CONTACT THE AUTHORITY

Our address is:  
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7th Floor, Southside, 105 Victoria Street, London SW1E 6QT  
[www.pmcpa.org.uk](http://www.pmcpa.org.uk)

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Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7747 8885 or [lmattews@pmcpa.org.uk](mailto:lmattews@pmcpa.org.uk)).

Direct lines can be used to contact members of the Authority.

Heather Simmonds: 020 7747 1438  
Etta Logan: 020 7747 1405  
Jane Landles: 020 7747 1415

The above are available to give informal advice on the application of the Code of Practice.

The Authority rather than the ABPI is the contact point for information on the application of the Code.

# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v BRISTOL-MYERS SQUIBB

## Clinical trial disclosure (Onglyza, Nulojix and Yervoy)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Nulojix (belatacept), Onglyza (saxagliptin) and Yervoy (ipilimumab).

The detailed response from Bristol-Myers Squibb is given below.

General detailed comments from the Panel are given below.

With regard to Nulojix (Case AUTH/2656/11/13), the Panel noted the CMRO publication in that two evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 71%. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 86%. A footnote stated that the undisclosed trial was completed in 2004 and was not subject to FDAAA 801 requirements.

The Panel noted Bristol-Myers Squibb's submission that both trials had been published; only one had UK involvement and had been published in 2002, before Nulojix was first approved and commercially available (July 2011). In this regard, the Panel ruled no breach of the Code including Clause 2.

With regard to Onglyza (Case AUTH/2654/11/13), the Panel noted the CMRO publication in that two evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 88%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 100%.

Onglyza was first approved and commercially available in July 2009. The Panel noted Bristol-Myers Squibb's submission that the trial which involved UK patients completed in April 2010 and the results were posted on clinicaltrials.gov in August 2011. As the results were not disclosed by April 2011, Bristol Myers-Squibb had not met the requirements of the Code. The Panel ruled a breach of the 2008 Code. The delay in disclosure of the results meant that high standards had not been maintained and a breach was ruled. As the data had been published, the Panel considered that there was no breach of Clause 2 and ruled accordingly.

With regard to Yervoy (Case AUTH/2656/11/13), the Panel noted the CMRO publication in that six evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 63%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 63%. A footnote stated that the undisclosed trials were not subject to FDAAA 801 requirements.

Yervoy was first approved and commercially available in April 2011. The Panel noted that the one trial that involved UK patients completed in July 2007 and the results should have been disclosed by April 2012. Bristol-Myers Squibb submitted that this trial was presented as a poster in September 2008 and fully published in September 2009. The Panel ruled no breach of the 2008 Code including Clause 2.

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

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## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Nulojix (belatacept), Onglyza (saxagliptin) and Yervoy (ipilimumab) as follows:

### Nulojix

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	6	1	5	3	60%	5	4	80%
Phase III	2	0	2	2	100%	2	2	100%
Phase IV	0	0	0	0	0%	0	0	0%
Other	0	0	0	0	0%	0	0	0%
<b>TOTAL</b>	<b>8</b>	<b>1</b>	<b>7</b>	<b>5</b>	<b>71%</b>	<b>7</b>	<b>6</b>	<b>86%</b>

### Onglyza

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	1	0	1	1	100%	1	1	100%
Phase III	15	0	15	13	87%	15	15	100%
Phase IV	2	1	1	1	100%	1	1	100%
Other	0	0	0	0	0%	0	0	0%
<b>TOTAL</b>	<b>18</b>	<b>1</b>	<b>17</b>	<b>15</b>	<b>88%</b>	<b>17</b>	<b>17</b>	<b>100%</b>

### Yervoy

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	15	2	13	8	62%	13	8	62%
Phase III	3	0	3	2	67%	3	2	67%
Phase IV	0	0	0	0	0%	0	0	0%
Other	0	0	0	0	0%	0	0	0%
<b>TOTAL</b>	<b>18</b>	<b>2</b>	<b>16</b>	<b>10</b>	<b>63%</b>	<b>16</b>	<b>10</b>	<b>63%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluable	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluable trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluable trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Bristol-Myers Squibb.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Bristol-Myers Squibb, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Bristol-Myers Squibb stated that Case AUTH/2654/11/13 related to Onglyza which was a joint development project with AstraZeneca. As Bristol-Myers Squibb was solely responsible for the Onglyza trials referred to in the complaint, it had confirmed with AstraZeneca that it would respond to this complaint; AstraZeneca had no part in the arrangements for disclosing the results of the two specific studies.

Bristol-Myers Squibb Limited was most concerned to receive these complaints from a member of the public following the publication of the ABPI commissioned study on disclosure rates of results of

company-sponsored trials. Bristol-Myers Squibb fully supported enhancing public access to clinical study information in a way that safeguarded the privacy of patients, respected the national regulatory systems and maintained incentives for investment in research and development.

The company's practice was to provide patients, clinicians and others with information about Bristol-Myers Squibb sponsored clinical trials that were conducted on investigational compounds and marketed products. During 2014 it would initiate publication of all Bristol-Myers Squibb Clinical Study Report Synopses from trials conducted on marketed products on the company website [www.BMS.com](http://www.BMS.com).

Bristol-Myers Squibb submitted that its policy was to comply with all regulatory and legal obligations for transparency of clinical trial information for all markets in which it conducted clinical research. For example, when Bristol-Myers Squibb conducted clinical research in the US it was bound by the requirements of Section 801 of the Food and Drug Administration Amendments Act (FDAAA). As a result Bristol-Myers Squibb used the [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (National Institutes of Health) website for the registration and publication of clinical trial results. A brief summary of the FDAAA and International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) provision was provided.

## Investigation of the complaint

Bristol-Myers Squibb submitted that the complaint related specifically to two overall measures for disclosure rates contained in the tabulated supplementary material which accompanied the CMRO publication:

- disclosure within 12 months of either the first EMA/FDA approval, or within 12 months of the completion of the trial if later, and
- disclosure at 31 January 2013.

The authors' conclusions in relation to disclosure rates for the relevant studies which involved Nulojix, Onglyza and Yervoy were as follows:

Product	Disclosure within 12 months of either the first EMA/FDA approval, or within 12 months of the completion of the trial if later	Disclosure at 31 January 2013
Nulojix	71% (5 of 7 studies)	86% (6 of 7 studies)
Onglyza	88% (13 of 15 studies)	100% (15 of 15 studies)
Yervoy	63% (10 of 16 studies)	63% (10 of 16 studies)

Bristol-Myers Squibb identified and reviewed the ten studies which the authors concluded had not been disclosed within the mentioned timelines (two Nulojix, two Onglyza and six Yervoy studies). Details of these studies were provided.

### **Nulojix studies**

Bristol-Myers Squibb stated that Nulojix was first authorized in June 2011.

One of the two studies (IM103-002) was a historic study which was published in 2002 before the Code included an obligation to post clinical trial data at Clause 21.3 and prior to the implementation of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.

The remaining Nulojix study (IM103-045), completed in June 2011 and was eligible for disclosure under the Joint Position in force at the time (2009). Results were published on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) approximately 15 months after the end of the study. In addition the study was submitted for full publication in May 2013 to the American Journal of Transplantation however, the study did not involve any UK patient.

### **Onglyza studies**

Bristol-Myers Squibb stated that Onglyza was first authorized in July 2009.

Both Onglyza studies (CV181-085 and CV181-057), completed after the first authorization, in May 2010 and April 2010 respectively. Results of both studies were published on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) approximately 16 months after the end of the study. Both were eligible for disclosure under the Joint Position (2009).

Study CV181-057 involved one UK site and eight UK patients (1.7% of the total). The study results were published in March 2012 in *Current Medical Research and Opinion*. Study CV185-085 was fully published in July 2013 in *Diabetes Therapy*.

### **Yervoy studies**

Bristol-Myers Squibb acquired Medarex (the company which developed ipilimumab) in 2009. Yervoy was first authorized in March 2011.

Study MDX010-07/CA184-019 completed in November 2004, which predated the implementation date of 1 July 2005 cited in the Joint Position 2008. No UK patients were involved.

Three of the Yervoy studies were completed after 1 July 2005 and before 1 July 2008. The first two of these studies (MDX011-12/CA184-015, MDX010-15/CA184-001) were exploratory (non-efficacy) studies and were excluded from disclosure requirements under the Joint Positions in force at the time (2005/2008). Neither of these studies involved UK patients.

The third (CA184-007) was a confirmatory trial which started in December 2005 and completed in July 2007 and involved a small number of UK patients (1.7% of the total). When the trial started the applicable Joint Position (2005) did not require disclosure as Yervoy was not approved for marketing and was not commercially available. From January 2006 to June 2012, Bristol-Myers Squibb actively posted on to its corporate website, clinical study report (CSR) synopses from trials conducted on marketed products. Bristol-Myers Squibb subsequently stopped posting this information on BMS.com as

much of it was already posted to [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov). However, from cached internet history, it could clearly be seen that the CA184-007 trial was posted by Bristol-Myers Squibb along with other trials. Bristol-Myers Squibb was not able to establish the timing for this posting (<http://webcache.googleusercontent.com/search?q=cache:2yl4aial1sQJ:ctr.bms.com/pdf//CA184-007%2520ST.pdf+&cd=2&hl=en&ct=clnk&gl=uk>). This trial was also presented as a poster at the ESMO Congress in September 2008 and fully published in *Clinical Cancer Research* in August 2009.

Study MDX101-28 was an observational study, which completed in April 2009 and was not required to be reported under the Joint Position in force at the time (2008). This study did not involve UK patients.

Study CA184-027 was a phase 1 exploratory trial completed in October 2009. This trial was also not required to be reported under the applicable Joint Position (2008). This study did not involve UK patients.

### **Response to complaint**

It was Bristol-Myers Squibb's opinion that in relation to this specific complaint it was not unreasonable to consider this as an ABPI Code matter.

Publication of clinical trial results was dealt with by Bristol-Myers Squibb's clinical research groups in the US, it was thus outside the remit of Bristol-Myers Squibb UK. Nevertheless, UK companies remained responsible for ensuring adherence to the UK Code.

In relation to Clause 21.3, Bristol-Myers Squibb had identified the three studies above where disclosure was delayed by 3-4 months. Only one of these studies involved UK patients and all three had since been submitted, or fully published, in the scientific literature, reinforcing Bristol-Myers Squibb's commitment to transparency. Bristol-Myers Squibb acknowledged that the PMCPA would need to determine how these isolated delays aligned with the applicable clause however Bristol-Myers Squibb considered that the fact of disclosure of this data broadly fulfilled its obligations under Clause 21.3. Bristol-Myers Squibb did not believe that the complainant had provided any evidence to suggest a breach of either Clauses 21.1 or 21.2.

Bristol-Myers Squibb did not consider that it was in breach of Clause 1.8 due to the explanations provided for each individual trial noted above.

In relation to Clause 9, Bristol-Myers Squibb submitted that the situation surrounding the short delay in disclosing the results of these three studies did not represent a significant failure to maintain high standards. Only study CV181-057 involved UK patients and all three studies had submitted to, or already published in peer-reviewed publications.

For similar reasons, its actions did not represent a breach of Clause 2. The short delays in disclosing the results of these three studies did not represent a risk to patient safety or competent care, nor did they discredit or reduce confidence in the pharmaceutical industry.

Bristol-Myers Squibb submitted that it should be recognised that these three studies represented a very small percentage (5.8%) of the 52 studies for the Bristol-Myers Squibb products Eliquis, Nulojix, Onglyza and Yervoy that were identified in the publication. Results of all of the Eliquis studies were disclosed in full accordance with the requirements of the Code.

Bristol-Myers Squibb would provide any of the CSR synopses to any individual that requested the synopses of a study.

As requested, Bristol-Myers Squibb provided copies of the summaries of product characteristics (SPCs) for Onglyza, Yervoy and Nulojix and also the following internal documents

- Clinical Trial Directive 003.02 Disclosure: Clinical Trial Registrations and Posting of Results
- Clinical Trial Directive 003.02 amendment 2 (GDMA Procedural document Variance Request Form)
- PRI Policy 010 Public Disclosure of BMS Pharmaceutical Information
- Standard Operating Procedure 007 Public Disclosure of BMS Pharmaceutical Information

However, based on the wording of the complaint, which Bristol-Myers Squibb noted clearly referred to the 'information published in the study', it appeared that the other information requested by the PMCPA was out of scope. Before providing this additional information Bristol-Myers Squibb would like to better understand the PMCPA's rationale for requesting it in light of the original complaint and the full and transparent explanation provided.

Bristol-Myers Squibb submitted that it acted with the best intentions with regard to data transparency and adhered to the requirements of the Code to ensure transparency. It had provided a full response to the specific complaint made to the PMCPA.

In response to a request for further information Bristol Myers-Squibb stated that Nulojix, Onglyza and Yervoy were first approved and commercially available in July 2011, July 2009 and April 2011 respectively.

#### **GENERAL COMMENTS FROM THE PANEL**

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested

transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to

reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered*

*within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

*'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

*The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.*



The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored

clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was

whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with

various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

#### **PANEL RULING IN CASES AUTH/2654/11/13 AND AUTH/2656/11/13**

The Panel noted Bristol-Myers Squibb's submission regarding the date of the trial completion in relation to which joint position was relevant. As set out above, the Panel considered that the determining factor was when the product was first approved and commercially available and if the trial completed after this date then the date of the trial completion was relevant.

#### **Nulojix (Case AUTH/2656/11/13)**

The Panel noted the CMRO publication in that two evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 71%. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 86%. A footnote stated that the undisclosed trial was completed in 2004 and was not subject to FDAAA 801 requirements.

The Panel noted Bristol-Myers Squibb's submission that both trials had been published. One study had been published in 2002 which was before Nulojix was first approved and commercially available (July 2011). In this regard, the Panel ruled no breach of Clause 21.3 of the 2011 Code and consequently no breach of Clauses 9.1 and 2. The Panel considered that as the second trial had no UK involvement, the matter did not come within the scope of the Code and therefore ruled no breach.

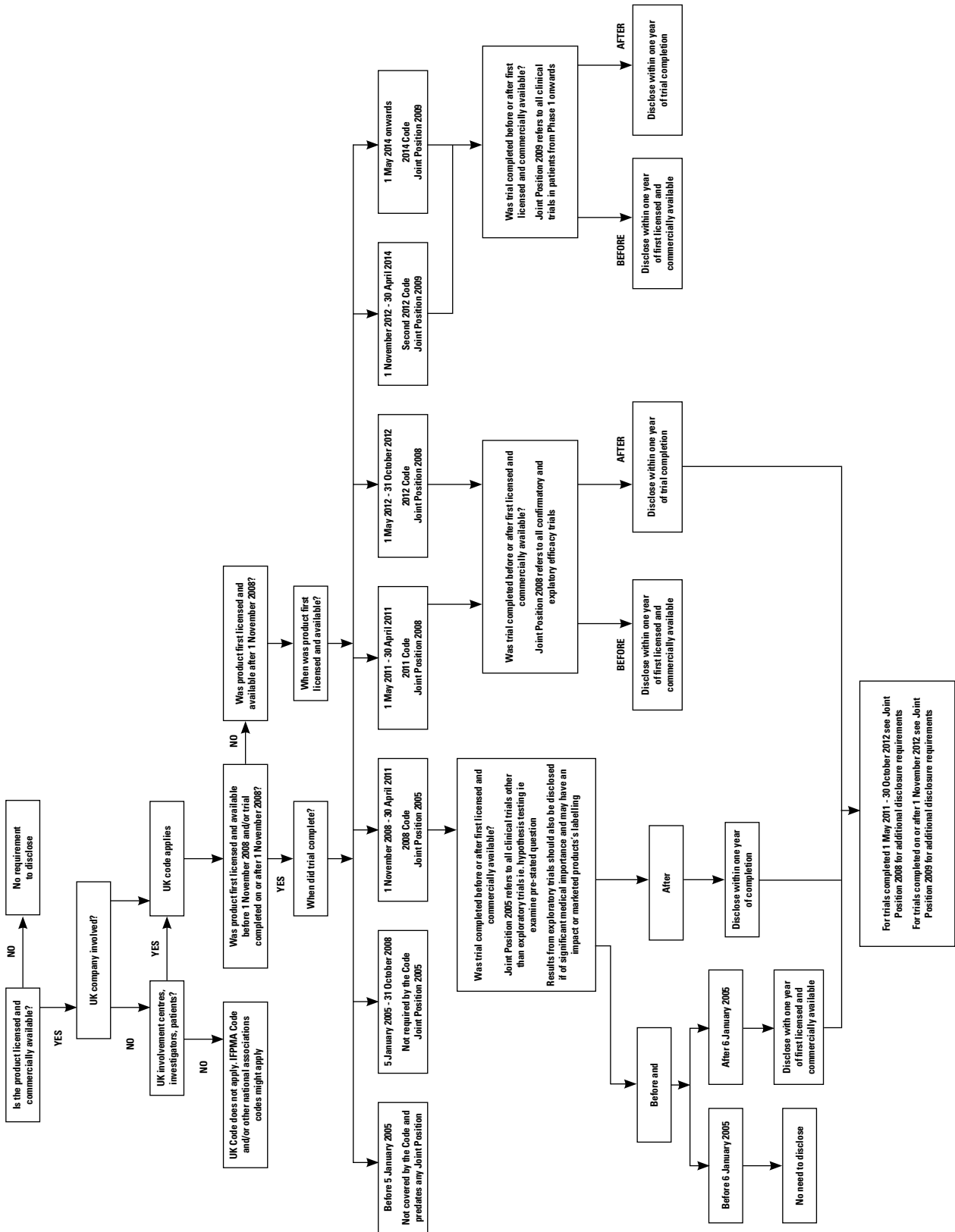
#### **Onglyza (Case AUTH/2654/11/13)**

The Panel noted the CMRO publication in that two evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 88%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 100%.

Onglyza was first approved and commercially available in July 2009. The Panel noted Bristol-Myers Squibb's submission that both trials had been published. Only one involved UK patients and this

# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results



completed in April 2010 and the results were posted on clinicaltrials.gov in August 2011. As the results were not disclosed by April 2011, Bristol Myers-Squibb had not met the requirements of the Code. The Panel ruled a breach of Clause 21.3 of the 2008 Code. The delay in disclosure of the results meant that high standards had not been maintained and a breach of Clause 9.1 was ruled. As the data had been published, the Panel considered that there was no breach of Clause 2 and ruled accordingly.

The Panel considered that as the second trial had no UK involvement, the matter did not come within the scope of the Code and therefore ruled no breach.

**Yervoy (Case AUTH/2656/11/13)**

The Panel noted the CMRO publication in that six evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 63%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 63%. A footnote stated that the undisclosed trials were not subject to FDAAA 801 requirements.

The Panel noted Bristol-Myers Squibb's submission that five of the non-disclosed trials did not involve UK patients. The Panel considered that as there was no UK involvement the matter did not come within the scope of the UK Code and therefore ruled no breach.

Yervoy was first approved and commercially available in April 2011. The Panel noted that the one trial that involved UK patients completed in July 2007 and the results should have been disclosed by April 2012. Bristol-Myers Squibb submitted that this trial was presented as a poster in September 2008 and fully published in September 2009. The Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

<b>Complaint received</b>	<b>21 November 2013</b>
<b>Case completed</b>	<b>31 March 2014</b>

# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v ASTRAZENECA

## Clinical trial disclosure (Iressa)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Iressa (gefitinib).

The detailed response from AstraZeneca is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that twenty-nine Iressa studies had not been disclosed in the timeframe. The disclosure percentage was 56%. Twelve studies had not been disclosed giving a disclosure percentage at 31 January 2013 for trials completed at 31 January 2012 of 84%. A footnote stated that the majority of Phase II/III trials were completed prior to FDAAA 801 requirements. The remaining undisclosed trials were in the process

of publication.

The Panel noted AstraZeneca's submission regarding the studies. Iressa was first approved and commercially available in Japan in 2002.

The Panel noted that of the remaining 38 trials (53 minus 15 investigator-sponsored trials), 35 were Phase I, exploratory Phase II or Phase III studies all of which completed before 1 November 2008. In that regard, there was no requirement under the Code to disclose these studies. The Panel thus ruled no breach of the 2008 Code including Clause 2.

An AstraZeneca Thailand non-interventional study completed in August 2010, which was after Iressa was first approved and commercially available. The Panel noted AstraZeneca's submission that these results were disclosed on its own website in November 2010. It was not clear whether there was any UK involvement and the Joint Position 2005 appeared not to require disclosure of the results of a non-interventional trial. In any event the results had been disclosed publicly within one year and thus the Panel ruled no breach of the 2008 Code including Clause 2.

The Panel noted that the results from two trials remained undisclosed – an AstraZeneca Canada study which completed in August 2011 and an AstraZeneca Taiwan study which completed in August 2009. AstraZeneca submitted that the publication of the results was expected.

The Panel considered that although AstraZeneca was a UK registered company, the company's arrangements were such that it was clear that the responsibility for disclosure was with the local company. It considered that the matter was potentially covered by the UK Code but as the responsibilities had been made very clear in a company standard operating procedure it ruled no breach of the 2008 Code including Clause 2 in relation to the AstraZeneca Taiwan trial and no breach of the 2011 Code including Clause 2 in relation to the AstraZeneca Canada study.

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## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for each product.

The data for Iressa (gefitinib) were as follows:

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	61	12	49	24	49%	57	48	84%
Phase III	13	3	10	8	80%	13	11	85%
Phase IV	7	0	7	5	71%	7	6	86%
<b>TOTAL</b>	<b>81</b>	<b>15</b>	<b>66</b>	<b>37</b>	<b>56%</b>	<b>77</b>	<b>65</b>	<b>84%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluable	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluable trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluable trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included AstraZeneca.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to AstraZeneca, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

AstraZeneca stated that it took its compliance with pharmaceutical industry codes of practice and all underlying legislation and regulations very seriously.

### General points on disclosure

AstraZeneca had a long-standing commitment to make information about its clinical research publicly available to enhance the scientific understanding of how its medicines worked and in the medical interest of patients. As a company, its disclosure policies went above and beyond the current legal mandated requirements.

AstraZeneca's investigational clinical trials were registered on the US National Library of Medicine's website before the first patient was enrolled and to other websites within timelines as required by law. Additionally, it posted basic information on the company website which was publicly accessible.

AstraZeneca considered that although transparency of clinical trial results and applicable information from its investigational clinical trials contributed to public confidence in medicines and improved public health and scientific knowledge, it recognised that increased transparency, in both the reactive and

proactive disclosure contexts, must be balanced with the legally required protection of personal data, intellectual property and confidential information.

Thus AstraZeneca was committed to communicating accurate and meaningful information about its sponsored clinical trials in a timely, accurate, balanced and complete manner, regardless of outcome. AstraZeneca's current and planned clinical trials transparency position met or exceeded all existing legally required and regulatory standards. AstraZeneca submitted that it:

- registered and posted results from all of its Phase I-IV interventional trials, including healthy volunteer trials, on ClinicalTrials.gov and other applicable legally required websites, as well as its own website
- registered non-interventional studies and disclosed the results of trials conducted on marketed products on any and all legally required websites in addition to its own website
- posted trial results, synopses and other information on its website for products approved in countries that did not legally require disclosure
- The timelines of disclosure were as follows:
  - Results of trials with already marketed medicines were posted within one year of completion. Results of trials with medicines in development were posted within 30 days of first regulatory approval for the new medicine where trials had completed at least one year. When a medicine in development was discontinued, results were published within one year of the public announcement of the decision, unless analysis and interpretation of the data were not sufficiently complete, in which case an explanation for the delay was posted together with the anticipated date when the results would be posted.
  - For marketed medicines and recently approved medicines where AstraZeneca considered there to be good cause to delay posting of results, it sought the necessary approval according to applicable law. Where approved, it posted an explanation for the delay and the anticipated date when the results would be posted.

In essence, AstraZeneca posted the results of all of its clinical trials in all stages of clinical development on several public websites – regardless of outcome (positive or negative) – and included products which had been discontinued in development.

### Comments on the complaint

AstraZeneca stated that the purpose of the CMRO study was to identify from the cohort of all completed company sponsored clinical trials, carried out in patients and relating to new medicines approved by the EMA in 2009, 2010 and 2011, studies for which results were not posted in a 'timely manner'; in other words and according to the protocol, studies identified through searching clinical trial registries and/or included in a European Public Assessment Report (EPAR) for which results had not been disclosed, either within twelve months of the later of either first regulatory approval or trial completion, or by 31 January 2013.

The complainant specifically referred to Iressa, which was first launched in Japan in 2002, followed by the US in 2003. The FDA subsequently updated the conditional approval indication in 2005 to exclude new patients following failure of the ISEL study to demonstrate extended survival and AstraZeneca subsequently withdrew the NDA in 2011. Following further research to identify the patient population most benefiting, the EMA approved Iressa for patients with EGFR mutation positive Non-Small Cell Lung Cancer (NSCLC) in 2009 based on the results of the IPASS study. A list of the worldwide marketing authorizations for Iressa was provided and was accurate when collated in October 2013.

AstraZeneca submitted that the scope of information requested by the case preparation manager was unreasonable, in that it went beyond the basis of the complaint which specifically referred to the CMRO publication. Therefore AstraZeneca had completed an in-depth response to the allegation that it had failed to disclose results according to requirements for clinical trials for the studies included within the CMRO publication, and had not responded to the broader request for a specific listing of all ongoing and completed Iressa clinical trials and the information pertaining to these trials. In addition, it had only completed the request for UK specific information for those trials where the company considered the information would inform the PMCPA with regard to the complaint and its scope. AstraZeneca had taken this approach in the interests of responding within PMCPA timelines.

AstraZeneca was asked to consider the requirements of Clause 21.3 in its response. Clause 21.3 (2008) required the posting of information about ongoing and completed clinical trials and referred to the 2005 IFPMA Joint Position on Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases. The only difference in Clause 21.3 (2011), as written, was recognition of the 2008 IFPMA Joint Position on Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases as the core reference. AstraZeneca submitted that the principal difference between the two joint positions was the commitment to publish exploratory as well as confirmatory trials.

### Summary

AstraZeneca submitted that it was not in breach of Clause 21.3, in that each of the Iressa clinical studies completed before the requirements of the Code or they fell outside its jurisdiction, as no UK patient, site, investigator, or UK-based AstraZeneca member of staff was involved.

In addition, the data below showed that many of the trials had been published in journals and those publications were listed on the ClinicalTrials.gov as provided by US National Institutes of Health, or on the US National Library of Medicine National Institutes of Health, and for those which had not yet been published, AstraZeneca remained committed to posting/publication of results, as stated in the publication that formed the basis of this complaint. This was in line with the AstraZeneca disclosure position.

## Investigation and findings

Following in-depth analysis of the publicly available information on the identified Iressa studies, the researchers gave AstraZeneca a list of studies that, in their opinion, failed to meet the requirements of the protocol. This list of 53 clinical trials was the principal basis upon which AstraZeneca investigated and responded to this complaint. A copy was provided. This number was higher than the highest assessment of undisclosed trials discovered by the researchers (n=44; total number of studies identified (n=81) minus those considered both evaluable and disclosed within timelines (n=37)); this was the most reliable and least conservative information regarding the clinical trials relevant to this complaint that AstraZeneca had. However, AstraZeneca confirmed that during an in-depth internal review of Iressa clinical trials, it had not discovered any other trials that fell within the scope of the Food and Drug Administration Amendments Act of 2007 Section 801, and/or any other applicable requirements, including of Clause 21.3 of the Code (2008 and 2011) and all applicable company policy requirements and where results were not disclosed accordingly.

A spreadsheet set out the data for each of the 53 trials listed. In summary:

- Fifteen of the studies identified by the researchers as potentially being out of compliance with the protocol were investigator sponsored studies, and therefore accountability for disclosure/publication of those results was with the sponsor of the study, not AstraZeneca. Consequently they fell out with the requirements of Clause 21.3 of the Code.
- Thirty-one of the studies identified by the researchers as potentially being out of compliance with the protocol were either Phase I or exploratory Phase II studies completed before the cut-off date of 6-months before publication of the 2008 IFPMA Joint Position; therefore they fell out with the requirements of disclosure/publication of this type of study, and consequently also Clause 21.3 of the ABPI Code (2011).
  - For 23 of the studies all results had since been disclosed, on [clinicaltrials.gov](http://clinicaltrials.gov) and/or [AstraZenecaClinicalTrials.com](http://AstraZenecaClinicalTrials.com) (Section 2.1).
  - The results from eight of the studies had not been published, though AstraZeneca remained committed to ensuring their publication over time (Section 2.2).
- Four of the studies identified by the researchers as potentially being out of compliance with the protocol were Phase III studies that were completed before the publication date of the 2005 IFPMA Joint Position; therefore they fell out with the requirements of publication of this type of study and consequently Clause 21.3 of the ABPI Code (2008 and 2011).
  - Two studies had not had results disclosed, though AstraZeneca remained committed to ensuring their publication over time.
  - The results from two studies had since been disclosed.

- One study was a local phase IV non-interventional study, sponsored by AstraZeneca Taiwan, which completed in August 2010. This study was identified incorrectly as being potentially out of compliance with the protocol, as it was not an interventional study and results were in fact disclosed on [AstraZenecaClinicalTrials.com](http://AstraZenecaClinicalTrials.com) in November 2010. A summary of the trial from the AstraZeneca website was provided.
- Of the remaining two studies, AstraZeneca UK recognised that the studies did not report results within the timelines required by the IFPMA Joint Position on Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2008); both studies were local studies, conducted overseas, with no UK patient, site, investigator and were both outwith the control or responsibility of the UK affiliate, or indeed any study team based within the UK.
  - One study was originally started as a local phase II investigator sponsored study in Canada, and completed in August 2011. This study was listed on [clinicaltrials.gov](http://clinicaltrials.gov) as AstraZeneca sponsored, in error, and any and all postings and/or disclosure of applicable information would be the responsibility of the investigator who initiated the study. To mitigate disclosure implications which led to a delay in disclosure of results, AstraZeneca Canada was working closely with the responsible investigator to ensure disclosure of results.
- The final study was a local phase IV study, again sponsored by AstraZeneca Taiwan, which was terminated in August 2009, with only 14 patients recruited and a safety summary produced.
  - The local study team in AstraZeneca Taiwan was currently expediting disclosure of these limited results on [clintrials.gov](http://clintrials.gov).

## Conclusion

AstraZeneca submitted as was evident from the information supplied above, each of the AstraZeneca Iressa clinical studies identified in the research which formed the basis of the complaint:

- was outside the legal requirements under Food & Drug Administration Amendments Act of 2007, (FDAAA, 2007) and/or
- had results reported on [clinicaltrials.gov](http://clinicaltrials.gov) and/or the AstraZeneca website
- was in the process of being published.

In addition, many had also been published in journals and those publications were listed on the [ClinicalTrials.gov](http://ClinicalTrials.gov) as provided by US National Institutes of Health, or on the US National Library of Medicine National Institutes of Health. For those that had not yet been published, AstraZeneca was committed to posting/publication of results, as stated in the report that forms the basis of this complaint and in line with the company disclosure position, as stated above.



AstraZeneca submitted that it was not in breach of Clause 21.3 (2008 or 2011), as the studies identified by the researchers as being out of compliance with their protocol, either fell outwith the requirements of the Code, in that their completion predated the requirements of the Code, or they fell outwith the jurisdiction of the Code as there was no UK involvement.

Subsequent to completion of the principal draft of its response, AstraZeneca was sent a spreadsheet detailing all trials identified by the researchers using the publication search protocol. AstraZeneca highlighted the trials where disclosure status was queried, to aid the PMCPA in cross-referencing.

In response to a request for additional information AstraZeneca stated that the two studies detailed as not reported within the joint position timeframe did not involve any UK team from within the Global AstraZeneca organisation. Accountability for the delivery of the study sat with the local study delivery team within the country (Canada and Taiwan, in this case). Responsibility for registration of the study and for the posting and publication of results sat with the local study team leader and accountability with the local director or vice president, medical.

AstraZeneca provided copies of SOPs that referred to clinical trial results and where the responsibility for disclosure sat. The current SOP was provided. The versions valid in 2009 and 2011 were not found, however, AstraZeneca submitted that there was no significant difference in process, roles and responsibilities between current and past versions.

AstraZeneca stated that the Clinical Trials Disclosures Procedures and Responsibilities document detailed the accountability of the marketing company (affiliate) medical director and the responsibility of the study team leader – namely to complete the required templates and submit them to the clinical trials transparency (CTT) team. This team then ensured that the documentation was checked by all the necessary central teams and posted on the appropriate websites. AstraZeneca stated that the responsibility and accountability for clinical trial registration and results posting sat clearly with the local study team who initiated the process by completing and submitting the templates in a timely fashion and ensured the accuracy and completeness of the submitted information; not the CTT team, whose responsibility, though important for compliance monitoring and tracking, was primarily administrative. This team was currently based in Poland, and was previously a US based team.

Iressa was first licensed in Japan in 2002. Iressa 250mg once daily originally received approval on 5 July, 2002. It was originally licensed for the treatment of inoperable or recurrent non-small cell lung cancer (NSCLC) in Japan, whilst the European licence, granted in 2009, was for EGFR mutation positive NSCLC; the broader indication was never granted in the EU.

## GENERAL COMMENTS FROM THE PANEL

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical

Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved

in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

*'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can*

*be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for

marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's

view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

#### **PANEL RULING IN CASE AUTH/2657/11/13**

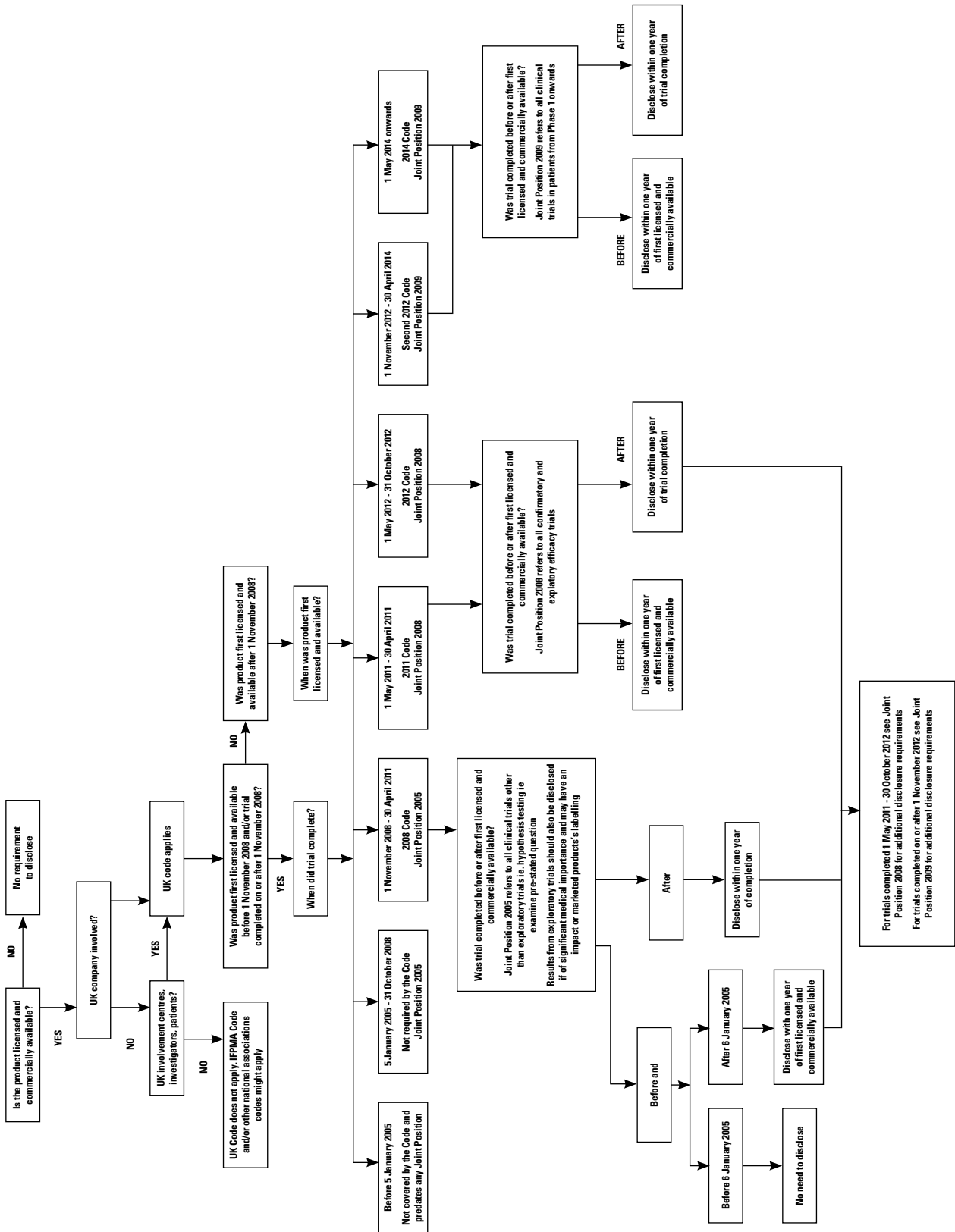
The Panel noted the CMRO publication in that twenty-nine Iressa studies had not been disclosed in the timeframe. The disclosure percentage was 56%. Twelve studies had not been disclosed giving a disclosure percentage at 31 January 2013 for trials completed at 31 January 2012 of 84%. A footnote stated that the majority of Phase II/III trials were completed prior to FDAAA 801 requirements. The remaining undisclosed trials were in the process of publication.

The Panel noted AstraZeneca's submission regarding the studies. It noted that AstraZeneca was a UK registered company. It could be argued that this meant the UK Code applied as the studies were in effect run by a UK company.

The Panel agreed with AstraZeneca that it was not responsible for disclosure of investigator-sponsored

# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results



studies (15 trials). It was good practice for a company to strongly advocate publication of such data but the Code and joint positions only related to pharmaceutical company sponsored studies. Thus the Panel ruled no breach of the Code as the matter was not within the scope of the Code.

The Panel noted that AstraZeneca first got a marketing authorization for Iressa in Japan in 2002 and in the Panel's view, this was when the company first became responsible for meeting any disclosure requirements. The first joint position (January 2005) was not referred to in the Code until the 2008 Code which was effective from 1 November 2008. Thus any Iressa trials completed before this date were not required to be disclosed under the Code.

The Panel noted that of the remaining 38 trials (53 minus 15 investigator-sponsored trials), 35 were Phase I, exploratory Phase II or Phase III studies all of which completed before 1 November 2008. In that regard, there was no requirement under the Code to disclose these studies. The Panel thus ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2. (The Panel noted that although there was no requirement under the Code to do so, the results for 23 of these trials had been disclosed).

An AstraZeneca Thailand non-interventional study completed in August 2010, which was after Iressa was first approved and commercially available. The Panel noted AstraZeneca's submission that these results were disclosed on its own website in November 2010. The study was a retrospective cohort study on patients

from two tertiary hospitals in Thailand. It was not an interventional study, it was not clear whether there was any UK involvement and the Joint Position 2005 appeared not to require disclosure of the results of a non-interventional trial. (In the Joint Position 2009 it was clear that only the results from interventional studies had to be disclosed). In any event the results had been disclosed publicly within one year and thus the Panel ruled no breach of Clauses 2, 9.1 and 21.3 of the 2008 Code.

The Panel noted that the results from two trials remained undisclosed – an AstraZeneca Canada study which completed in August 2011 and an AstraZeneca Taiwan study which completed in August 2009. AstraZeneca submitted that the publication of the results was expected.

The Panel considered that although AstraZeneca was a UK registered company, the company's arrangements were such that it was clear that the responsibility for disclosure was with the local company. It considered that the matter was potentially covered by the UK Code but as the responsibilities had been made very clear in a company SOP it ruled no breach of Clause 21.3 of the 2008 Code in relation to the AstraZeneca Taiwan trial and no breach of Clause 21.3 of the 2011 Code in relation to the AstraZeneca Canada study. The Panel consequently ruled no breaches of Clauses 9.1 and 2 of the respective Codes.

**Complaint received**                      **21 November 2013**

**Case completed**                              **20 March 2014**

# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v PFIZER

## Clinical trial disclosure (Conbriza and Xiapex)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Conbriza (bazedoxifene) and Xiapex (collagenase clostridium histolyticum).

The detailed response from Pfizer is given below.

General detailed comments from the Panel are given below.

With regard to Xiapex, the Panel noted the CMRO publication in that two of the eleven evaluable studies had not been disclosed within the timeframe giving a disclosure percentage of 82%. The percentage disclosed at 31 January 2013 of all trials completed before the end of January 2012 was 91% with one evaluable study not disclosed. A footnote stated that the undisclosed trial was sponsored by Auxilium and was in the process of publication.

The Panel noted Pfizer's submission that on 29 October 2013 it issued the basic results of the Xiapex trial it sponsored which completed in October 2012. The posting was awaited on clinicaltrials.gov. There was no documentation showing that the results had been made publicly available. The Panel further noted that Pfizer had not provided any evidence that clinicaltrials.gov had agreed to a request for delayed disclosure for example due to publication in a peer reviewed journal. Thus the Panel ruled a breach of the 2012 Code. The delay in disclosure meant that high standards had not been maintained and a breach was ruled. These rulings were appealed. The Panel noted the date of completion of this study and that the results had been provided to clinicaltrials.gov and that a manuscript had been accepted by the Journal of Hand Surgery. On balance the Panel decided that the delay to disclose in these circumstances did not warrant a ruling of a breach of Clause 2 and ruled accordingly.

Upon appeal by Pfizer the Appeal Board noted that Pfizer had not made it clear in its submission to the Panel which of the studies referred to in its response were the evaluable studies and which were the non evaluable studies. The Panel had not been provided with documentation to show that the results had been made publicly available. The Appeal Board noted from Pfizer that the study results had now been publicly disclosed.

The Appeal Board noted from the data provided by Pfizer in its appeal, that the Xiapex Point X study was not completed until October 2012 which was after the cut off date of the end of January 2012 for it to be considered an evaluable study within the CMRO publication. The Appeal Board considered that as the study was non evaluable at the end of January 2012, it was outwith the scope of the complaint and so it ruled no breach of the 2012 Code. The appeal was successful.

With regard to Conbriza, the Panel noted the CMRO publication in that five of the eleven evaluable studies had not been disclosed within the timeframe giving a disclosure percentage of 55%. The percentage disclosed at 31 January 2013 of all trials completed before the end of January 2012 was 82%; two studies had not been disclosed. A footnote stated that the undisclosed trials were sponsored by Wyeth prior to acquisition by Pfizer and were not subject to FDAAA801 requirement.

The Panel noted Pfizer's submission regarding a Phase III Conbriza study which completed in July 2004 and the earliest date of posting of summary results was April 2008. As the date of first approval and commercial availability of Conbriza was May 2010, Pfizer needed to disclose the results before May 2011. Pfizer had done this and thus the Panel ruled no breach of the 2008 Code including Clause 2.

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public

Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Conbriza (bazedoxifene) and Xiapex (collagenase clostridium histolyticum) as follows:

### Conbriza

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	4	0	4	1	25%	4	3	75%
Phase III	7	0	7	5	71%	7	6	86%
<b>TOTAL</b>	<b>11</b>	<b>0</b>	<b>11</b>	<b>6</b>	<b>55%</b>	<b>11</b>	<b>9</b>	<b>82%</b>

### Xiapex

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	4	0	4	3	75%	4	3	75%
Phase III	12	5	7	6	86%	7	7	100%
Phase IV	1	1	0	0	0%	0	0	0%
<b>TOTAL</b>	<b>17</b>	<b>6</b>	<b>11</b>	<b>9</b>	<b>82%</b>	<b>11</b>	<b>10</b>	<b>91%</b>



The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluable	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluable trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluable trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Pfizer.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Pfizer, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Pfizer submitted that the disclosure of clinical trials information, in accordance with the ABPI Code and other applicable regulatory and self-regulatory guidelines worldwide, was important to public health and the reputation of the pharmaceutical industry. The disclosure of clinical trials information for Xiapex and Conbriza came within the scope of the ABPI Code as described in Clause 21.3. Pfizer submitted that as explained below, it had not breached Clauses 1.8, 2, 9 or 21.

### **Xiapex**

Pfizer stated that Auxilium Pharmaceuticals Inc was the originator of Xiapex and sponsored the significant majority of clinical trials. In the EU,

pursuant to an agreement with Auxilium, Pfizer was the marketing authorization holder for Xiapex until 9 April 2013, when it was transferred to Auxilium UK Limited. Xiapex had been available to UK patients since its launch in the UK in April 2011.

Pfizer was only the sponsor for Study B1531002 (Point X Study - completed) for which it issued the basic results on 29 October 2013. The posting was awaited on the ClinicalTrials.gov site. The basic results were provided. There were clinical trial sites in the UK, Ireland, Sweden, Germany, France, Italy, Spain, Netherlands, Hungary and Denmark. The primary manuscript for the Point X Study had been accepted for publication in the Journal of Hand Surgery (British).

There was a second study, B1531005, for which Pfizer was the sponsor, and this was an EMA post-approval commitment. This study was ongoing but the sponsorship of it was transferred from Pfizer to Auxilium in June 2013, following the transfer of the marketing authorization. Auxilium would therefore be responsible for the basic results posting. There were clinical trial sites in the UK, Spain, Austria, Norway, Germany, Switzerland, Italy and Belgium.

All the other studies conducted with Xiapex were sponsored by Auxilium and therefore Auxilium was responsible for posting/publication of results. This included the study identified as non-disclosed in the CMRO publication.

### **Conbriza**

Pfizer stated that Wyeth held the marketing authorization for Conbriza until Pfizer acquired Wyeth, after which the marketing authorization was transferred to Pfizer. Conbriza was centrally approved in the EU in April 2009. A list of countries where the product was authorised was provided. Conbriza had not been launched in all EU markets, and had not been launched in the UK. It had therefore not been available to UK patients outside of clinical trials. A list of launch dates was provided.

Two studies were described as non-disclosed in the publication. However, publications were identified for both studies, but not in time for them to be reflected in the manuscript submitted to CMRO.

The first study was a mammography sub-study from one of the Phase III trials, looking at effects of Conbriza on breast density (Harvey *et al* 2009). The CT.gov locator was: <http://clinicaltrials.gov/ct2/show/NCT00418236?term=NCT00418236&rank=1>.

The second study was a Phase II Chinese study that was published in the Chinese Pharmaceutical Journal, evaluating the effects of Conbriza on biochemical markers of bone metabolism in healthy postmenopausal Chinese women (X Ling *et al* 2007).

Using the raw data spreadsheet compiled for the CMRO publication, Pfizer provided a list of the postings and publications for the Phase II and III Conbriza trials. The publication citations for the above two studies had been added to the spreadsheet.

Finally, the Phase II and III Conbriza trials and the countries involved in the studies, including whether they included any sites in the UK were listed. Pfizer submitted that this showed that only one Phase III study included a UK site.

A copy of the standard operating procedure (SOP) CT20 POL; Public Disclosure and Authorship was provided.

Pfizer submitted that given that all the trials for which Pfizer had responsibility had been disclosed it denied any breach of Clauses 1.8 or 21 of the Code. High standards had been maintained (no breach of Clause 9) and the company submitted that it had not brought the industry into disrepute (no breach of Clause 2).

#### **GENERAL COMMENTS FROM THE PANEL**

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about

ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary

information to Clause 7.5 of the 2006 Code:

**'Clause 7.5 Data from Clinical Trials**

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superseded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

**'Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superseded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial

Results in the Scientific Literature. Clause 21.3 now stated:

*'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

**'Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It

noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

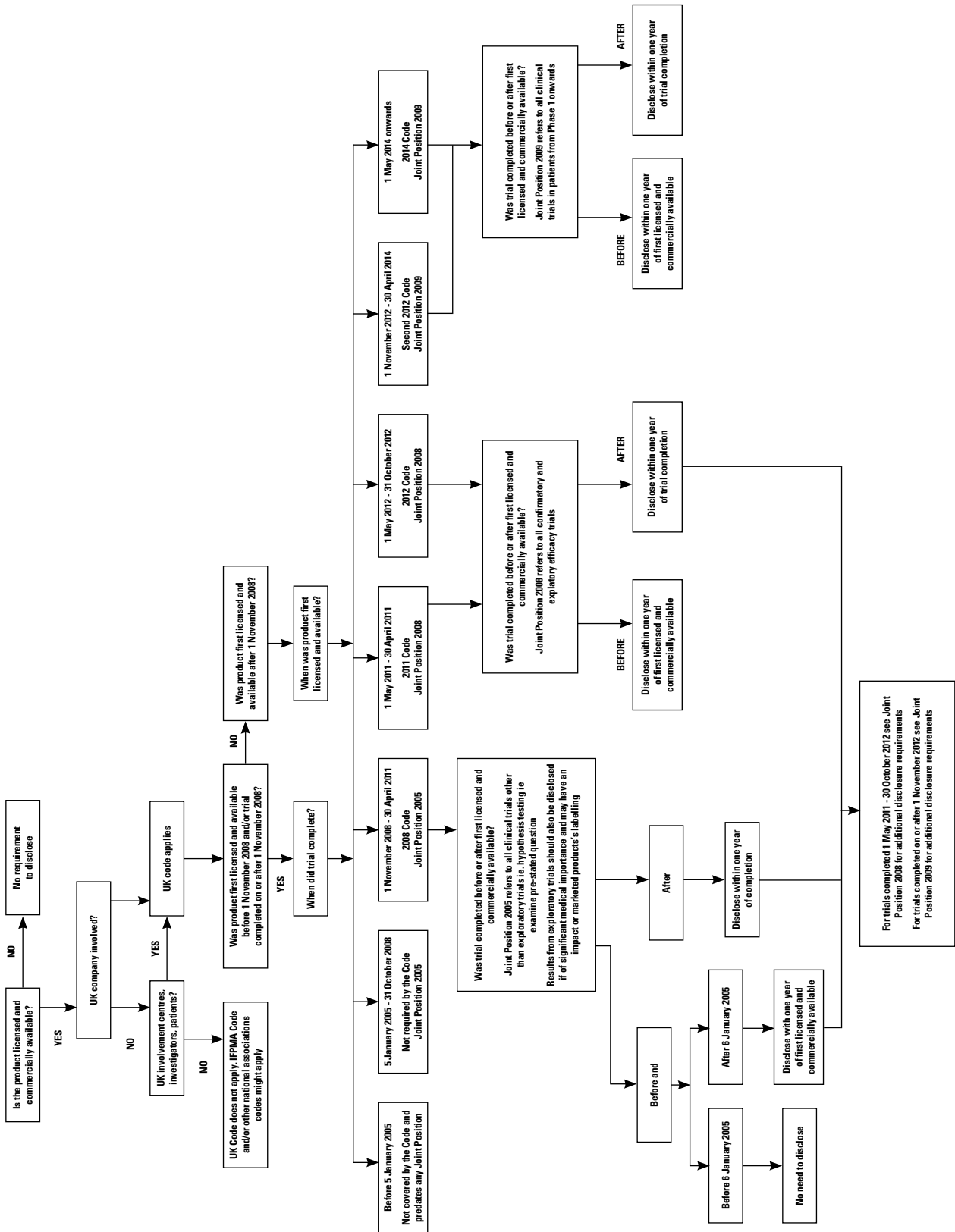
For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results



During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause

1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

## **PANEL RULING IN CASE AUTH/2659/11/13**

### **Xiapex**

The Panel noted the CMRO publication in that two of the eleven evaluable studies had not been disclosed within the timeframe giving a disclosure percentage of 82%. The percentage disclosed at 31 January 2013 of all trials completed before the end of January 2012 was 91% with one evaluable study not disclosed. A footnote stated that the undisclosed trial was sponsored by Auxilium and was in the process of publication.

The Panel noted Pfizer's submission that on 29 October 2013 it issued the basic results of the trial it sponsored which completed in October 2012 and included UK patients. The posting was awaited on [clinicaltrials.gov](http://clinicaltrials.gov). The Panel examined the material provided by Pfizer. It included a document showing that the results had been provided to [clinicaltrials.gov](http://clinicaltrials.gov) but there was no documentation showing that the results had been made publicly available. The Panel further noted that Pfizer had not provided any evidence that [clinicaltrials.gov](http://clinicaltrials.gov) had agreed to a request for delayed disclosure for example due to publication in a peer reviewed journal. Thus the Panel ruled a breach of Clause 21.3 of the 2012 Code. The delay in disclosure meant that high standards had not been maintained. A breach of Clause 9.1 was ruled. These rulings were appealed. The Panel noted the date of completion of this study and that the results had been provided to [clinicaltrials.gov](http://clinicaltrials.gov) and that a manuscript had been accepted by the *Journal of Hand Surgery*. On balance the Panel decided that the delay to disclose in these circumstances did not warrant a ruling of a breach of Clause 2. No breach of Clause 2 was ruled.

Pfizer sponsored a second study but this was ongoing and sponsorship had transferred to Auxilium in June 2013. Pfizer submitted that the completed undisclosed trial was an Auxilium trial. The Panel considered that as far as Pfizer was concerned the matter did not come within the scope of the Code and therefore ruled no breach.

### **Conbriza**

The Panel noted the CMRO publication in that five of the eleven evaluable studies had not been disclosed within the timeframe giving a disclosure percentage of 55%. The percentage disclosed at 31 January 2013 of all trials completed before the end of January 2012 was 82%; two studies had not been disclosed. A footnote stated that the undisclosed trials were sponsored by Wyeth prior to acquisition by Pfizer and were not subject to FDAAA801 requirement.

The Panel noted the information supplied by Pfizer. This indicated that all the trial results had been disclosed. The Panel noted that Conbriza was approved in April 2009 and first launched in May 2010. This meant that for trials completed before May 2010 the results needed to be disclosed by May 2011. The Panel noted that the results of all eleven evaluable studies had been disclosed by May 2011.

The Panel noted Pfizer's submission that the two studies referred to in the CMRO publication as not being disclosed by 31 January 2013 had been published (one accepted for publication March 2009 and the other in 2007). The publications had not been identified in time for them to be reflected in the CMRO publication. It appeared to the Panel that neither of these studies involved UK patients.

The Panel considered that Pfizer was responsible under the Code for publication of the Wyeth studies. Conbriza had not been launched in the UK. The Panel was only concerned with studies that were run by the UK company or had UK involvement. The Panel examined the information provided by Pfizer and noted the company's submission that only one Phase III study involved UK patients. It appeared that this study completed in July 2004 and the earliest date of posting of summary results was April 2008. As the date of first approval and commercial availability of Conbriza was May 2010, Pfizer needed to disclose the results before May 2011. Pfizer had done this and thus met the requirements of the 2008 Code. The Panel ruled no breach of Clause 21.3 and consequently no breach of Clauses 9.1 and 2. The Panel noted that the ten other studies had no UK involvement. The Panel considered that these did not come within the scope of the UK Code and therefore ruled no breach.

#### **APPEAL BY PFIZER**

##### **Xiapex**

Pfizer understood that the Panel's ruling with regard to clinical trial disclosure was for evaluable studies only, and one of the criteria for this was that the completion of the study needed to be by the end of January 2012. Pfizer submitted that as the Xiapex Point X study completed in October 2012 (as noted on the raw data spreadsheet for the CMRO publication (copy provided)) it was not an evaluable

study, thus it was outwith the scope of the Panel's decision.

Pfizer appealed the Panel's rulings of a breach of Clause 9.1 and 21.3.

#### **COMMENTS FROM THE COMPLAINANT**

There were no comments from the complainant.

#### **APPEAL BOARD RULING**

The Appeal Board noted that Pfizer had not made it clear in its submission to the Panel which of the studies referred to in its response were the evaluable studies and which were the non evaluable studies.

The Appeal Board noted that the Panel had not been provided with documentation to show that the results had been made publicly available. The Appeal Board noted from the Pfizer representatives at the appeal that the study results had now been publicly disclosed.

The Appeal Board noted from the raw data spreadsheet for the CMRO publication, provided by Pfizer in its appeal, that the Xiapex Point X study was not completed until October 2012 which was after the cut off date of the end of January 2012 for it to be considered an evaluable study within the CMRO publication. The Appeal Board considered that as the study at issue was non evaluable at the end of January 2012, it was outwith the scope of the complaint and so it ruled no breach of Clauses 9.1 and 21.3 of the 2012 Code. The appeal was successful.

<b>Complaint received</b>	<b>21 November 2013</b>
<b>Case completed</b>	<b>12 June 2014</b>

# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v FERRING

## Clinical trial disclosure (Firmagon)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Firmagon (degarelix).

The detailed response from Ferring is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that four evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 83%. The disclosure percentage at 31 January 2013 of trials completed by end of the January 2012 was 91%. Two trials had not been disclosed. A footnote stated that Ferring agreed publication/delayed publication of results in advance with clinicaltrials.gov. One undisclosed Phase III trial was now available.

The Panel noted that Firmagon was first licensed and commercially available in March 2009. The 2008 Code and Joint Position 2005 were relevant for studies completed prior to March 2009.

Trial NCT00116753 completed in November 2006 and was disclosed in October 2010. As the results were not disclosed by March 2010 (ie one year after Firmagon was first licensed and available), Ferring had not met the requirements of the Code. The Panel ruled a breach of the 2008 Code. The delay in disclosure meant that high standards had not been maintained and a breach was ruled. As the data had been disclosed the Panel considered there was no breach of Clause 2 and ruled accordingly.

Trial NCT00451958 was disclosed in October 2012 one year after completion (October 2011). Thus the Panel ruled no breach of the 2011 Code including Clause 2.

Trial NCT00946920 which completed in March 2011 was on an unlicensed formulation and had been granted delayed results disclosure due to 'certify new use'. The Panel decided there was, as yet, no requirement to disclose the results of this study. The Panel ruled no breach of the 2008 Code including Clause 2.

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

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## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for each product. The Firmagon (degarelix) data were as follows:

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	14	2	12	10	83%	12	12	100%
Phase III	14	3	11	9	82%	11	9	82%
<b>TOTAL</b>	<b>28</b>	<b>5</b>	<b>23</b>	<b>19</b>	<b>83%</b>	<b>23</b>	<b>21</b>	<b>91%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluable	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluable trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluable trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Ferring.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Ferring, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Ferring stated that due to the complex nature of its response, the company had responded according to the phase of the trial and the relevant version of the ABPI Code. A template was provided.

Ferring submitted that it had complied with the Code with regard to all Phase I trials.

Only three Phase II trials fell within the scope of the Code as follows:

- CS27 which had been disclosed on Clinicaltrials.gov
- CS36 and 08 – delayed results reporting was granted on Clinicaltrials.gov due to 'certify new use'. CS36 had a delayed results certification on Clinicaltrials.gov as demonstrated in the link provided. For Trial 000008, the delayed results certification was dated November 2013 (1 year after primary completion date), however, this had not been released to the public yet as it was waiting for quality control on Clinicaltrials.gov. Information to confirm this was provided.

Ferring submitted that this was in line with the 100% disclosure in the CMRO publication.

For Phase III trials, 14 trials were included in the analysis as follows:

- 8 trials were completed and declared on Clinicaltrials.gov
- 2 trials were not completed: one trial was withdrawn and another one was discontinued. Both were declared on Clinicaltrials.gov as demonstrated in each individual link.
- 4 trials were completed, but had been granted delayed results reporting on Clinicaltrials.gov due to 'certify new use'. CS29 and CS37 investigated the use of Firmagon in a new dosing schedule, outside the approved labelling. CS35 and CS35A investigated the use of Firmagon in a new formulation, outside the approved labelling. Firmagon was not commercially available in any country for the formulations or dosing schedules.

In addition to the 14 trials mentioned in the CMRO publication, there was one more on-going Phase III trial and a link to the relevant declaration was provided.

All Phase IV trials (observational) were currently on-going and the relevant declaration link was provided.

Ferring had chosen to use Clinicaltrials.gov as according to Ferring's standard operating procedure (SOP), this was the primary registry used. However for trials run in the EU, the protocol information was also available on the EU Clinical Register (<https://www.clinicaltrialsregister.eu/>). Results were not yet available in the EU Clinical Trials Register as EudraCT V9 had just been launched.

Based upon the above Ferring submitted that it had complied with the requirements of Clause 21.3 and it was not in breach of any of the relevant versions of this clause.

Ferring genuinely believed that high standards had been maintained at all times and that the sponsorship of trials had been clearly declared. As a result it had complied with Clauses 9.1 and 9.10.

As outlined in its template, six Phase III trials had UK involvement and all of them had the declaration link provided. Two of these Phase III trials with UK involvement had delayed results reporting granted on Clinicaltrials.gov due to 'certify new use'. Therefore Ferring submitted that it had complied with all applicable versions of the Code according to Clause 1.8.

To conclude, Ferring submitted that it had consistently complied with Clauses 21.3, 1.8, 9.1 and 9.10 in relation to various versions of the Code and joint positions. Therefore Ferring had not brought any discredit to, or reduced confidence in the industry and it denied a breach of Clause 2.

In response to a request for further information Ferring submitted that Firmagon was first licensed and commercially available on 2 March 2009 (in the US).

In response to a request for further information about which four trials were referred to in the CMRO publication as not being disclosed within the timeframe, Ferring submitted that three of the four trials ((NCT00116753) (NCT00451958)

(NCT00946920)) had UK sites. These trials completed in November 2006, October 2011 and March 2011 respectively. Trial NCT00946920 was not yet disclosed as this looked at a new formulation of Firmagon which was not licensed. The other two trials (NCT00116753 and NCT00451958) were disclosed on 6 October 2010 and 10 October 2012 respectively. Trial NCT00468286 did not have any UK sites.

## GENERAL COMMENTS FROM THE PANEL

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical*

*Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

*'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion

– an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May

2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

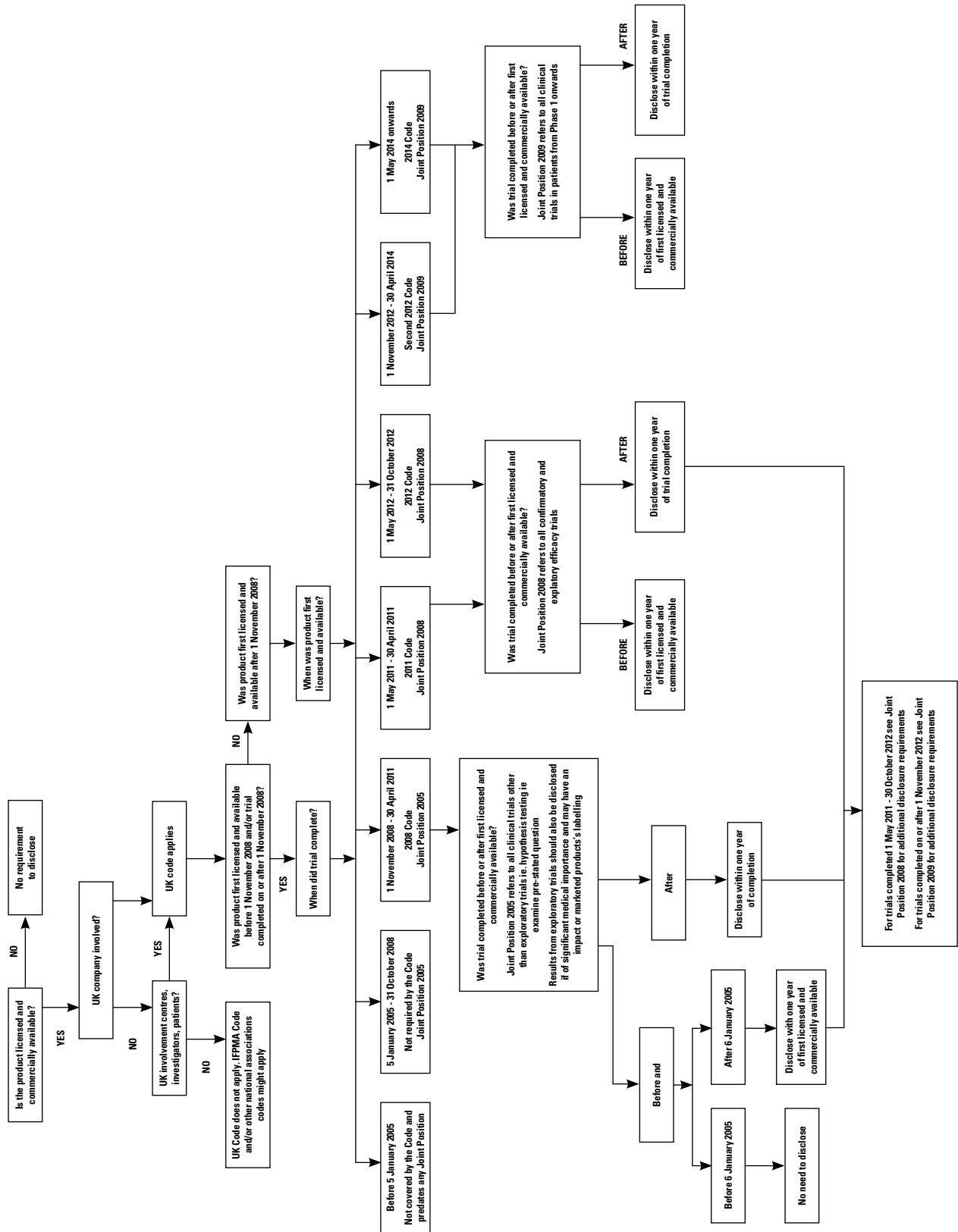
The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *de facto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results



**PANEL RULING IN CASE AUTH/2661/11/13**

The Panel noted the CMRO publication in that four evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 83%. The disclosure percentage at 31 January 2013 of trials completed by end of the January 2012 was 91%. Two trials had not been disclosed. A footnote stated that Ferring agreed publication/delayed publication of results in advance with clinicaltrials.gov. One undisclosed Phase III trial was now available.

The Panel noted that Firmagon was first licensed and commercially available in March 2009. The 2008 Code and Joint Position 2005 were relevant for studies completed prior to March 2009.

Trial NCT00116753 completed in November 2006 and was disclosed in October 2010. As the results were not disclosed by March 2010 (ie one year after Firmagon was first licensed and available), Ferring had not met the requirements of the Code. The Panel ruled a breach of Clause 21.3 of the 2008 Code. The delay in disclosure meant that high standards had not been maintained and a breach of Clause 9.1 was ruled. As the data had been disclosed the Panel considered there was no breach of Clause 2 and ruled accordingly.

Trial NCT00451958 was disclosed in October 2012 one year after completion (October 2011). Thus the Panel ruled no breach of Clause 21.3 of the 2011

Code and consequently no breach of Clauses 9.1 and 2.

The Panel considered that as trial NCT00468286 had no UK involvement the matter did not come within the scope of the Code and it therefore ruled no breach.

The final trial (NCT00946920) which completed in March 2011 was on an unlicensed formulation and had been granted delayed results disclosure due to 'certify new use'. Taking all the circumstances into account, it decided there was, as yet, no requirement to disclose the results of this study. The Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

During its consideration of this case, the Panel noted that from the information about studies not covered in the CMRO publication it appeared that some of these had not been disclosed within the one year timeframe (NCT00268892, NCT00831233 and NCT00215683). These appeared to have UK involvement. All the trial results had been disclosed. The Panel requested that its concerns were drawn to Ferring's attention.

**Complaint received                    21 November 2013**

**Case completed                        24 March 2014**

# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v NOVARTIS

## Clinical trial disclosure (Ilaris and Gilenya)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Ilaris (canakinumab) and Gilenya (fingolimod).

The detailed response from Novartis is given below.

General detailed comments from the Panel are given below.

With regard to Ilaris, the Panel noted the CMRO publication in that three evaluable trials had not been disclosed in the timeframe. The disclosure percentage was 91%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 100%.

The Panel noted that Ilaris was first approved in August 2006. Two trials with UK involvement completed after this date.

The Panel noted that one trial completed on 4 August 2010 and was published on 22 November 2010. This was within a year of completion and thus the Panel ruled no breach of the 2008 Code including Clause 2.

Another trial completed on 23 October 2009 with the results submitted by 30 August 2012 and posted by December 2012. The results had not been published within the timeframe and thus the Panel ruled a breach of the 2008 Code as acknowledged by Novartis. High standards had not been maintained and a breach was ruled. As the results had been disclosed the Panel considered that there had been no breach of Clause 2 and ruled accordingly.

With regard to Gilenya, the Panel noted the CMRO publication in that one evaluable trial had not been disclosed in the timeframe. The disclosure percentage was 96%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 96%. A footnote stated that the undisclosed trial was completed in 2004 and the clinical study report was in the process of being posted on the company trial registry.

The Panel noted that Gilenya was first approved in August 2010. The 2008 Code and thus the Joint Position 2005 applied. The Panel noted that the trial in question completed in November 2004. The Joint Position 2005 did not require studies completed before January 2005 to be published thus the Panel ruled no breach of the 2008 Code including Clause 2.

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

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Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their

clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Ilaris (canakinumab) and Gilenya (fingolimod) as follows:

### Ilaris

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	22	0	22	19	86%	22	22	100%
Phase III	13	2	11	11	100%	11	11	100%
<b>TOTAL</b>	<b>35</b>	<b>2</b>	<b>33</b>	<b>30</b>	<b>91%</b>	<b>33%</b>	<b>33%</b>	<b>100%</b>

### Gilenya

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	11	1	10	9	90%	10	9	90%
Phase III	17	1	16	16	100%	16	16	100%
Phase IV	4	3	1	1	100%	1	1	100%
<b>TOTAL</b>	<b>32</b>	<b>5</b>	<b>27</b>	<b>26</b>	<b>96%</b>	<b>27</b>	<b>26</b>	<b>96%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluative	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluative trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later

disclosure percentage	proportion of evaluative trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Novartis.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Novartis, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Novartis submitted that it had focused only on those aspects which were directly relevant to the CMRO publication which formed the basis of the complaint.

Other considerations to note were the relevant applicable ABPI Code and IFPMA Joint Position which would have been in place when the medicine was first licensed anywhere in the world.

Novartis provided a copy of its relevant standard operating procedure (SOP) which educated

and trained relevant Novartis associates on the requirements for clinical trial disclosure for background information. In addition Novartis provided a copy of its position statement on the Disclosure of Clinical Research Information which was posted on its corporate website.

Novartis summarised the relevant ABPI Codes and their reference to the Joint Position in the table below.

Code of Practice 2008, 2011, 2012	Code of Practice 2012 (Edition 2)
<p><b>Clause 21.3</b> Companies must disclose details of clinical trials</p>	<p><b>Clause 21.3</b> Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature</p>
<p><b>Supplementary Information</b> <b>Clause 21.3 Details of Clinical Trials</b> <i>'This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2008 (<a href="http://clinicaltrials.ifpma.org">http://clinicaltrials.ifpma.org</a>).</i></p> <p><i>Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.</i></p> <p><i>[Joint Position dated Nov 2008]</i></p>	<p><b>Supplementary Information</b> <b>Clause 21.3 Details of Clinical Trials</b> <i>'This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <a href="http://clinicaltrials.ifpma.org">http://clinicaltrials.ifpma.org</a>.</i></p> <p><i>Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.</i></p> <p><i>[Joint Position dated Nov 2009]</i></p>
<p><b>In Scope Trial* completion dates:</b>  <b>Ilaris (NCT00927810, CACZ885H2251E1) 01-Aug-2010</b>  <b>Ilaris (NCT00663169, CACZ885A2212) 01-Oct-2009</b>  <b>Gilenya (NCT00239902, CFTY720A0121E1) 01-Nov-2011</b></p>	

Under Clause 1.8 Novartis submitted that only those trials which included UK trial sites were in scope of the ABPI Code.

Ilaris (first licensed in Finland and New Zealand on 2 August 2006)

Novartis stated that the CMRO publication identified a disclosure percentage of 91% within the required timeframe but noted that this was 100% as of 31 January 2013.

There were 3 Phase II trials for Ilaris which were considered evaluable by the CMRO publication and for which the disclosure timelines were outside the required timeframe.

One of these, trial NCT00554606, had been excluded

from this response as Novartis submitted this trial had no UK sites or UK involvement and would therefore be outside the scope of the ABPI Code as outlined by Clause 1.8. A further two trials which were considered not capable of evaluation were also excluded as there were no UK sites or no UK involvement.

Novartis submitted that there were two trials which would be considered within scope as follows:

### **NCT00927810; CACZ885H2251E1**

This trial completed on 4 August 2010 and was published on the Novartis clinical trial results database (CTRD) on 21 November 2011. In this regard the results were published within 15 months of the clinical trial completing and not

the recommended 12 months. On investigation it appeared that the internal results report - the Clinical Study Report - was published on 22 November 2010. Therefore it was apparent that the trial disclosure was published within 12 months of this report.

#### **NCT00663169; CACZ885A2212**

This trial was completed on 23 October 2009 and results were submitted to the CT.gov registry 30 August 2012 and verified and posted online by CT.gov December 2012. They were posted on the Novartis CTRD September 2012. The results of this clinical trial were published some 33 months after the study completed. Novartis acknowledged a breach of Clause 21.3 in delayed disclosure of the trial results.

Gilenya (first licensed in Russia on 17 August 2010)

Novartis stated that the background statistics for the publication identified a disclosure percentage of 96% within the required timeframe and also as of 31 January 2013.

#### **NCT00239902; CFTY720A0121E1**

This was a Phase II trial which was noted to have not had results disclosed - Efficacy and Safety of FTY720 in *de Novo* Adult Renal Transplant Recipients [two year extension], and was for a cohort of renal transplant patients. The study ended on 30 November 2004. Novartis submitted that this trial would have been out of scope for both the ABPI Code and also the Joint Position. IFPMA launched the Clinical Trials Portal in March 2006, which was after the completion of this trial. The trial was registered on CT.gov in October 2005 but at the time there was no policy in place to post studies or their results retrospectively. Colleagues in Novartis' clinical trial disclosure department advised that this would not have been in accordance with the requirements of the CT.gov registry at the time. However, in the interests of transparency, Novartis had published the results of this trial on its CTRD.

Novartis therefore submitted that the 2011 Code and the referenced 2008 Joint Position did not require trials completed before the medicine was first licensed to have been disclosed retrospectively and for indications for which they were never licensed. Consequently, Novartis did not believe that it was in breach of Clause 21.3.

A further five studies were determined to be non-evaluative by the authors; none of these studies had UK sites or UK involvement and were thus outside the scope of the ABPI Code as outlined by Clause 1.8.

In conclusion, Novartis acknowledged a single breach of Clause 21.3 but that in itself did not prove in any way a lack of high standards. Novartis submitted that the disclosure rate shown in CMRO publication for 31 January 2013 demonstrated the company's ongoing commitment to abide by the Joint Position and it was not in breach of Clause 9.1.

Consequently Novartis had not brought discredit

upon or reduced confidence in the pharmaceutical industry warranting a ruling of a breach of Clause 2.

A copy of this response and the findings of the CMRO publication had been made available to Novartis global colleagues to investigate any trials which were considered to be outside the reporting times but which were considered outside the scope of the ABPI Code.

#### **GENERAL COMMENTS FROM THE PANEL**

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific

Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with*

*the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

*'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion

– an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May

2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

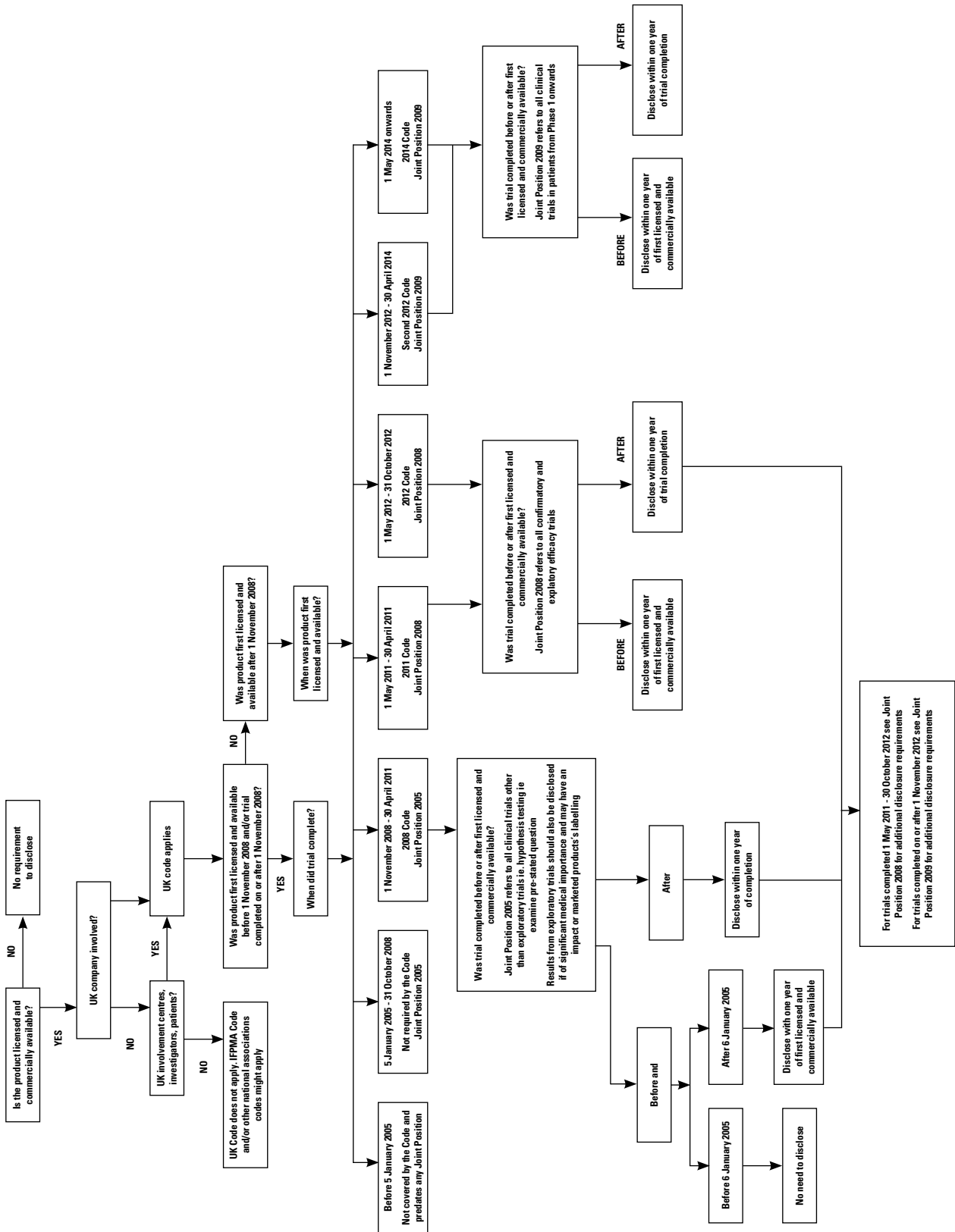
The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results



## PANEL RULING IN CASE AUTH/2662/11/13

The Panel noted that Novartis's submission regarding retrospective publication of clinical trial results. The Panel considered that laws might not require retrospective publication but the Joint Positions 2008 and 2009 did in relation to medicines first approved and commercially available in any country.

### **Ilaris**

The Panel noted the CMRO publication in that three evaluable trials had not been disclosed in the timeframe. The disclosure percentage was 91%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 100%.

The Panel noted that one of the three trials had not involved UK sites, nor the UK company. The Panel considered that as there was no UK involvement the matter did not come within the scope of the UK Code and therefore ruled no breach.

The Panel noted that Ilaris was first approved in August 2006. The remaining two trials completed after this date.

The Panel noted the second trial completed on 4 August 2010 and was published on 22 November 2010. This was within a year of completion and thus the Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 2 and 9.1.

The third trial completed on 23 October 2009 with the results submitted by 30 August 2012 and posted by December 2012. The results had not been published within the timeframe and thus the Panel ruled a breach of Clause 21.3 of the 2008 Code as acknowledged by Novartis. High standards had not been maintained and a breach of Clause 9.1 was ruled. As the results had been disclosed the Panel considered that there had been no breach of Clause 2 and ruled accordingly.

### **Gilenya**

The Panel noted the CMRO publication in that one evaluable trial had not been disclosed in the timeframe. The disclosure percentage was 96%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 96%. A footnote stated that the undisclosed trial was completed in 2004 and the clinical study report was in the process of being posted on the company trial registry.

The Panel noted that Gilenya was first approved in August 2010. The 2008 Code and thus the Joint Position 2005 applied. The Panel noted that the trial in question completed in November 2004. The Joint Position 2005 did not require studies completed before January 2005 to be published thus the Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

**Complaint received**                      **21 November 2013**

**Case completed**                              **24 March 2014**



# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v PIERRE FABRE

## Clinical trial disclosure (Javlor)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Javlor (vinflunine).

The detailed response from Pierre Fabre is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that seven evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 72%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 74%. Seven studies had not been disclosed. A footnote stated that two of the undisclosed trials were not subject to FDAAA 801 requirements; Javlor was not approved in the US.

The Panel noted that Javlor was first approved and commercially available in November 2009. This meant that for trials completed before then, the 2008 Code and hence the Joint Position 2005 were relevant.

The Panel noted Pierre Fabre's submission that a Phase I pharmacokinetic study completed in November 2005 was not considered of significant medical importance and a report was available. The Panel considered that this study could be considered an exploratory trial and thus the results did not need to be disclosed under the Joint Position 2005 unless they were deemed to have significant medical importance and might have an impact on product labelling. The complainant had made no submission in this regard. The Panel considered that, on the basis of the information before it, there appeared to be no requirement for the trial to be disclosed and thus it ruled no breach of the Code, including Clause 2.

The Panel noted that the results for one trial on an unlicensed indication had not been disclosed and the results of a second trial, a Phase I study completed in quarter 2 2010, were not published until 1 November 2013. The Panel considered there was no requirement as yet to disclose the results of either study. The Panel ruled no breach of the Code including Clause 2.

The results of a Phase I pharmacokinetic study (trial IN104) in patients with liver impairment appeared to be referred to in the Javlor summary of product characteristics (SPC). The study completed on 13 December 2005 and was published in June 2013. In the Panel's view, these trial results, given that they had an impact on product labelling, should have been disclosed by November 2010. The Panel ruled a breach of the 2008 Code. The delay in disclosure meant that high standards had not been maintained and a breach was ruled. These rulings were appealed. As the results had been disclosed, the Panel considered that there was no breach of Clause 2 and ruled accordingly.

Upon appeal by Pierre Fabre the Appeal Board noted that Pierre Fabre's submission to the Panel was incorrect in relation to the earliest publication date of trial IN104 and that the results were first published in 2007. This was before the required disclosure date of November 2010 and so no breach of the 2008 Code was ruled. The appeal was successful.

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in

Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product.

This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Javlor (vinflunine) as follows:

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	25	3	22	17	77%	24	19	79%
Phase III	4	1	3	1	33%	3	1	33%
<b>TOTAL</b>	<b>29</b>	<b>4</b>	<b>25</b>	<b>18</b>	<b>72%</b>	<b>27</b>	<b>20</b>	<b>74%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluative	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluative trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluative trials which were fully disclosed

completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Pierre Fabre.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Pierre Fabre, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Pierre Fabre stated that it fully cooperated with the ABPI and PMCPA and strove to maintain the highest levels of professional and ethical conduct in all areas of its business. Thus, it took the complaint very seriously and had investigated thoroughly.

The company's corporate headquarters in France had overall responsibility for conducting and

managing all company sponsored trials. Trials which involved UK sites or physicians were overseen by Pierre Fabre's clinical operations team in the UK but all data and results were collated, analysed and held by the corporate clinical research group in France.

Pierre Fabre had forwarded the complaint and the supplementary information provided to clinical research colleagues in France who helped to formulate the company's response. Pierre Fabre stated that two of the undisclosed trials were not subject to FDAAA 801 requirements and some of the trial data were from 2006/2007 and needed to be unarchived so that the company could investigate.

In a further response, Pierre Fabre stated that the case outlined seven trials which were showing as not disclosed at the time of the study.

Two of the seven trials had been published this year already as highlighted in the spread sheet provided and a further three trials had Bristol-Myers Squibb as the registering company during a time of collaboration between the two companies which broke down so the responsibility remained with Bristol-Myers Squibb and not Pierre Fabre. Out of the remaining two trials, one was a phase 3 trial in a new indication and was expected to get a marketing authorization in 2014 with an abstract being submitted for ASCO 2014 and as such the findings were of high commercial sensitivity until then.

The final trial was a Phase 1 pharmacokinetic study during the Javlor development stage and was not considered of significant medical importance and a report was available.

Pierre Fabre prided itself on compliance and professionalism at all times and would continue to work closely with the PMCPA to resolve this matter quickly.

In response to a request for further information, Pierre Fabre submitted that Javlor was first approved and commercially available in November 2009.

In response to a further request for additional information, Pierre Fabre stated that Study IN104 completed on 13 December 2005 and Study IN108 on 30 November 2005. The synopsis of Study IN108 was made available from global to each country. The three studies sponsored by Bristol-Myers Squibb were discontinued when the licence agreement ended. The database of these studies was not transferred to Pierre Fabre.

#### **GENERAL COMMENTS FROM THE PANEL**

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the

consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific

Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

'Companies must disclose details of clinical trials.'

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later

than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint

positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a

number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

#### **PANEL RULING IN CASE AUTH/2663/11/13**

The Panel noted the CMRO publication in that seven evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 72%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 74%. Seven studies had not been disclosed. A footnote stated that two of the undisclosed trials were not subject to FDAAA 801 requirements; Javlor was not approved in the US.

The Panel noted that Javlor was first approved and commercially available in November 2009. This meant that for trials completed before then, the 2008 Code and hence the Joint Position 2005 were relevant.

The Panel noted that a Phase I pharmacokinetic study (IN108) completed in November 2005. This had not been disclosed. In response to a request about whether the report was publicly available Pierre Fabre stated that a synopsis was made available from global to each country. The Panel noted Pierre Fabre's submission that this trial was not considered of significant medical importance and a report was available. The Panel considered



that this study could be considered an exploratory trial and thus the results did not need to be disclosed under the Joint Position 2005 unless they were deemed to have significant medical importance and might have an impact on product labelling. The complainant had made no submission in this regard. The Panel considered that, on the basis of the information before it, there appeared to be no requirement for the trial to be disclosed and thus no breach of Clause 21.3 of the 2008 Code was ruled and consequently there was no breach of Clauses 9.1 and 2.

The Panel noted that the results for one trial (IN303) on an unlicensed indication had not been disclosed and the results of a second trial (GE106), a Phase I study which completed in quarter 2, 2010, were not published, in an on-line journal, until 1 November 2013. Although not part of Pierre Fabre's submission the Panel noted that this trial was also on an unlicensed indication and in that regard the company was not bound to publish the results within 12 months; the delay might have been due to consideration of intellectual property rights or the company might have regarded the study as an exploratory study in which case the Joint Position 2005 required disclosure of results only if they were deemed to have significant medical importance or a possible impact on product labelling. The complainant had made no submission in this regard. On the basis of the information before it, the Panel considered there was no requirement as yet to disclose the results of study IN303. The Panel ruled no breach of Clause 21.3 of the 2011 Code and consequently no breach of Clauses 9.1 and 2. Similarly the Panel considered that there appeared to be no requirement for the results of study GE106 to have been disclosed by quarter 2, 2011 and it thus ruled no breach of Clause 21.3 of the 2008 Code and there was consequently no breach of Clauses 9.1 and 2.

Trial IN104 was a Phase I pharmacokinetic study in patients with liver impairment. The results appeared to be referred to in the Jaylor SPC. The study which completed on 13 December 2005 was listed as published in June 2013. In the Panel's view, the results from this trial, given that they had an impact on product labelling, should have been disclosed by November 2010. The Panel ruled a breach of Clause 21.3 of the 2008 Code. The delay in disclosure meant that high standards had not been maintained. A breach of Clause 9.1 was ruled. As the results had been disclosed, the Panel considered that there was no breach of Clause 2 and ruled accordingly.

With regard to the three remaining trials, the Panel noted a difference of opinion as to whether Bristol-Myers Squibb or Pierre Fabre was responsible for disclosure. It also noted Bristol-Myers Squibb's submission that there was no UK involvement in these trials (Case AUTH/2686/1/14).

The Panel considered that despite contacting both companies, it could not easily decide which of the two was responsible under the Code. In the interests of pragmatically dealing with the complaint in these very unusual circumstances, the Panel decided that both companies were responsible under the Code. However, the Panel considered that as there was no UK involvement, the matter did not come within the scope of the UK Code and it therefore ruled no breach.

#### **APPEAL BY PIERRE FABRE**

Pierre Fabre submitted that its appeal was based on the fact that the results from study IN104 were first published in 2007 as an abstract at the ASCO meeting by Paule *et al*. The spreadsheet provided in Pierre Fabre's response to the complaint was inaccurate as it implied that the trial was first published by Delord *et al* in 2013 (and September 2012 online). Pierre Fabre apologised for the error and for any inconvenience this had caused.

Pierre Fabre confirmed that Paule *et al* and Delord *et al* were both about trial IN104. Pierre Fabre submitted that a table of data in the EMA Public Assessment Report for vinflunine was evidence that the abstract and paper were about the same trial as the list of all phase 1 studies conducted with vinflunine as a single agent referred to only one study which had evaluated pharmacokinetics and safety in liver-impaired patients ie L00070 IN 104 Q0, abbreviated to IN104. This study was the basis of Section 5.2 of the Jaylor SPC.

Pierre Fabre therefore appealed the Panel's rulings of a breach of Clauses 9.1 and 21.3.

#### **COMMENTS FROM THE COMPLAINANT**

There were no comments from the complainant.

#### **APPEAL BOARD RULING**

The Appeal Board noted that Pierre Fabre's submission to the Panel was incorrect in relation to the earliest publication date of trial IN104.

The Appeal Board noted that the abstract Paule *et al* and the paper by Delord *et al* both published the results from trial IN104. The Appeal Board noted that as the results for trial IN104 had first been published in 2007 (Paule *et al*), this was before the required disclosure date of November 2010, consequently it ruled no breach of Clauses 9.1 and 21.3 of the 2008 Code. The appeal was successful.

<b>Complaint received</b>	<b>21 November 2013</b>
<b>Case completed</b>	<b>12 June 2014</b>



# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v TAKEDA

## Clinical trial disclosure (Mepact, Edarbi and Daxas)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Mepact (mifamurtide), Edarbi (azilsartan medoxomil) and Daxas (roflumilast).

The detailed response from Takeda is given below.

General detailed comments from the Panel are given below.

With regard to Daxas, the Panel noted the CMRO publication in that eleven evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 39%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 44%. Ten evaluable trials had not been disclosed. A footnote stated that all the

undisclosed trials were now publicly available on the Takeda website.

The Panel noted that Daxas was first approved and commercially available in August 2010. This meant that for studies completing before that date the 2008 Code and Joint Position 2005 were thus relevant. The Panel examined the data provided by Takeda. This related to 15 completed studies with UK involvement. The Panel noted the discrepancy between Takeda's data and the CMRO publication and the further data provided by Takeda regarding the eight trials referred to in the CMRO publication. The Panel noted that trials completed after 5 January 2005 and before the date Daxas was first approved and commercially available (August 2010) needed to be disclosed by August 2011. Four studies had not been disclosed in the timeframe. The Panel ruled a breach of the 2008 Code. The delay in disclosure meant that high standards had not been maintained and a breach was ruled. As the results had been disclosed, the Panel considered there was no breach of Clause 2 and ruled accordingly.

A further three studies were listed with last patient last visit dates of 29 April 2008, 3 July 2007 and 31 January 2008 and 'Results Submission Dates' as 17 March 2011. The Panel noted Takeda's submission that the date of publication of the results was not known. These could have been publicly disclosed anytime between 30 days and 60 days after the results were submitted to clinicaltrials.gov. The Panel noted this gave a theoretical latest date of publication and thus disclosure of the results as 60 days from 17 March 2011, ie 16 May 2011. This was before one year after Daxas was first approved and commercially available, ie August 2011. The Panel ruled no breach of the 2008 Code including Clause 2.

Eight studies completed before 6 January 2005 and therefore the results did not need to be disclosed under the Joint Position 2005. No breach of the 2008 Code including Clause 2 was ruled.

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

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## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for each product. The data for Mepact (mifamurtide), Edarbi (azilsartan medoxomil) and Daxas (roflumilast) was as follows:

### Mepact

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	11	0	11	6	55%	11	6	55%
Phase III	1	0	1	1	100%	1	1	100%
<b>TOTAL</b>	<b>12</b>	<b>0</b>	<b>12</b>	<b>7</b>	<b>58%</b>	<b>12</b>	<b>7</b>	<b>58%</b>

### Edarbi

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	3	0	3	1	33%	3	1	33%
Phase III	17	2	15	15	100%	15	15	100%
<b>TOTAL</b>	<b>20</b>	<b>2</b>	<b>18</b>	<b>16</b>	<b>89%</b>	<b>18</b>	<b>16</b>	<b>89%</b>

### Daxas

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	2	1	1	0	0%	1	1	100%
Phase III	18	1	17	7	41%	17	7	41%
Phase IV	2	2	0	0	0%	0	0	0%
<b>TOTAL</b>	<b>22</b>	<b>4</b>	<b>18</b>	<b>7</b>	<b>39%</b>	<b>18</b>	<b>8</b>	<b>44%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluative	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluative trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluative trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Takeda.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Takeda, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Takeda understood that the original intent of the ABPI study was to demonstrate that there was greater transparency than the public commonly believed about research conducted by the pharmaceutical industry. It was not to highlight non-compliance with the ABPI Code. Takeda contacted the ABPI to confirm the intent of the CMRO publication and a copy of the response was provided.

Takeda willingly participated in line with its commitment to the principles of transparency. Since the survey, it had continued its commitment by completing ongoing results disclosure in line with its planned revised transparency policy (which went

beyond the transparency required legally or by the Code).

Takeda did not consider that the complaint about disclosure of the results of clinical trials was within the scope of the ABPI Code Second 2012 Edition which clearly stated in Clause 21.3 that ‘Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature’. Previous Codes (2008 and 2011) stated ‘Companies must disclose details of clinical trials’. Supplementary information stated ‘This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country’.

The clinical trials concerned, according to the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 and 2008 respectively were ‘all clinical trials, other than exploratory trials ... initiated on or after July 1, 2005’ (Joint Position, 2005) or ‘all confirmatory clinical trials ... initiated on or after July 1, 2005 ... and all exploratory efficacy trials ... initiated 6 months prior the publication of this Joint Position’ (Joint Position, 2008).

The 2008 and 2011 Codes only specified disclosure of the details of clinical trials on databases such as clinicaltrials.gov. Disclosure of results was not specified until the 2012 Code.

Takeda submitted that the UK Code applied where the study involved some UK centres or patients or alternatively if a medicine was available in the UK, then the details of the studies must be disclosed. This was the case with each of these products except Edarbi. The ABPI Code for disclosure of details applied to Mepact and Daxas. Given that the disclosure of details was not the subject of the complaint Takeda had restricted its response to the matter of results disclosure. Should the PMCPA, however, determine that additional data regarding disclosure of details were required, data could be provided on the expectation that this would be supporting information and not the subject of the complaint.

Takeda stated that it acquired Mepact from IDM Pharma in June 2009 and it was granted its first marketing authorization globally by the European Commission on 6 March 2009. The first countries in which it was commercially available were Austria, Germany and the UK in February 2010 and thus Takeda submitted that the 2008 Code applied.

Edarbi was granted its first marketing authorization by the FDA in February 2011. The first country in which it was commercially available was the US in April 2011. Therefore Takeda submitted that the 2011 ABPI Code applied.

Takeda became responsible for Daxas on the

acquisition of Nycomed in 2011. Daxas was granted its first marketing authorization globally by the European Commission on 5 July 2010. It was first commercially available in Germany in August 2010. Therefore Takeda submitted that the 2008 ABPI Code applied.

Turning to the specific studies highlighted in the complaint, the Mepact trials were sponsored by another company, IDM Pharma, and were completed between 1988 and 1996. This was before the implementation of the 2005 Joint Position referred to in the 2008 Code. Therefore regardless of the complaint about results being outside the scope of the Code, the Mepact studies predated the remit of the 2005 Joint Position.

The azilsartan trials referred to in the CMRO publication only concerned Azilva. The clinical trials for Azilva (which contained the active form of azilsartan vs azilsartan medoxomil found in Edarbi) were outside the scope of the Code as there were no links to the UK and the product was only available in Japan. No studies relating to Edarbi were cited in the CMRO study. As such Takeda submitted that this negated the complaint.

All clinical trial details for Daxas were disclosed on clinicaltrials.gov as required by the 2008 ABPI Code. This information was provided as guidance to PMCPA and not for the purposes of responding to the complaint which referred to results; Takeda referred to its position on the scope of the Code set out above.

Takeda stated that although clinical trial results disclosure was not mandated by the ABPI Code before the 2012 Code, and then only for specific studies falling into certain criteria, Takeda was committed to transparency and thus had spent significant time to ensure that the results for these acquired products were disclosed according to a consistent standard applied to all of Takeda's other products. As such, the company noted its ongoing actions that supported its commitment to transparency whereby all of the studies discussed for the medicines referred to in the complaint had had results disclosed by the time the CMRO study was published and thus before the complaint was made.

Thus in response to the complaint regarding clinical trial disclosure concerning Mepact, Edarbi and Daxas, Takeda sincerely believed that the 2008 and 2011 Codes did not apply to the disclosure of results of clinical studies and as such the complaint was not within the scope of the relevant Codes. In addition it strongly refuted the complaint and all alleged breaches of the Code.

Takeda submitted that the supplementary information to Clause 1.8 that 'Pharmaceutical companies must ensure that they comply with all applicable codes, laws and regulations to which they are subject' could refer to the 2005 and 2008 Joint Positions on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases. However, it believed that these joint positions were not within the scope of Clause 1.8 as they were guidance rather than governmental-issued

legislation/edicts or directives or codes of practice mandating adherence as issued by an industry association. This was reinforced by the ABPI's own position in changing the wording of Clause 21.3 in the 2012 edition of the Code.

Takeda submitted it was committed to the spirit and letter of the Code as well as the principle of transparency. As stated above, the results of all the studies referred to were available in the public domain. Since 2010 Takeda had had a global policy on 'Registration and Results Disclosure of Clinical Trial Information'; a new version came into force in January 2014 and confidential copies were provided.

In response to a request for additional information, Takeda provided more information about the Daxas trials. In response to a request for yet more information, the company confirmed that the phrase 'Results Submission Dates' on the spreadsheet detailing the Daxas trials was the date that results were submitted to clinicaltrials.gov. The dates when these studies were publicly disclosed after submission was unknown. Clinicaltrials.gov did not publicly document when results were disclosed publicly (ie when results were published on the website) it only documented when results were first submitted. It took approximately 30 to 60 days for clinicaltrials.gov to review results submissions and it would only publish information once submissions were accepted without requiring further clarification from the submitting organization.

Takeda submitted, therefore, that the date of submission was the date that the data were disclosed to clinicaltrials.gov. It was impossible to be completely accurate on the date clinicaltrials.gov actually publicly disclosed the data.

Takeda stated it had provided this information in the spirit of transparency but it referred to its comments above where it clearly stated that the disclosure of results for these medicines was outside the scope of the relevant codes.

In response to a request for further information about Daxas, Takeda submitted that eight of the fifteen completed trials listed in appendix 4 to the company's response were referred to in the CMRO publication. They were BY217/M2-012, BY217/M2-013, BY217/M2-112, BY217/M2-121, BY217/M2-124, BY217/M2-125, BY217/M2-127 and BY217/M2-128 and details of the studies and results had been disclosed.

The differences between the various study lists in this complaint were because of the differences in lists from the CMRO publication and the scope of the complaint whereby the focus was upon studies with UK involvement. The complete study lists to include all countries involved had been provided.

#### **GENERAL COMMENTS FROM THE PANEL**

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under

the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that

companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006

Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

‘Companies must disclose details of clinical trials.’

The relevant supplementary information stated:

**‘Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.’*

In the 2011 Code (which superseded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

‘Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.’

The relevant supplementary information stated:

**‘Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such*

*information must not constitute promotion to health professionals, appropriate administrative staff or the public.’*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint

Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

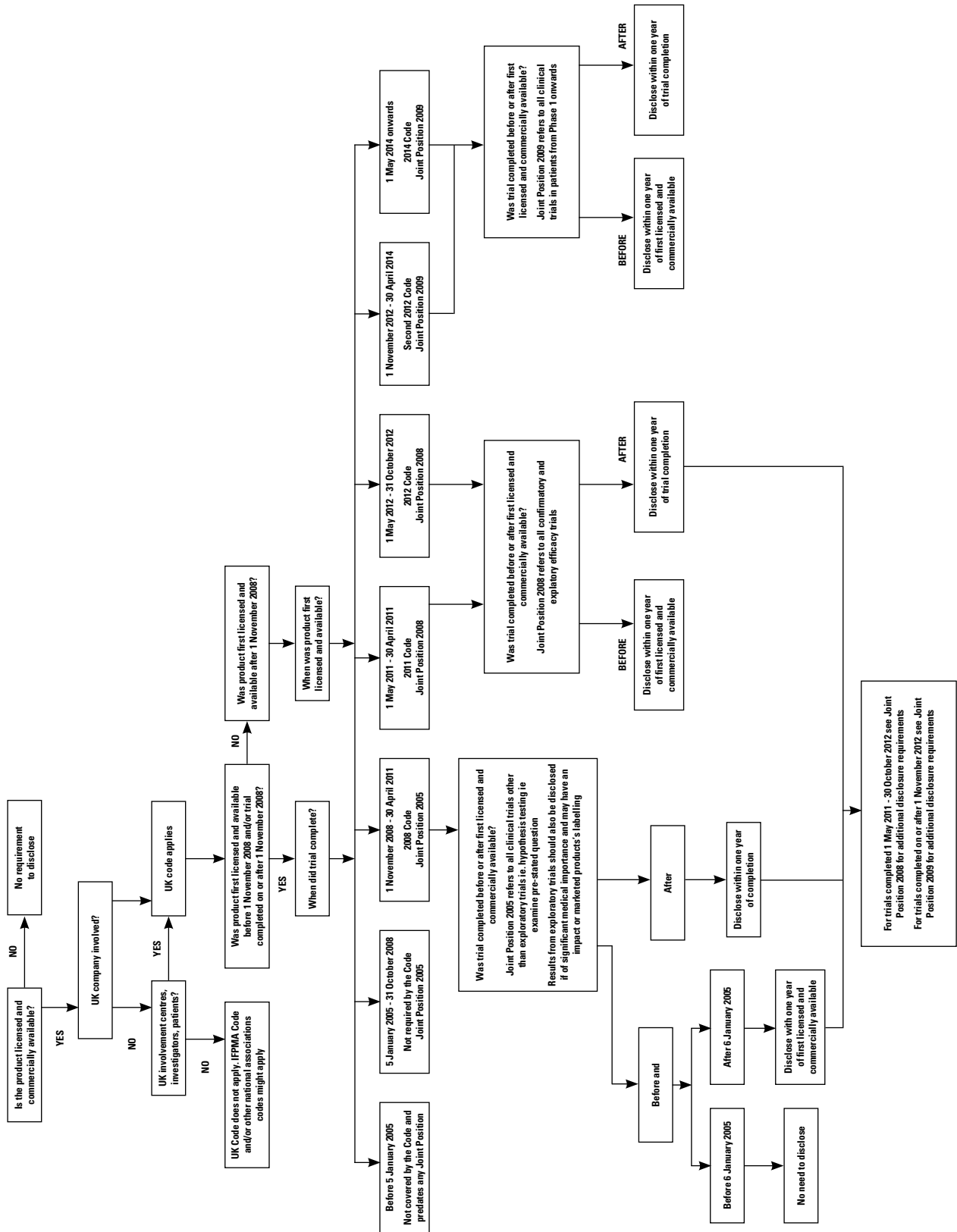
Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results





The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

#### **PANEL RULING IN CASE AUTH/2664/11/13**

The Panel noted Takeda's comments about the various codes. It disagreed with its submission about when the need to disclose data was first introduced in the Code and considered this aspect was covered in its general comments above.

The Panel considered that Takeda was responsible under the Code for the publication of the Nycomed studies.

#### **Mepact**

The Panel noted the CMRO publication in that five evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 58%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 58%. A footnote stated that the undisclosed trials were sponsored by IDM Pharma and completed in 1993 and that Takeda was in the process of sourcing the information for disclosure.

The Panel noted that the Mepact trials which were completed after 6 January 2005 would need to be disclosed, however according to Takeda's submission, the studies highlighted in the CMRO publication were not sponsored by Takeda and had no UK involvement. The Panel considered that as there was no UK involvement, the matter did not come within the scope of the Code, and therefore ruled no breach.

#### **Edarbi**

The Panel noted the CMRO publication in that two evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 89%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 89%. A footnote stated that all studies had now been disclosed on Takeda.com. The two outstanding studies primarily related to the Japanese version of azilsartan (Azilva) which was approved in May 2012 and the studies were disclosed within one year of that approval.

The Panel noted Takeda's submission that there was no UK involvement in the two trials that had not been disclosed. It also noted that the results of these two trials were disclosed within a year of Azilva being approved. The Panel considered as there was no UK involvement, the matter did not come within the scope of the UK Code and therefore ruled no breach.

#### **Daxas**

The Panel noted the CMRO publication in that eleven evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 39%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 44%. Ten evaluable trials had not been disclosed. A footnote stated that all the undisclosed trials were now publicly available on the Takeda website (address provided).

The Panel noted that Daxas was first approved and commercially available in August 2010. This meant that for studies completing before that date the 2008 Code and Joint Position 2005 were thus relevant. The Panel examined the data provided by Takeda. This related to 15 completed studies with UK involvement. The Panel noted the discrepancy between Takeda's data and the CMRO publication and the further data provided by Takeda regarding the eight trials referred to in the CMRO publication. The Panel noted that trials completed after 5 January 2005 and before the date Daxas was first approved and commercially available (August 2010) needed to be disclosed by August 2011. Four studies (ref BY217/M2-012, -013, -121 and -124) had not been disclosed in the timeframe. The Panel ruled a breach of Clause 21.3 of the 2008 Code. The delay in disclosure meant that high standards had not been maintained and a breach of Clause 9.1 was ruled. As the results had been disclosed, the Panel considered there was no breach of Clause 2 and ruled accordingly.

A further three studies were listed with last patient last visit dates of 29 April 2008, 3 July 2007 and 31

January 2008 and 'Results Submission Dates' as 17 March 2011. The Panel noted Takeda's submission that the date of publication of the results was not known. These could have been publicly disclosed anytime between 30 days and 60 days after the results were submitted to clinicaltrials.gov. The Panel noted this gave a theoretical latest date of publication and thus disclosure of the results as 60 days from 17 March 2011, ie 16 May 2011. This was before one year after Daxas was first approved and commercially available, ie August 2011. The Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

Eight studies completed before 6 January 2005 and therefore the results did not need to be disclosed under the Joint Position 2005. No breach of Clause 21.3 and consequently Clauses 9.1 and 2 of the 2008 Code was ruled.

**Complaint received**            **21 November 2013**

**Case completed**                **27 March 2014**

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# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v GENZYME (SANOFI)

## Clinical trial disclosure (Mozobil and Renvela)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Mozobil (plerixafor) and Renvela (sevelamer carbonate).

The detailed response from Sanofi is given below.

General detailed comments from the Panel are given below.

With regard to Renvela, the Panel noted that five of the evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 38%. Two studies had not been disclosed at all. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 75%. A footnote stated that the undisclosed trials were not applicable under FDAAA requirements.

The Panel noted Sanofi's submission that Renvela was first approved on 19 October 2007 and commercially available that month and that only two of the non-disclosed trials had UK patients or involvement in the UK company. These had completed in January and March 2007. The Panel noted that the date of first approval was before the requirement to disclose the results of clinical trials was included in the ABPI Code (1 November 2008). The matter was not covered by the 2006 Code as such and there could be no breach of it. Thus the Panel ruled no breach of the 2006 Code including Clause 2.

With regard to Mozobil, the Panel noted that seven of the evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 61%. Seven trials had not been disclosed at all. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 61%.

The Panel noted Sanofi's submission that Mozobil was first approved and commercially available on 28 December 2008 and that only one Mozobil trial had sites or investigators in the UK. This trial completed in November 2010. The Panel noted that Sanofi had failed to disclose the results of the trial by November 2011. The Panel ruled a breach of the 2008 Code. The delay in disclosure meant that high standards had not been maintained and a breach was ruled. The results had been disclosed and thus the Panel ruled no breach of Clause 2.

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

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referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

to relevant information which included the published study plus detailed information for each product that was assessed.

## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for each product. The data for Mozobil (plerixafor) and Renvela (sevelamer carbonate) were as follows:

### Mozobil

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	15	2	13	9	69%	13	9	69%
Phase III	5	0	5	2	40%	5	2	40%
<b>TOTAL</b>	<b>20</b>	<b>2</b>	<b>18</b>	<b>11</b>	<b>61%</b>	<b>18</b>	<b>11</b>	<b>61%</b>

### Renvela

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	3	0	3	2	67%	3	2	67%
Phase III	4	0	4	0	0%	4	3	75%
Phase IV	1	0	1	1	100%	1	1	100%
<b>TOTAL</b>	<b>8</b>	<b>0</b>	<b>8</b>	<b>3</b>	<b>38%</b>	<b>8</b>	<b>6</b>	<b>75%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluative	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluative trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluative trials which were fully disclosed

completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Genzyme.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Genzyme, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Although this case was cited as a complaint to Genzyme (which operated as an individual company in the UK) and many of the relevant events were historical, Genzyme on a global and at a research

and development level, was now a part of the Sanofi group. Mozobil and Renvela had been transferred to the Sanofi portfolio within the UK from an operational perspective; however much of what might be considered in this case occurred before that integration took place.

Sanofi noted that the debate around clinical trial transparency was already a very public and inclusive one, with industry engaged in dialogue between concerned parties and working together as an industry to ensure appropriate data could be made available to enable further high quality scientific research and ultimately benefit patients. Sanofi fully supported the ABPI initiative to gain a greater understanding of the degree to which data on approved products was publicly available (the CMRO publication) and was working with the ABPI to implement future guidelines on monitoring and enforcing the established and evolving requirements.

Sanofi asked the Panel to carefully consider the global nature of pharmaceutical research and development. Whilst Sanofi was fully engaged in the debate as well as the industry wide efforts to responsibly share clinical trial data, this debate and any resulting actions were by necessity regional (European) and global in nature. No single country affiliate or industry association could operate in a silo if real progress was to be made.

Sanofi fully supported the five Principles for Responsible Clinical Trial Data Sharing jointly released by PhRMA and EFPIA on 24 July 2013; and its global organisation would make it clear exactly how Sanofi would meet those commitments.

### **Scope of the Code**

Sanofi also asked the Panel to carefully consider the degree to which any country affiliate of an international pharmaceutical company such as Sanofi was involved in the separate activities that made up the conduct of global clinical trials and, importantly in this case, the degree to which local affiliates were involved in the specific activity of registration, disclosure and publication of global clinical trial information. Sanofi was not headquartered in the UK and had no UK research and development facility. Even when a global clinical trial had UK investigators or sites, the activity consisted of an investigator or trial site which recruited and treated patients within the global study protocol (as predefined outside of the UK), together with the infrastructure and activity required to administer and monitor the sites in line with Good Clinical Practice. The specific activity which was the subject of this complaint was the registration, disclosure and publication of clinical trial information. For Sanofi global clinical trials and trials undertaken by other regions/countries, these activities, and indeed the analysis and writing of the information which was disclosed, were all activities conducted wholly outside of the UK by company teams elsewhere in the world. It was only locally initiated and conducted studies undertaken to produce local information by the UK affiliate which

would have such activities undertaken in the UK. Sanofi drew attention to the supplementary information to Clause 1.8 that 'Activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European Country as well as the national code of the country in which the activity takes place or the materials are used'.

In order to fully understand the information in the CMRO publication and to establish a clear view of the applicability of the Code, Sanofi analysed the list of trials that were considered by the authors. None of the trials were conducted by the Sanofi UK affiliate. Registration, disclosure and publication for each of the trials listed where Sanofi was a sponsor, were managed outside of the UK, by non-UK teams.

Sanofi submitted therefore that the complaint about the CMRO publication was outside of the scope of the Code as per Clause 1.8 and should not be further considered by the Panel.

### **Response to the complaint**

Notwithstanding the above, Sanofi noted that it was the Panel's responsibility to interpret the breadth of the complaint and whether the matter was covered by the UK Code and so, as requested, it responded to the points raised by the case preparation manager.

To inform its response, Sanofi sought further information from the author of the CMRO publication, concerning the intent, purpose and methodology of the study. The reply was provided. In summary, it was clear that the ABPI study had been undertaken to produce a quantitative benchmark of disclosure rates for industry sponsored clinical trials and to provide the industry with information with which to respond to media and professional body enquiries and inform a response to the Science and Technology Select Committee.

In relation to the complaint the relevant clause of the Code was Clause 21.3. The methodology described by the author, both in the publication and in the email to Sanofi was that this study did not audit or compare disclosure rates against any given disclosure requirement and did not limit assessment to any given laws or requirements in specific territories. Nor did the CMRO publication present any detailed information from which the degree of compliance with the detailed aspects of the IFPMA Joint Position (such as defined timelines or availability on the specific types of registries), and therefore Clause 21 of the Code, could be ascertained.

Sanofi stated that, although the CMRO publication listed overall disclosure rates for Mozobil and Renvela as defined within that study, it did not list Genzyme/Sanofi as a company which had not disclosed its clinical trial results in line with the Code. It followed therefore, that Sanofi did not believe this publication provided any evidence of a breach of Clauses 21, 9 or 2 of the Code.

## Additional Information

Notwithstanding Sanofi's view on the applicability of the Code or, in spite of that, in its response to the complaint, the company gave some more detail on some aspects of the trials which were considered by the authors in preparation for the CMRO publication.

Mozobil was first approved in the US on 15 December 2008.

Renvela was first approved in the US on 19 October 2007.

Sanofi submitted that when analysing the list of trials that were considered by the authors of the CMRO publication, and cross referencing that with its clinical trials management systems and databases, it was clear that only three company sponsored studies on Mozobil and Renvela had sites or investigators in the UK.

For each of those three trials, the following tables provided the information requested by the PMCPA and copies of the relevant public registry entries were provided.

### Renvela

Study Identifier as used by author of CMRO publication.	NCT00267514 / SVCARB00205
Study Type	Phase 3 Clinical Trial
Study Description	Study to Demonstrate Equivalence of Sevelamer Carbonate Powder and Sevelamer HCl Tablets in Haemodialysis Patients
Date of Commencement of the Trial	31 January 2006
Listing of Trial on Public Registry (Y/N)	Yes
Date of Public Registry Entry	20 December 2005
Location of Public Registration at Commencement	Clinical trials.gov
Date of Trial Completion	15 March 2007
Date and location of Disclosure of Results on a Public Database	January 2009, Genzymeclinicalresearch.com
Submitted for Publication in Scientific Literature within 12-18 months Y/N	No – Study Completed prior to the 2010 declaration on Publication of Clinical Trial Information in Scientific Literature

Publication	Fan <i>et al.</i> A randomized, crossover design study of sevelamer carbonate powder and sevelamer hydrochloride tablets in chronic kidney disease patients on haemodialysis. <i>Nephrol Dial Transplant.</i> 2009 Dec; 24(12):3794-9. doi: 10.1093/ndt/gfp372. Epub 2009 Aug 7. posted on Genzyme results website: <a href="http://www.genzymeclinicalresearch.com/results/output/product/gzcr_res_Renvela_study3.aspx#TopOfPage">http://www.genzymeclinicalresearch.com/results/output/product/gzcr_res_Renvela_study3.aspx#TopOfPage</a>
Comment	Registration on public registry was within 21 days. Posting of results to a public registry was made but exceeded the 12 month period. The reason for this delay was not documented or recalled by current staff. Submission for peer review publication was not subject to IFPMA declaration as trial completed prior to 2010.  Sanofi submitted that as the study completed prior to the inclusion of the requirement to disclose clinical trial information as per IFPMA declarations being incorporated into the 2008 edition of the Code (effective from 1 July 2008) none of the IFPMA declaration requirements would have been covered by the Code.

Study Identifier as used by author of CMRO publication.	NCT00681941 / SVCARB00105 / ACTRN012606000380594
Study Type	Phase 3
Study Description	An Open Label Dose Titration of Sevelamer Carbonate Tabs 3 Times a Day in Hyperphosphatemic CKD Patients Not On Dialysis
Date of Commencement of the Trial	January 2006
Listing of Trial on Public Registry (Y/N)	Yes
Date of Public Registry Entry	19 May 2008
Location of Public Registration at Commencement	Clinicaltrial.Gov
Date of Trial Completion	January 2007
Date and location of Disclosure of Results on a Public Database	November 2008, genzymeclinicalresearch.com

Submitted for Publication in Scientific Literature within 12-18 months Y/N	No – Study Completed prior to the 2010 declaration on Publication of Clinical Trial Information in Scientific Literature
Comment	<p>Trial commencement was registered on a public registry but not within 21 days. Trial results were posted to a public registry but not within 12 months of completion. The reason for these delays was not documented and was not recalled by current staff. There was no submission for publication in scientific literature as the completion date preceded the IFPMA declaration of 2010.</p> <p>Sanofi submitted that as this study completed prior to the inclusion of the requirement to disclose clinical trial information as per IFPMA declarations being incorporated into the 2008 edition of the Code (effective from 1st July 2008) none of the IFPMA declaration requirements would have been covered by the Code.</p>

Publication	Russell <i>et al</i> , Plerixafor and granulocyte colony-stimulating factor for first-line steady-state autologous peripheral blood stem cell mobilization in lymphoma and multiple myeloma: Results of the prospective PREDICT trial. <i>Haematologica</i> 2013 98:2 (172-178).
Comment	<p>The commencement of this trial was posted to a public registry but not within the 21 day time frame. The results had not been posted on a public registry. The reasons for the delay in registration and lack of posting of results on public registry was not documented and not recalled by current staff.</p> <p>A manuscript was submitted for publication in scientific literature on 7 June and accepted by <i>Haematologica</i> on 26 July 2012. This fell outside the requirements of the 2010 IFPMA declaration to submit within 18 months by three weeks.</p>

### Mozobil

Study Identifier as used by author of CMRO publication.	NCT00838357 MOZ00808, 2008-000689-21
Study Type	Phase 4 (Expanded Access Program)
Study Description	Plerixafor and G-CSF for the Mobilisation of Peripheral Blood Stem Cells for Autologous Stem Cell Transplantation in Patients With Non-Hodgkin's Lymphoma (NHL), Hodgkin's Disease (HD) or Multiple Myeloma (MM) – Safety Study in a General Autologous Transplant Population
Date of Commencement of the Trial	September 2008
Listing of Trial on Public Registry (Y/N)	Yes
Date of Public Registry Entry	5 February 2009
Location of Public Registration at Commencement	clinical trials.gov
Date of Trial Completion	18 November 2010
Date and location of Disclosure of Results on a Public Database	Results not publicly disclosed
Submitted for Publication in Scientific Literature within 12-18 months	No

### Summary

Sanofi stated that although the matters raised in the complaint were not covered by the UK Code, in providing a response to a potentially broader interpretation of the complaint, Sanofi believed the CMRO publication did not, as alleged, provide any evidence as to the compliance or otherwise of Sanofi or Genzyme with the specific requirements of Clauses 21, 21.3, 9 or 2 or the IFPMA declarations, as evidenced by the methodology of the study detailed by the authors.

In a response to a request for further information regarding what appeared to be an inconsistency between Sanofi's response and the attachments, Sanofi confirmed that only two Renvela trials had sites or investigators in the UK. The additional trial referred to in the attachments was conducted on a different product, Renagel and thus was not relevant.

In response to a request for further information, Sanofi confirmed that Mozobil was first approved and commercially available on 28 December 2008.

### GENERAL COMMENTS FROM THE PANEL

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under

the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation

on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

#### **'Clause 7.5 Data from Clinical Trials**

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.



In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

'Companies must disclose details of clinical trials.'

The relevant supplementary information stated:

#### **'Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'

The relevant supplementary information stated:

#### **'Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially

available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until

30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted. From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results



had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

#### **PANEL RULING IN CASE AUTH/2665/11/13**

##### **Renvela**

The Panel noted that five of the evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 38%. Two studies had not been disclosed at all. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 75%. A footnote stated that the undisclosed trials were not applicable under FDAAA requirements.

The Panel noted Sanofi's submission that Renvela was first approved on 19 October 2007 and commercially available that month and that only two of the non-disclosed trials had UK patients or involvement in the UK company. These had completed in January and March 2007. The Panel noted that the date of first approval was before the requirement to disclose the results of clinical trials was included in the ABPI Code (1 November 2008). The matter was not covered by the 2006 Code as such and there could be no breach of it. Thus the Panel ruled no breach of Clauses 9.1 and 2 of the 2006 Code.

##### **Mozobil**

The Panel noted that seven of the evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 61%. Seven trials had not been disclosed at all. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 61%.

The Panel noted Sanofi's submission that Mozobil was first approved and commercially available on 28 December 2008 and that only one Mozobil trial had sites or investigators in the UK. This trial completed in November 2010. The Panel noted that Sanofi had failed to disclose the results of the trial by November 2011. It was not clear why the results had not been disclosed. The applicable Joint Position 2005 gave some flexibility if results were to be published in a peer reviewed medical journal so as not to compromise such publication. In any event Sanofi acknowledged that it had missed the deadline. The Panel ruled a breach of Clause 21.3 of the 2008 Code.

The Panel noted that the study was submitted for publication on 7 June 2012 and accepted on 26 July 2012. In the Panel's view the delay in disclosure meant that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that the results had been disclosed and considered that in the circumstances the matter was covered by its rulings of breaches of Clauses 9.1 and 21.3. It thus ruled no breach of Clause 2.

The Panel noted Sanofi's submission that of the trials referred to in the CMRO publication, only the one detailed above had any UK involvement. With regard to the other studies, the Panel considered that as there had been no UK involvement, the matter did not come within the scope of the Code and therefore ruled no breach.

**Complaint received**                      **21 November 2013**

**Case completed**                              **24 March 2014**

# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v SANOFI

## Clinical trial disclosure (Multaq and Jevtana)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Jevtana (cabazitaxel) and Multaq (dronedarone).

The detailed response from Sanofi is given below.

General detailed comments from the Panel are given below.

With regard to Jevtana, the Panel noted that three of the evaluable trials were not disclosed within the timeframe. The disclosure percentage was 57%. Two of the trials had not been disclosed at all. The disclosure percentage at 31 January of trials completed by the end of January 2012 was 71%. A footnote stated that four of the undisclosed trials were completed at or before the IFPMA Joint Position of 2005 and FDAAA of 2007.

The Panel noted that Jevtana was first approved in the US on 17 June 2010 and was first commercially available in July 2010.

The Panel noted that the one Jevtana trial (NCT00417079) which included UK patients completed on 25 September 2009 and the results were disclosed on 20 September 2010. This was within one year of the product receiving its first approval (17 June 2010). The Panel ruled no breach of the 2008 Code including Clause 2.

With regard to Multaq, the Panel noted that three of the evaluable trials were not disclosed within the timeframe. The disclosure percentage was 75%. One trial had not been disclosed at all. The disclosure percentage at January 2013 of trials completed by the end of January 2012 was 92%. A footnote stated that the undisclosed trial was in the process of public disclosure preparation at the time of evaluation.

The Panel noted that Multaq was first approved and commercially available in July 2009. The relevant Code was 2008 and Joint Position 2005.

The Panel noted a discrepancy between Sanofi's submission that four studies had not been disclosed and the CMRO publication which referred to three studies. It decided to rule on the four studies referred to by Sanofi. With regard to the first study which completed before January 2005 there was no requirement under the Joint Position 2005 to disclose the results. The results from the second trial (completed in March 2008) were published on 24 July 2009 ie the same month that the product was first approved and available. The third trial completed on 14 December 2011 and the results were disclosed in May 2013. It was to be published with data from another study. The fourth trial completed in September 2011 and the results were disclosed in September 2012. Thus the Panel considered that the result of trial 1 did not need to be disclosed under the Code and ruled no breach of the 2008 Code including Clause 2. The results of trials 2 and 4 were disclosed within a year of Multaq being first approved and commercially available (trial 2) or within a year of the trial completion (trial 4). No breach of the 2008 Code including Clause 2 was ruled for trial 2. No breach of the 2011 Code including Clause 2 was ruled in relation to trial 4.

The Panel noted that Sanofi submitted the results of the third trial were disclosed in May 2013. These results should have been disclosed by 14 December 2012. Sanofi submitted that the delay in disclosure was in line with the joint position in relation to not compromising publication in a peer review journal.

The Panel noted that Sanofi changed its mind about peer review publication due to the early discontinuation of the trial and reduced recruitment for a similar second trial and decided to combine and disclose the results of trial 3 with the similar second study.

The Panel noted that the company disclosed the results when it decided not to publish them in a peer reviewed journal. It was not clear whether the data had been submitted to a peer review journal.

The Panel noted that Sanofi had neither disclosed the data nor submitted it for publication in a peer review medical journal within the relevant timeframe. However, the Panel decided that as the relevant Joint Position (2008) stated that the schedule for disclosure could be adjusted so as to avoid compromising publication in a peer review journal there was no breach of the 2008 Code

including Clause 2.

## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for each product. The data for Jevtana (cabazitaxel) and Multaq (dronedarone) were as follows:

### Jevtana

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	6	0	6	3	50%	6	4	67%
Phase III	1	0	1	1	100%	1	1	100%
<b>TOTAL</b>	<b>7</b>	<b>0</b>	<b>7</b>	<b>4</b>	<b>57%</b>	<b>7</b>	<b>5</b>	<b>71%</b>

### Multaq

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	1	0	1	1	100%	1	1	100%
Phase III	7	0	7	7	100%	7	7	100%
Phase IV	6	2	4	1	25%	4	3	75%
<b>TOTAL</b>	<b>14</b>	<b>2</b>	<b>12</b>	<b>9</b>	<b>75%</b>	<b>12</b>	<b>11</b>	<b>92%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluable	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment

results disclosed in timeframe	evaluative trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluative trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time

disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed
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The complainant listed the companies he/she would like to complain about and this included Sanofi.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Sanofi, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Sanofi noted that the debate around clinical trial transparency was already a very public and inclusive one, with industry engaged in dialogue between concerned parties and working together as an industry to ensure appropriate data could be made available to enable further high quality scientific research and ultimately benefit patients. Sanofi fully supported the ABPI initiative to gain a greater understanding of the degree to which data on approved products was publicly available (the CMRO publication) and was working with the ABPI to implement future guidelines on monitoring and enforcing the established and evolving requirements.

Sanofi asked the Panel to carefully consider the global nature of pharmaceutical research and development. Whilst Sanofi was fully engaged in the debate as well as the industry wide efforts to responsibly share clinical trial data, this debate and any resulting actions were by necessity regional (European) and global in nature. No single country affiliate or industry association could operate in a silo if real progress was to be made.

Sanofi fully supported the five Principles for Responsible Clinical Trial Data Sharing jointly released by PhRMA and EFPIA on 24 July 2013; and its global organisation would make it clear exactly how Sanofi would meet those commitments.

### Scope of the Code

Sanofi also asked the Panel to carefully consider the degree to which any country affiliate of an international pharmaceutical company such as Sanofi was involved in the separate activities that made up the conduct of global clinical trials and, importantly in this case, the degree to which local affiliates were involved in the specific activity of registration, disclosure and publication of global clinical trial information. Sanofi was not headquartered in the UK and had no UK research and development facility. Even when a global clinical trial had UK investigators or sites, the activity consisted of an investigator or trial site which recruited and treated patients within the global study protocol (as predefined outside of the UK), together with the infrastructure and activity required to administer and monitor the sites in line with Good Clinical Practice. The specific activity

which was the subject of this complaint was the registration, disclosure and publication of clinical trial information. For Sanofi global clinical trials and trials undertaken by other regions/countries, these activities, and indeed the analysis and writing of the information which was disclosed, were all activities conducted wholly outside of the UK by company teams elsewhere in the world. It was only locally initiated and conducted studies undertaken to produce local information by the UK affiliate which would have such activities undertaken in the UK.

Sanofi drew attention to the supplementary information to Clause 1.8 that 'Activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European Country as well as the national code of the country in which the activity takes place or the materials are used'.

In order to fully understand the information in the CMRO publication and to establish a clear view of the applicability of the Code, Sanofi analysed the list of trials that were considered by the authors. None of the trials were conducted by the Sanofi UK affiliate. Registration, disclosure and publication for each of the trials listed where Sanofi was a sponsor, were managed outside of the UK, by non-UK teams.

Sanofi submitted therefore that the complaint about the CMRO publication was outside of the scope of the Code as per Clause 1.8 and should not be further considered by the Panel.

### Response to the complaint

Notwithstanding the above, Sanofi noted that it was the Panel's responsibility to interpret the breadth of the complaint and whether the matter was covered by the UK Code and so, as requested, it responded to the points raised by the case preparation manager.

To inform its response, Sanofi sought further information from the author of the CMRO publication, concerning the intent, purpose and methodology of the study. The reply was provided. In summary, it was clear that the ABPI study had been undertaken to produce a quantitative benchmark of disclosure rates for industry sponsored clinical trials and to provide the industry with information with which to respond to media and professional body enquiries and inform a response to the Science and Technology Select Committee.

In relation to the complaint the relevant clause of the Code was Clause 21.3. The methodology described by the author, both in the publication and in the email to Sanofi was that this study did not audit or compare disclosure rates against any given disclosure requirement and did not limit assessment to any given laws or requirements in specific territories. Nor did the CMRO publication present any detailed information from which the degree of compliance with the detailed aspects of the IFPMA Joint Position (such as defined timelines or availability on the specific types of registries), and therefore Clause 21 of the Code, could be ascertained.

Sanofi stated that, although the CMRO publication listed overall disclosure rates for Jevtana and Multaq, it did not list Sanofi as a company which had not disclosed its clinical trial results in line with the Code. It followed, therefore, that Sanofi did not believe the CMRO publication provided any evidence of a breach of Clauses 21, 9 or 2 of the Code.

#### Additional information

Notwithstanding Sanofi's view on the applicability of the Code or, in spite of that, it gave some more detail on some aspects of the trials which were considered by the authors in preparation for the publication in order to provide some of the relevant additional information requested by the PMCPA.

Jevtana was first approved in the US on 17 June 2010 and Multaq on 1 July 2009.

In response to a request for further information, Sanofi stated that Jevtana was first commercially available in July 2010 and Multaq in July 2009.

#### Specific trials of interest

When analysing the list of trials that were considered by the authors of the CMRO publication, and cross referencing that with Sanofi's clinical trials management systems and databases, it was clear that only five company sponsored studies on Jevtana and Multaq had sites or investigators in the UK.

For each of those five trials, the following tables provided the information requested by the PMCPA.

Copies of the relevant public registry entries were provided.

#### Jevtana

Study Identifier as used by author of CMRO publication.	NCT00417079 / EFC6193
Study Type	Phase 3 Clinical Trial
Study Description	XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer (TROPIC)
Date of Commencement of the Trial (Patient Enrolment)	15 December 2006
Listing of Trial on Public Registry	Yes
Date of Public Registry Entry	28 December 2006
Location of Public Registration at Commencement	Clinicaltrials.gov
Date of Trial Completion	25 September 2009
Date and location of Disclosure of Results on a Public Database	20 September 2010, Sanofi.com
Submitted for Publication in Scientific Literature within 12-18 months	Yes

Publication	de Bono <i>et al</i> ; TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. <i>Lancet</i> . 2010 Oct 2;376(9747):1147-54. <a href="http://www.ncbi.nlm.nih.gov/pubmed/20888992?dopt=Abstract">http://www.ncbi.nlm.nih.gov/pubmed/20888992?dopt=Abstract</a>
Comments	Sanofi submitted that all the requirements of relevant IFPMA declarations were met.

#### Multaq

Study Identifier as used by author of CMRO publication.	NCT00259428, EFC3153
Study Type	Phase 3
Study Description	EUROPEAN TRIAL IN ATRIAL FIBRILLATION (AF) OR FLUTTER (AFL) PATIENTS RECEIVING DRONEDARONE FOR THE MAINTENANCE OF SINUS RHYTHM (EURIDIS)
Date of Commencement of the Trial	19 November 2001
Listing of Trial on Public Registry	Yes
Date of Public Registry Entry	25 November 2005
Location of Public Registration at Commencement	clinicaltrials.gov
Date of Trial Completion	14 August 2003
Date and location of Disclosure of Results on a Public Database	Results not publicly disclosed
Submitted for Publication in Scientific Literature within 12-18 months	No
Publication	Singh <i>et al</i> ; EURIDIS and ADONIS Investigators. Dronedaron for maintenance of sinus rhythm in atrial fibrillation or flutter. <i>N Engl J Med</i> . 2007 Sep 6;357(10):987-99.
Comment	Sanofi submitted that this trial fell outside the requirements of both Joint Positions; as it started prior to July 2005 and completed prior to 2010. However, registration of the trial on clinicaltrials.gov was undertaken retrospectively on a voluntary basis and the results published in scientific literature.



Study Identifier as used by author of CMRO publication.	NCT00174785, EFC5555, Eudra CT Number: 2005-000715-9
Study Type	Phase 3
Study Description	A Trial With Dronedaron to Prevent Hospitalization or Death in Patients With Atrial Fibrillation (ATHENA)
Date of Commencement of the Trial	29 June 2005
Listing of Trial on Public Registry (Y/N)	Yes
Date of Public Registry Entry	13 September 2005
Location of Public Registration at Commencement	clinicaltrials.gov
Date of Trial Completion	5 March 2008
Date and location of Disclosure of Results on a Public Database	24 July 2009, clinicaltrials.gov
Submitted for Publication in Scientific Literature within 12-18 months	No
Publication	Hohnloser <i>et al.</i> Rationale and design of ATHENA: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/ atrial flutter. J Cardiovasc Electrophysiol. 2008 Jan;19(1):69-73. Epub 2007 Nov 21.
Comment	Sanofi submitted that this trial fell outside of the Joint Position; as it started prior to July 2005 and completed prior to 2010. However, it was registered on the trial on clinicaltrial.gov by 13 September 2005 (as specified in the Joint Position 2005. Results were disclosed outside of the 12 months post study completion, but was achieved within 12 months of first registration of the medicine as per the Joint Position of 2008 (the first country approval was in the USA July 2009). The results have been published in scientific literature despite falling outside of the requirements.

Study Identifier as used by author of CMRO publication.	NCT01140581, DRONE_C_03668, EudraCT Number: 2009-016818-24
Study Type	Phase 4
Study Description	Optimal Timing of Dronedaron Initiation After Conversion in Patients With Persistent Atrial Fibrillation (ARTEMIS Load)
Date of Commencement of the Trial	13 September 2010
Listing of Trial on Public Registry	Yes
Date of Public Registry Entry	8 June 2010
Location of Public Registration at Commencement	clinicaltrials.gov
Date of Trial Completion	14 December 2011
Date and location of Disclosure of Results on a Public Database	24 May 2013, Sanofi.com
Submitted for Publication in Scientific Literature within 12-18 months	No
Comment	Sanofi submitted that the posting of the results to a public register was initially delayed in line with Joint Position, as disclosure would have compromised peer review publication. However, due to early discontinuation of the trial and reduced recruitment time for a similar but longer term trial from the same program (NCT01199081 - ARTEMIS LT), it was deemed to make scientific and clinical sense to combine the results of both trials for publication. Once the publication of ARTEMIS Load was no longer going ahead alone but in combination with ARTEMIS LT as a whole programme, the results were then posted on a public registry with a delay that met the Joint Position. Scientific literature publication of this study alone would not occur, but the data was being prepared for joint publication in scientific literature in combination with the ARTEMIS LT data, which completed on 18 April 2012. The manuscript of the combined ARTEMIS Load and ARTEMIS LTI study was submitted within 18 months of completion of the ARTEMIS LT trial, as per the declaration on publication in the scientific literature

	and was undergoing revision at the request of the reviewers. Sanofi submitted that the requirements of the Joint Position had been met.
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Inconsistency between response letter and the attachments and information on study NCT 01151137, Sanofi stated that on re-examining the information, it noted an unintentional omission not to have included the information table for this trial. Sanofi submitted that the disclosure and publication status of the trial fully complied with the requirements of the Joint Positions and thus the Code.

Study Identifier as used by author of CMRO publication.	NCT01151137, EFC11405, EudraCT Number: 2010-019791-73, U1111-1116-5566
Study Type	Phase 3
Study Description	Permanent Atrial fibrillation Outcome Study Using Dronedaron on Top of Standard Therapy (PALLAS)
Date of Commencement of the Trial	19 July 2010
Listing of Trial on Public Registry (Y/N)	Yes
Date of Public Registry Entry	22 June 2010
Location of Public Registration at Commencement	Clinicaltrials.gov
Date of Trial Completion	21 Sept 2011
Date and location of Disclosure of Results on a Public Database	14 Sept 2012, Clinicaltrials.gov
Submitted for Publication in Scientific Literature within 12-18 months	Yes
Publication	Connolly <i>et al</i> ; PALLAS Investigators. Dronedaron in high-risk permanent atrial fibrillation. N Engl J Med. 2011 Dec 15;365(24):2268-76. Epub 2011 Nov 14.
Comment	Sanofi submitted that all requirements of the Joint Position had been met.

Sanofi stated that although the matters raised in the complaint were not covered by the UK Code, in responding to a potentially broader interpretation of the complaint, Sanofi submitted that the CMRO publication did not as alleged, provide any evidence as to the compliance or otherwise of Sanofi with the specific requirements of Clauses 21, 21.3, 9 or 2 of the Code or the joint positions, as evidenced by the methodology of the study detailed by the author.

Sanofi submitted that the detail concerning the submission for publication of the combined data from the ARTEMIS Load and ARTEMIS LT trial programme in the Journal of Cardiovascular

Pharmacology was confidential and under embargo until the manuscript was accepted and published.

## GENERAL COMMENTS FROM THE PANEL

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical

Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

**'Clause 7.5 Data from Clinical Trials**

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not

required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

**'Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

*'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

**'Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the*

*Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process. The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than

exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the

Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be

well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

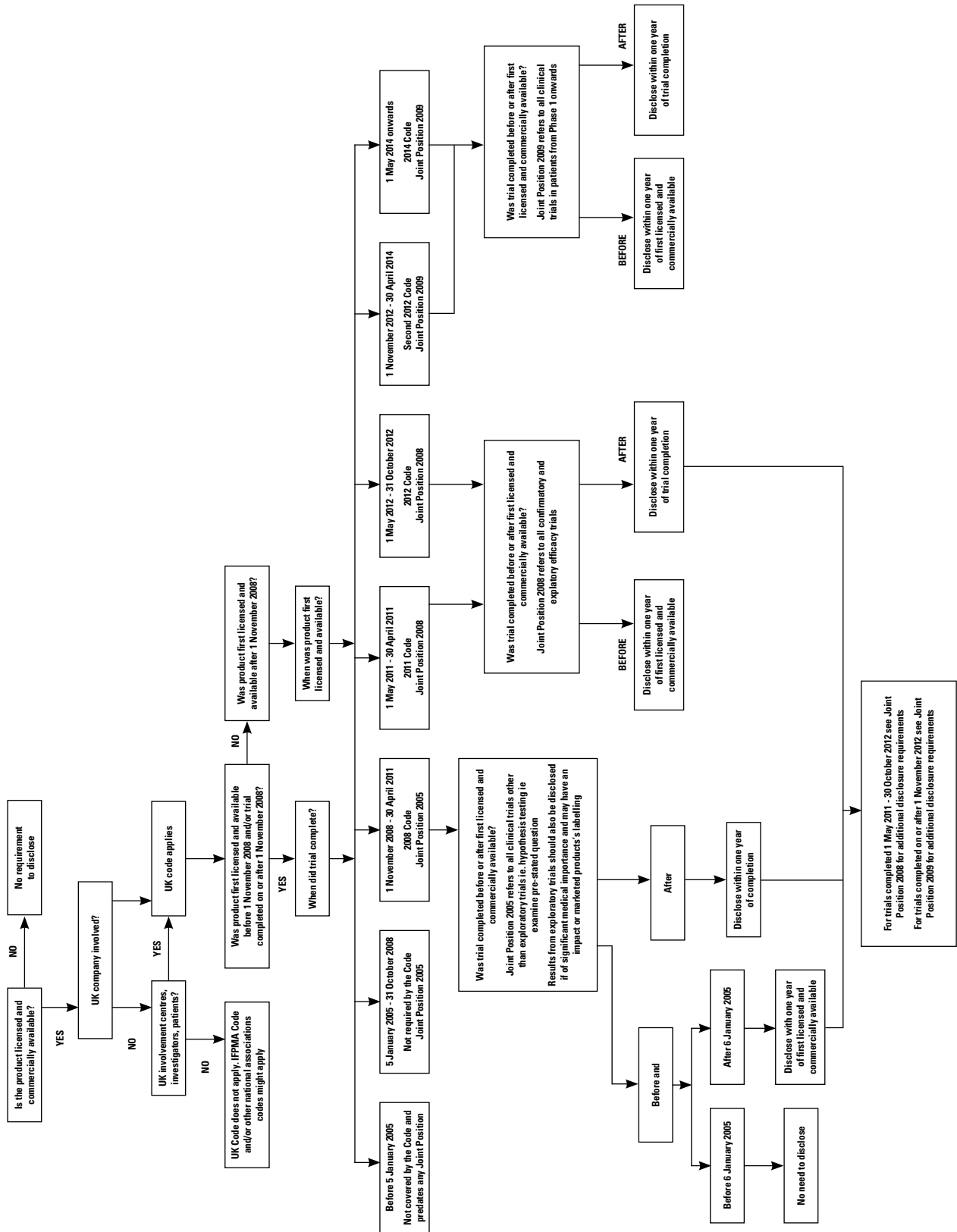
The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, Applicability of Codes, *inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

#### **PANEL RULING IN CASE AUTH/2666/11/13**

The Panel did not agree with Sanofi's submission that the CMRO publication did not show evidence of a breach of the Code. The Panel considered that any product with less than 100% disclosure percentage, be that within the timeframe or at 31 January 2013, potentially could be a breach of the ABPI Code. The Panel accepted that even a disclosure percentage of 100% in the CMRO publication could still be a breach of the Code.

# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results



The Panel did not accept that, due to the global nature of research, the UK Code did not apply at all. As stated above, the Panel was concerned with clinical trials run by the UK company or with UK involvement.

#### **Jevtana**

The Panel noted that three of the evaluable trials were not disclosed within the timeframe. The disclosure percentage was 57%. Two of the trials had not been disclosed at all. The disclosure percentage at 31 January of trials completed by the end of January 2012 was 71%. A footnote stated that four of the undisclosed trials were completed at or before the IFPMA Joint Position of 2005 and FDAAA of 2007.

The Panel noted that Jevtana was first approved in the US on 17 June 2010 and was first commercially available in July 2010.

The Panel noted the company's submission that global clinical trials undertaken by other regions/countries were all conducted wholly outside the UK. The Panel considered that trials with no UK involvement did not come within the scope of the UK Code and therefore ruled no breach. The Panel noted that the one Jevtana trial (NCT00417079) which included UK patients completed on 25 September 2009 and the results were disclosed on 20 September 2010. This was within one year of the product receiving its first approval (17 June 2010). The Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

#### **Multaq**

The Panel noted that three of the evaluable trials were not disclosed within the timeframe. The disclosure percentage was 75%. One trial had not been disclosed at all. The disclosure percentage at January 2013 of trials completed by the end of January 2012 was 92%. A footnote stated that the undisclosed trial was in the process of public disclosure preparation at the time of evaluation.

The Panel noted that Multaq was first approved and commercially available in July 2009. The relevant Code was 2008 and Joint Position 2005.

The Panel noted a discrepancy between Sanofi's submission that four studies had not been disclosed and the CMRO publication which referred to three studies. It decided to rule on the four studies referred to by Sanofi. With regard to the first study (NCT00259428, completed August 2003) it appeared that the results were not published on a public database but were published in a medical journal in 2007. As the study completed before January 2005 there was however no requirement under the Joint Position 2005 to disclose the results. The results from the second trial (NCT00174785, completed March 2008) were published on a public database

on 24 July 2009 ie the same month that the product was first approved and available. The third trial (NCT01140581) completed on 14 December 2011 and the results were disclosed on Sanofi.com in May 2013. It was to be published with data from another study. The fourth trial completed in September 2011 and the results were disclosed in September 2012. Thus the Panel considered that the result of trial 1 did not need to be disclosed under the Code and ruled no breach of Clauses 21.3, 9.1 and 2 of the 2008 Code. The results of trials 2 and 4 were disclosed within a year of Multaq being first approved and commercially available (trial 2) or within a year of the trial completion (trial 4). No breach of Clause 21.3 of the 2008 Code and consequently Clauses 9.1 and 2 were ruled for trial 2. No breach of Clause 21.3 of the 2011 Code and consequently Clauses 9.1 and 2 were ruled in relation to trial 4.

The Panel noted that Sanofi submitted the results of the third trial were disclosed in May 2013. These results should have been disclosed by 14 December 2012. Sanofi submitted that the delay in disclosure was in line with the joint position in relation to not compromising publication in a peer review journal.

The Panel noted that Sanofi changed its mind about peer review publication due to the early discontinuation of the trial and reduced recruitment for a similar second trial and decided to combine and disclose the results of trial 3 with the similar second study.

The Panel was concerned about the arrangements, companies should decide about submitting studies for publication in a peer review journal well before the timeframe to disclose. It was also concerned that the joint position on publication referred to submitting for publication wherever possible within 12 months and no later than 18 months of completion of trials. In this case the Panel noted that the company disclosed the results when it decided not to publish them in a peer reviewed journal. It was not clear whether the data had been submitted to a peer review journal.

The Panel noted that Sanofi had neither disclosed the data nor submitted it for publication in a peer review medical journal within the relevant timeframe. However, the Panel decided that as the relevant Joint Position (2008) stated that the schedule for disclosure could be adjusted so as to avoid compromising publication in a peer review journal there was no breach of Clause 21.3 of the 2008 Code. It consequently ruled no breach of Clauses 9.1 and 2.

**Complaint received**                      **21 November 2013**

**Case completed**                              **20 March 2014**

# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v AMGEN

## Clinical trial disclosure (Nplate and Prolia)

An anonymous contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Nplate (romiplostim) and Prolia (denosumab).

The detailed response from Amgen is given below.

General detailed comments from the Panel are given below.

With regard to Nplate, the Panel noted that eight evaluable Nplate trials had not been disclosed within the timeframe. The disclosure percentage was 58%. One study completed before the end of January 2012 had not been disclosed. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 95%. A footnote stated that the undisclosed trial reflected a terminated study with primary results analysis carried out in July 2012.

The Panel noted that Nplate was first approved and commercially available on 25 August 2008.

The Panel noted that Amgen submitted data to show that five trials with UK involvement completed in May 2008, August 2008, July 2009, December 2011 and one was ongoing. The results of two trials which completed before Nplate was first approved and commercially available did not need to be disclosed under the Code as the product was available prior to the requirement in the 2008 Code. The matter was not covered by the 2006 Code as such and there could be no breach of it. Thus the Panel ruled no breach of the 2006 Code including Clause 2.

The two trials which completed after Nplate was first approved and commercially available completed in July 2009 and December 2011. These needed to be disclosed by July 2010 and December 2012 respectively. Amgen submitted that these were disclosed in October 2010 and December 2012 on clinicaltrial.gov. The Panel ruled no breach of the 2011 Code including Clause 2 in relation to the second trial. The Panel ruled a breach of the 2008 Code in relation to the first trial which completed in July 2009 and the results were not disclosed until October 2010. The delay in disclosure meant that high standards had not been maintained and a breach was ruled. The results had been disclosed and the Panel considered that there was no breach of Clause 2 and ruled accordingly.

An anonymous contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was



referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link

to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for each product. The data for Nplate (romiplostim) and Prolia (denosumab) were as follows:

### Nplate

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	10	0	10	5	50%	10	9	90%
Phase III	9	1	8	6	75%	9	9	100%
Other	1	0	1	0	0%	1	1	100%
<b>TOTAL</b>	<b>20</b>	<b>1</b>	<b>19</b>	<b>11</b>	<b>58%</b>	<b>20</b>	<b>19</b>	<b>95%</b>

### Prolia

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	10	0	10	9	90%	10	10	100%
Phase III	18	2	16	15	94%	16	16	100%
<b>TOTAL</b>	<b>28</b>	<b>2</b>	<b>26</b>	<b>24</b>	<b>92%</b>	<b>26</b>	<b>26</b>	<b>100%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluative	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluative trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluative trials which were fully disclosed

completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Amgen.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Amgen, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Amgen addressed each clause in turn.

### Clause 1.8

Amgen stated that the CMRO publication reflected research conducted between December 2012 and 31

January 2013 by the ABPI to show the baseline rate of disclosure of clinical trial results – which at 89% at survey close was good - and to provide a benchmark to better understand the current landscape. As the authors noted a disclosure rate of 100% was not expected given the range of years over which trials that were included in the assessment were conducted (some more than 10 years ago and therefore pre-dating key disclosure requirements) and the broad scope of study types included. The survey was not designed to assess compliance with the Code and following publication of the survey Amgen was not contacted by the PMCPA (other than in connection with this anonymous complaint) to suggest, based on the survey results, that it was in breach of the Code.

Amgen submitted that the substantive provisions of the Code did not address the application of the clinical trial disclosure requirements in Clause 21.3 in circumstances where the clinical trial was a foreign clinical trial. It was clear from Clause 1.1 and its supplementary information that the Code governed activities in the UK and activities directed toward UK health professionals. If an activity involved several European countries, the supplementary information to Clause 1.8 required that the national code of the country where the activity took place applied as well as the national code of the country where the company performing the activities resided (if the company was outside Europe it must comply with the EFPIA Code). It followed that the Code did not apply to activities with no UK nexus. The Nplate and Prolia trials identified as having no UK participation were conducted in countries other than the UK. There was no UK site, investigator, health professional or patient participation and as such these trials fell outside the scope of the Code.

### **Clause 21.3**

Amgen submitted that the CMRO publication did not concern companies' scientific services and although the complainant referred generally to Clause 21, the complaint only related to Clause 21.3.

The supporting information for the CMRO publication referred to eight Nplate trials and two Prolia trials that did not, according to the authors, meet the definition of appropriate publication requirements (defined in the CMRO publication as summary results disclosed (in registry or journal) within 12 months of either first regulatory approval or trial completion, whichever was later). In addition to the above trials, a further Nplate trial and two Prolia trials were considered by the researchers as unevaluable because either the trial completion date or the publication date was unclear. These trials were excluded from the analysis but Amgen included them in its response.

### **Nplate trials**

Amgen submitted that four out of the nine alleged non-disclosed/unevaluable Nplate trials had no UK investigator, site, patient or health professional participation and accordingly fell outside the scope of the Code (as set out above). The remaining five trials had UK sites and Amgen had therefore assessed each of these trials against the version of

Clause 21.3 that was in force at the relevant time.

The five trials were initiated between February 2006 and July 2008, four were completed between May 2008 and December 2011 and one was ongoing. Clinical trial disclosure requirements were first introduced in the 2008 version of the Code and compliance was required as from the 1 November 2008 ie the date upon which the transitional period for the 2008 Code ended. Accordingly, each of the five trials was initiated and two were completed before any disclosure requirements came into force. The other two completed trials ended in July 2009 and December 2011 when the Clause 21.3 requirements under the 2008 and 2011 versions of the Code were in force respectively. The disclosure provisions contained in Clause 21.3 of each of these two versions of the Code were identical as was the accompanying supplementary information (save for the reference to the dates of the Joint Position on Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases). In these versions of the Code, Clause 21.3 simply required companies to: 'disclose details of clinical trials'. The supplementary information stated that further information was to be found in the Registries and Databases Joint Position. Unlike the current version of the Code (Second 2012 Edition), there was no mandatory requirement to disclose clinical trial results in accordance with the Joint Position. The results for the two trials that completed after 1 November 2008 but before the entry into force of the current Code had been disclosed and notwithstanding that there was no mandatory timetable for results posting or publication applicable to these trials, the results were disclosed in accordance with the Registries and Databases Joint Position or the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

### **Prolia trials**

Amgen submitted that the four alleged non-disclosed/unevaluable Prolia trials, two, were categorized in the CMRO publication as non-evaluatable. Amgen did not sponsor one of the non-evaluatable Prolia trials and whilst it sponsored the other, the trial was on an alternative formulation of denosumab, not Prolia. Accordingly, neither of the non-evaluatable trials fell within scope of this response.

The remaining two Prolia trials had no UK investigator, site, patient or health professional participation. Amgen submitted that they fell outside the scope of the Code.

In summary, based on the above, Amgen submitted that it had met the relevant Code disclosure requirements for both the Nplate and Prolia clinical trials that were the subject of the complaint and accordingly there had been no breach of Clause 21.3.

### **Clauses 9 and 2**

Amgen assumed that the complainant's concern related to Clause 9.1. In meeting, and in some cases exceeding, the relevant disclosure requirements for Nplate and Prolia under Clause 23.1, Amgen submitted that it had maintained the high standards

required under the Code in compliance with Clause 9.1.

Amgen submitted that having more than complied with disclosure requirements under Clause 23.1 for both products, it had not breached the Code and certainly not committed a serious breach which would warrant a finding under Clause 2.

In response to a request for additional information Amgen stated that Nplate and Prolia were first approved and commercially available on 25 August 2008 and 1 June 2010 respectively.

#### **GENERAL COMMENTS FROM THE PANEL**

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use

in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

### **'Clause 7.5 Data from Clinical Trials**

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

### **'Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

*'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

### **'Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and

was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the



responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

## PANEL RULING IN CASE AUTH/2667/11/13

The Panel noted that eight evaluable Nplate trials had not been disclosed within the timeframe. The disclosure percentage was 58%. One study completed before the end of January 2012 had not been disclosed. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 95%. A footnote stated that the undisclosed trial reflected a terminated study with primary results analysis carried out in July 2012.

### Nplate

The Panel noted Amgen submitted details of nine trials which were cited in the CMRO publication as either non-compliant or non-evaluable. It appeared from the information provided by Amgen that study NCT00614523 which was referred to as having an incorrect completion date in clinicaltrials.gov at that time was the non-evaluable trial. The error had been corrected.

The Panel noted that Nplate was first approved and commercially available on 25 August 2008.

The Panel noted that four of the non-disclosed trials had no UK involvement. The Panel considered that, as there had been no UK involvement, the matter did not come within the scope of the Code and therefore ruled no breach.

The Panel noted that Amgen submitted data to show that the remaining five trials completed in May 2008, August 2008, July 2009, December 2011 and one was ongoing. The two trials which completed before Nplate was first approved and commercially available did not need to be disclosed under the Code as the product was available prior to the requirement in the 2008 Code. The matter was not covered by the 2006 Code as such and there could be no breach of it. Thus the Panel ruled no breach of Clauses 9.1 and 2 of the 2006 Code.

The trials which completed after Nplate was first approved and commercially available completed in July 2009 (NCT00415532) and December 2011 (NCT00472290). These needed to be disclosed by July 2010 and December 2012 respectively. Amgen submitted that these were disclosed in October 2010 and December 2012 on clinicaltrial.gov.

The Panel ruled no breach of Clauses 21.3 and consequently no breach of Clauses 9.1 and 2 of the 2011 Code in relation to NCT00472290. Trial NCT00415532 completed in July 2009 and was not disclosed until October 2010. The Panel did not accept Amgen's submission regarding the timeline for publication. The joint positions were clear regarding the disclosure timeframe with flexibility to avoid compromising publication in a peer review journal. On the information supplied by Amgen this was not relevant. The results were first published on clinicaltrials.gov which, in the Panel's view, was not a peer review journal as meant by the joint positions. The Panel ruled a breach of Clause 21.3 of the 2008 Code.

The delay in disclosure meant that high standards

had not been maintained and a breach of Clause 9.1 was ruled. The results had been disclosed and the Panel considered that there was no breach of Clause 2 and ruled accordingly.

The results of ongoing trials did not need to be disclosed. The Panel noted that the non-evaluable trial, NCT00614523, was ongoing. In addition the Panel considered that this non-evaluable trial was not within the scope of the complaint. The CMRO publication disclosure data were in relation to evaluable trials. The Panel therefore decided it did not need to make any ruling regarding this trial.

**Prolia**

The Panel noted that two evaluable Prolia trials had not been disclosed within the timeframe. The disclosure percentage was 92%. The Panel noted the submission from Amgen that the two studies had no UK involvement and the study results had been disclosed. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 100%. The Panel considered, as there was no UK involvement, the matter did not come within the scope of the UK Code and therefore ruled no breach.

**Complaint received            21 November 2013**

**Case completed                24 March 2014**



# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v SHIRE

## Clinical trial disclosure (Resolor)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Resolor (prucalopride).

The detailed response from Shire is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that five evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 77%. Four studies had not been disclosed giving a disclosure percentage at 31 January 2013 of trials completed before the end of January 2012 of 82%.

The Panel noted that Resolor was first approved in October 2009 and commercially available in

January 2010. This meant that the 2008 Code and Joint Position 2005 were relevant. Resolor trials completed before 6 January 2005 did not need to be disclosed under the Joint Position 2005.

The Panel noted that four studies completed in the late 1990s and given that Resolor was first approved and commercially available in January 2010, there was no requirement to disclose the results of these trials. The Panel ruled no breach of the 2008 Code.

The Panel noted Shire's submission that one study was a Phase I study on healthy volunteers and it did not need to be disclosed. The data had been published in February 2012. The relevant Code was the 2008 Code and hence the Joint Position 2005. This did not require disclosure of exploratory trials unless they were of significant medical importance and might have an impact on marketed product's labelling. The Panel was unsure whether the results were of significant medical importance. The complainant had not provided any details in this regard. The Panel considered that publication of such data was preferable, however on the information before it there appeared to be no need to disclose the trial results under the 2008 Code and so it ruled no breach of the Code including Clause 2.

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for each product. The data for Resolor (prucalopride) were as follows:

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	14	0	14	10	71%	14	11	79%
Phase III	11	3	8	7	88%	8	7	88%
Phase IV	1	1	0	0	0%	0	0	0%
<b>TOTAL</b>	<b>26</b>	<b>4</b>	<b>22</b>	<b>17</b>	<b>77%</b>	<b>22</b>	<b>18</b>	<b>82%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluable	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluable trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluable trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Shire.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Shire, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Shire submitted that it was not in breach of the Code. Cases such as this encompassed the full complexity of global pharmaceutical development. An important part of Shire's response related to the history of ownership of Resolor (prucalopride), and the contractual nature of the rights governing Shire's access to historical clinical trial information.

In 2006, a Belgian company, Movetis N.V., acquired rights to a family of compounds that included Resolor from its original owners, Janssen Pharmaceutica N.V. and Ortho-McNeil Pharmaceutical, Inc. (now Janssen Pharmaceuticals, Inc.). Janssen Pharmaceutica N.V. developed Resolor prior to licensing it to Movetis. Nearly all of the Resolor trials pre-dated Shire's 2010 purchase of Movetis. While a complex history of ownership did not relieve any individual company of a legal or Code requirement to provide access to clinical trial data, the retrospective nature of this subject needed to be addressed, particularly in relation to Clause 21.3 of the Code.

Shire submitted that the PMCPA's decision in relation to these questions needed to take into account how retrospective application of existing norms and requirements for clinical trials should apply; and whether the pharmaceutical company

responsible for marketing a product had the right to divulge to the public clinical trial information relating to that product that was the property of another entity, and to which it only had a licence. In this regard, the two IFPMA Joint Positions (the Disclosure of Clinical Trial Information via Clinical Trial Registries and Database and Disclosure of Clinical trial Information via Clinical Trial Registries and Databases) were relevant. The former stated that 'such publication' and the latter stated that 'Such disclosure' 'must maintain protections for ... contract rights'. This was important, because Clause 21.3 of the Code obliged companies to follow both of the Joint Positions in their disclosure practices.

With regard to Resolor, Shire submitted that its 2006 licence classified clinical trial information as confidential information belonging to the licensor. Under the licence, the sole means of Shire being able to disclose such information would be where it was required to do so by law or by regulation. While Shire took its responsibilities under the Code very seriously, a Code requirement was not the same as a legal requirement or a regulation. In this regard, Shire contractually could not divulge information about trials that were not its property, and to which it only had a licence covering certain R&D and commercial activities.

Therefore Shire submitted that the PMCPA must take into account the importance of the specific licence provisions governing each company's access to such information in its assessment of whether there had been a breach of the Code, as the Joint Position required.

### **History of the clinical trial programme**

Shire submitted that the four Resolor studies (GBR-7, PRU-USA-8, PRU-INT-14, PRU-INT-17) that were not disclosed were completed in the late 1990s before the 1 January 2006 publication of Clause 7.5 'Data from Clinical Trials' ABPI Code of Practice, and before the 1 July 2005 disclosure date established by the Joint Position 2005, which was referenced in the 2006 Code. It was also before the 27 September 2007 disclosure date established by the FDA Amendments Act of 2007, and therefore the studies were not required to be registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **PRU-US-27**

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature implied that an abstract was considered sufficient public disclosure, if sufficient information was included. Shire understood that an abstract was published for this study. However, PRU-US-27 was an American trial. It was completed before the 27 September 2007 disclosure date established by the FDA Amendments Act of 2007 and so there was no contemporaneous requirement to be registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **Study NCT00793247 GBR-7**

This study started in August 1997 and ended in June 1999. The clinical study report (CSR) was

dated October 2001, which also pre-dated posting requirements. Movetis posted an update to the CSR in 2008 and disclosed the study in the Movetis section of the [clinicaltrials.gov](http://clinicaltrials.gov) website (this pre-dated Shire's ownership in 2010). Although this was done 13 months after the update to the CSR, the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature stated that disclosure should occur 'whenever possible within 12 months and no later than 18 months'.

One study, M0001-C102 did not predate the regulations, but was a Phase I study in healthy volunteers, which did not require posting.

Shire reiterated its position that there was no breach of any clauses of the Code.

In response to a request for additional information, Shire stated that Resolor was first approved on 15 October 2009 and first commercially available in Germany in January 2010.

In response to a request for additional information, Shire confirmed that Study PRU-US-27 was carried out in the US and was sponsored by Movetis.

Study M0001-C102 completed on 21 April 2009 and was published in February 2012.

### **GENERAL COMMENTS FROM THE PANEL**

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially

available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly

introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

*'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World

Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and

companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

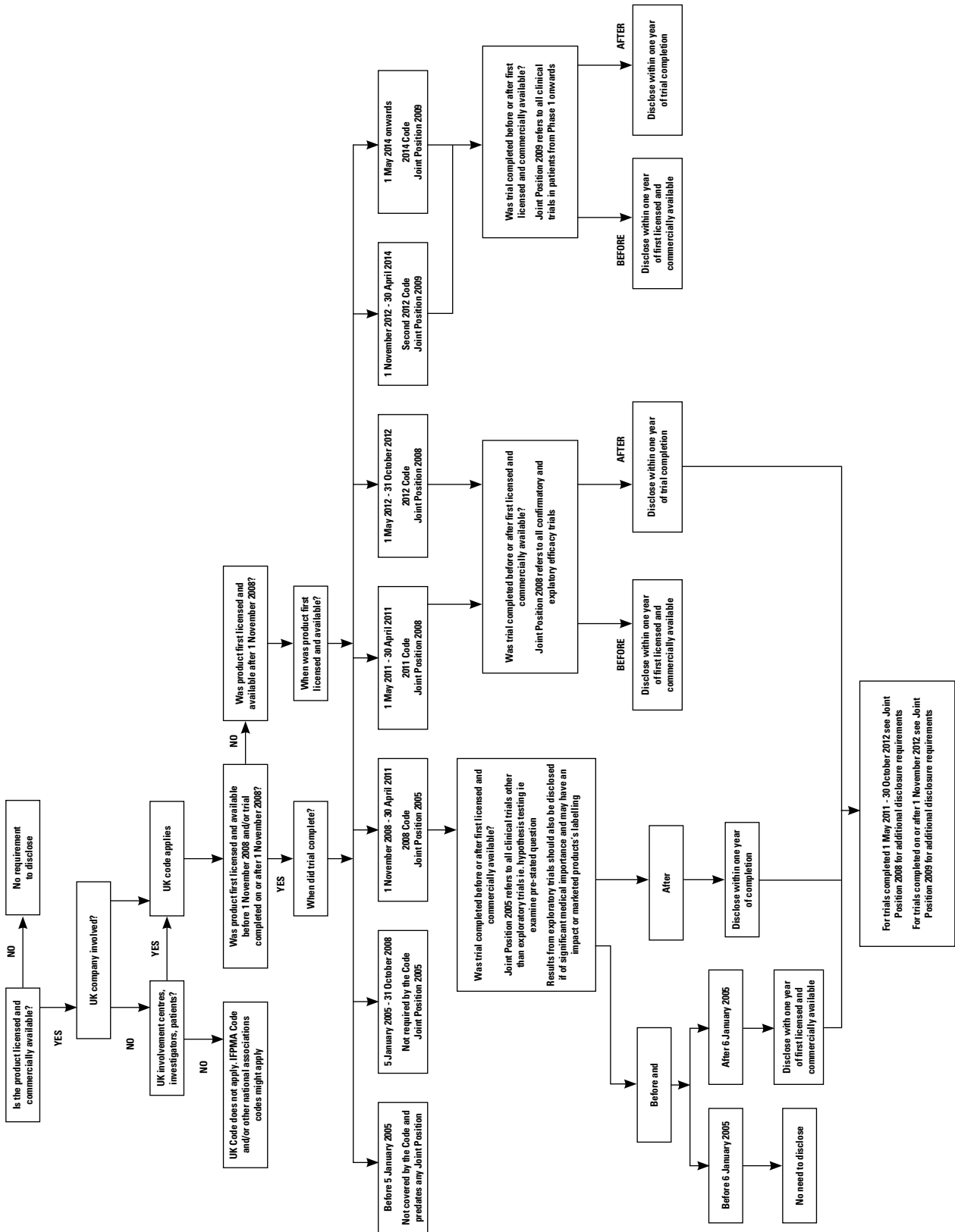
The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with

# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results



the companies. The supplementary information to Clause 1.8, Applicability of Codes, *inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

#### **PANEL RULING IN CASE AUTH/2669/11/13**

The Panel noted the CMRO publication in that five evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 77%. Four studies had not been disclosed giving a disclosure percentage at 31 January 2013 of trials completed before the end of January 2012 of 82%.

The Panel noted that Resolor was first approved in October 2009 and commercially available in January 2010. This meant that the 2008 Code and Joint Position 2005 were relevant. Resolor trials completed before 6 January 2005 did not need to be disclosed under the Joint Position 2005.

The Panel noted that four studies completed in the late 1990s (GBR-7, PRU-USA-8, PRU-INT 14, and PRU-INT-17) and given that Resolor was first approved and commercially available in January

2010, there was no requirement to disclose the results of these trials. The Panel ruled no breach of the 2008 Code.

With regard to study PRU-US-27 the Panel noted Shire's submission that it was a US trial that completed before 27 September 2007, which was before Shire purchased the product. There was no UK involvement. According to Shire an abstract had been posted. The Panel considered that as far as Shire was concerned the matter did not come within the scope of the UK Code and therefore ruled no breach.

With regard to Study M0001-C102 the Panel noted Shire's submission that as it was a Phase I study on healthy volunteers, it did not need to be disclosed. The data had been published in February 2012. The relevant Code was the 2008 Code and hence the Joint Position 2005. This did not require disclosure of exploratory trials unless they were of significant medical importance and might have an impact on marketed product's labelling. The Panel was unsure whether the results were of significant medical importance. The complainant had not provided any details in this regard. The Panel considered that publication of such data was preferable, however on the information before it there appeared to be no need to disclose the trial results under the 2008 Code and so it ruled no breach of Clause 21.3 and consequently no breach of Clauses 9.1 and 2.

**Complaint received**                      **25 November 2013**

**Case completed**                              **19 February 2014**



# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v OTSUKA

## Clinical trial disclosure (Samsca)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Samsca (tolvaptan).

The detailed response from Otsuka is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that 18 evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 36%. Ten studies completed before the end of 2012 had not been disclosed. The disclosure percentage at 31 January 2013 of trials completed before the end of January 2012 was 64%. A footnote stated that the undisclosed Phase I/II trials comprised of trials completed before reporting requirements. Trials with no US IND therefore not subject to FDAAA 801

requirements. The undisclosed Phase III trial was being prepared for publication.

The Panel noted that Samsca was first approved on 5 May 2009. This meant that the 2008 Code applied and the Joint Position 2005. One trial with UK involvement completed in July 2006 and Otsuka submitted it was published in JAMA in March 2007. The study had been published within one year of Samsca being approved and commercially available as required. The Panel ruled no breach of the 2008 Code including Clause 2.

The Panel noted Otsuka's submission that seven other trials were either Phase 1 trials on healthy volunteers and/or used a different formulation of tolvaptan to that licensed. The Panel noted that the Joint Position 2005 did not require disclosure of exploratory trials unless they were of significant medical importance and might have an impact on the marketed product's labelling. The Panel was unsure whether the results were of significant medical importance. The complainant had not provided any details in this regard. The Panel considered publication of such data was preferable, however on the information before it there appeared to be no need to disclose the results of the trials under the 2008 Code. The Panel ruled no breach of the 2008 Code including Clause 2.

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

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## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for each product. The data for Samsca (tolvaptan) were as follows:

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	18	0	18	6	33%	18	9	50%
Phase III	13	3	10	4	40%	10	9	90%
<b>TOTAL</b>	<b>31</b>	<b>3</b>	<b>28</b>	<b>10</b>	<b>36%</b>	<b>28</b>	<b>18</b>	<b>64%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluative	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluative trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluative trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Otsuka.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Otsuka, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

In its initial response Otsuka UK stated that as the UK affiliate of an international pharmaceutical company it had no clinical research department, did not sponsor any good clinical practice (GCP) studies and did not fund any investigator-initiated studies for any of its products including Samsca. All Otsuka sponsored clinical trials were organised, funded and managed by the global organisation which was not located in the UK. Otsuka stated that Samsca was first authorised in the US on 5 May 2009 and in the EU on 3 August 2009. It was currently authorised in 40 countries and marketed in 14.

The case preparation manager asked Otsuka UK to provide further information.

Otsuka summarised the tolvaptan clinical trials and provided what it described as an exhaustive, confidential, list from the tolvaptan investigators' brochure. Of the trials listed only one had a UK nexus. This trial was in heart failure with a clinicaltrial.gov identifier, NCT00071331. A link was provided to the registry entry.

A printout of the entry was provided. There was a link at the bottom of the results page to the main results publication (Konstam *et al* March 2007). This paper was available on the Journal of the American Medical Association (JAMA) website free of charge

by following the JAMA link from the results page. Otsuka submitted that this therefore fulfilled the requirements laid out in the Joint Position.

Given that the results were published within a year of completing the study and linked to the registry entry and that the results publication from that link was available free of charge Otsuka submitted that there had been no breach of Clause 21. Equally, as Otsuka had fulfilled its requirements in this regard there was no breach of Clause 1.8. Clearly as there was no breach of other clauses there was no breach of Clauses 9.1 and 2.

In response to a request for further information Otsuka confirmed that three multicentre, international trials identified by the Panel from the list provided by Otsuka did not involve UK sites.

With regard to the Panel's query about seven studies on the list provided by Otsuka, the company submitted that these studies were conducted before the European database EudraCT was established. Otsuka submitted that the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2005 & 2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010) were established subsequent to these dates and did not mandate retroactive publication of studies. Four of the studies were Phase 1 studies in healthy controls and at that time did not require reporting. Moreover they were with the spray-dried formulation and hence not the approved formulation. Two studies were Phase 1 studies in healthy subjects. One study was also Phase 1 with tolvaptan sachets which was not an approved formulation.

#### **GENERAL COMMENTS FROM THE PANEL**

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code

would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The

disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

*'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond

at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should

be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

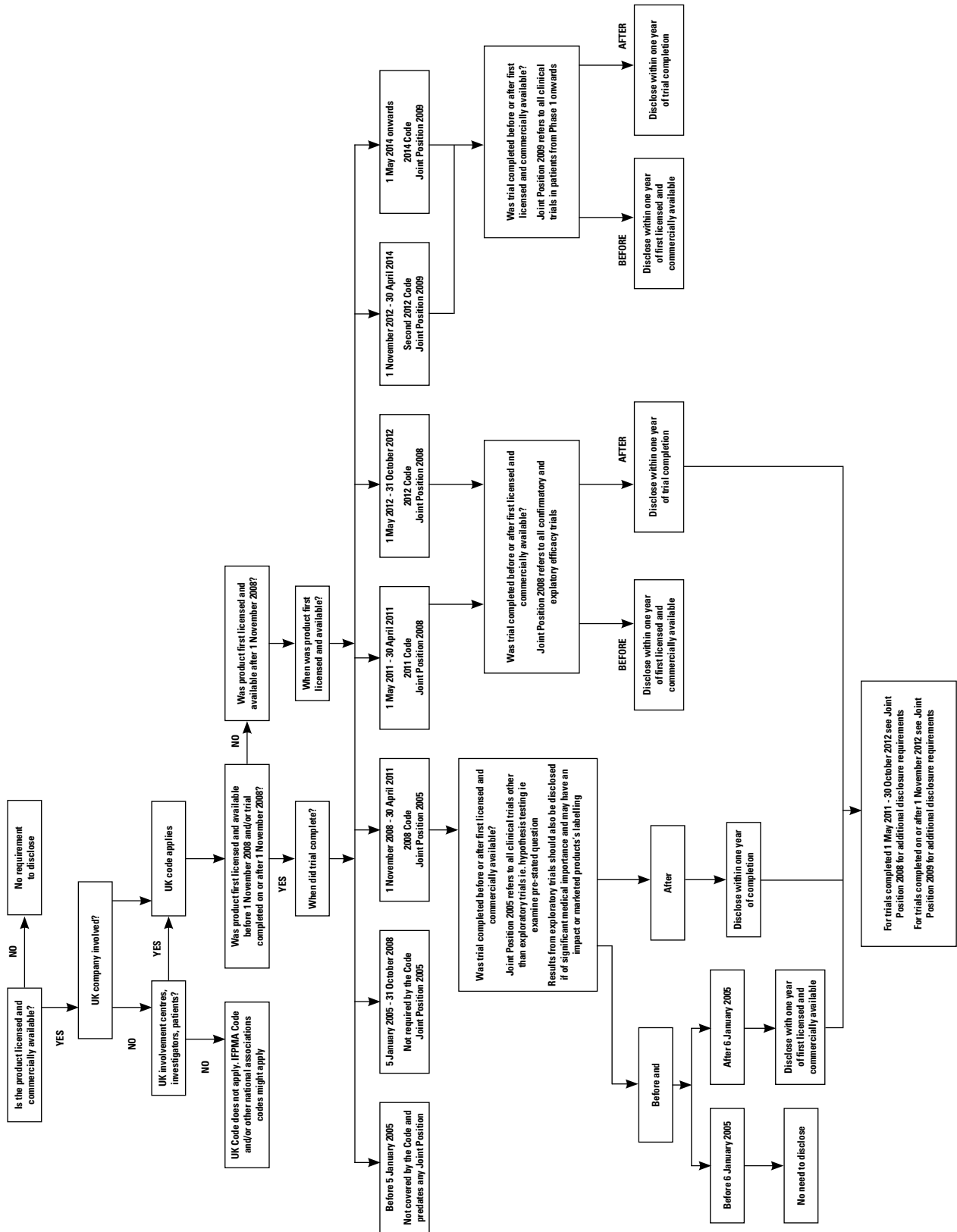
For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after

# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results



the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study

ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

#### **PANEL RULING IN CASE AUTH/2670/11/13**

The Panel noted the CMRO publication in that 18 evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 36%. Ten studies completed before the end of 2012 had not been disclosed. The disclosure percentage at 31 January 2013 of trials completed before the end of January 2012 was 64%. A footnote stated that the undisclosed Phase I/II trials comprised of trials completed before reporting requirements. Trials with no US IND therefore not subject to FDAAA 801 requirements. The undisclosed Phase III trial was being prepared for publication.

The Panel noted that Samsca was first approved on 5 May 2009. This meant that the 2008 Code applied and the Joint Position 2005. One trial with UK involvement completed in July 2006. Otsuka submitted it was published in JAMA in March 2007 and so in this regard the study had been published within one year of Samsca being approved and commercially available as required. The Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

The Panel noted Otsuka's submission that another three trials queried by the Panel had no UK involvement. The Panel did not know whether the results of these trials had been disclosed. However as there was no UK involvement the Panel considered the matter did not come within the scope of the UK Code and therefore ruled no breach.

The Panel noted Otsuka's submission that seven other trials were either Phase 1 trials on healthy

volunteers and/or used a different formulation of tolvaptan to that licensed. The Panel noted that the Joint Position 2005 did not require disclosure of exploratory trials unless they were of significant medical importance and might have an impact on marketed product's labelling. The Panel was unsure whether the results were of significant medical importance. The complainant had not provided any details in this regard. The Panel considered publication of such data was preferable, however on the information before it there appeared to be no need to disclose the results of the trials under the 2008 Code. The Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

The Panel noted that none of the additional seven trials had any UK involvement and the Panel considered the matter did not come within the scope of the Code and therefore ruled no breach.

**Complaint received**            **21 November 2013**

**Case completed**                **20 March 2014**

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# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v SERVIER

## Clinical trial disclosure (Valdoxan)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for Valdoxan (agomelatine).

The detailed response from Servier is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that twelve evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 63%. Six studies completed before the end of 2012 had not been disclosed. The disclosure percentage at 31 January 2013 of trials completed before the end of January 2012 was 83%. A footnote stated that the undisclosed trials were in the process of being prepared for publication.

The Panel noted that Valdoxan was approved for use in Europe in February 2009. In response to a question whether this was when the product was first approved and commercially available anywhere in the world. Servier stated that the relevant date was March 2009.

The Panel was only concerned with studies which involved UK patients or involved the UK company. Two studies (25 and 26) which completed in September 2008 and April 2009 had, according to Servier, not been disclosed within the timeframe. It appeared from the information provided by Servier that the abstracts for the studies were published in June 2010 and March 2011 with publication in 2011 and 2013 respectively.

The Panel noted that the relevant Code was 2008 and the Joint Position 2005. Servier should have disclosed the results for one study (Study 25) by March 2010 and the other study (Study 26) by April 2010. As the results were not disclosed within this timeframe Servier had not met the requirements of the Code. The Panel ruled a breach of the 2008 Code as acknowledged by Servier. The delay in disclosure meant that high standards had not been maintained and a breach was ruled. As the results had been disclosed the Panel considered that on balance there was no breach of Clause 2 and ruled accordingly.

The results of a further three studies (29, 30 and 31) which involved UK patients and completed in September 2011, August 2011 and December 2008 were still to be disclosed. The Panel considered that Servier, by not disclosing the results within 12 months of study completion (Study 30) or by one year after first approval (Study 31) ie by August 2012 and March 2010 respectively, the company had not met the requirements of the Code. The Panel ruled a breach of the 2011 Code in relation to the study which completed in August 2011 (Study 30). The study which completed in December 2008 (Study 31) was ruled in breach of the 2008 Code.

Study 29 completed in September 2011 and was carried out on a different formulation. The relevant Code was the 2011 Code and thus the Joint Position 2008 which stated that if trial results for an investigational product that had failed in development had significant medical importance, study sponsors were encouraged to post the results. The Panel was unsure whether the product had 'failed in development' or whether the results were of significant medical importance. Further companies were only encouraged to post results if possible. The complainant had not provided any details in this regard. The Panel considered that publication of such data was preferable, however failure to publish was not necessarily out of line

with the Joint Position 2008. Thus the Panel ruled no breach of the 2011 Code including Clause 2.

The Panel noted that Servier knew from the CMRO publication that some of its trial data results had not been disclosed. The ABPI study was conducted between December 2012 and January 2013 but in the 9½ months that had elapsed between the end of the study and the receipt of this complaint, the company had not subsequently disclosed the missing data (Studies 30 and 31). Notwithstanding the company's submission that the missing data was being prepared for publication, the Panel considered that failure to disclose the data meant that high standards had not been maintained and a breach was ruled.

The Panel also considered that failure to disclose meant that Servier had brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

The Panel noted there was no way of identifying from the list of 49 studies provided by Servier which were the remaining seven studies cited in the CMRO publication. If these studies had no UK involvement the matter did not come within the scope of the UK Code. If these studies had UK involvement but were completed before 5 January 2006 they would be exempted under the 2005 Joint Position. The Panel noted that the results from all studies, apart from the three (29, 30, 31) considered above, had been disclosed. The results of studies that completed before 5 January 2005 did not need to be disclosed. Thus the Panel ruled no breach of the 2008 Code including Clause 2.

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in

Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

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## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for each product. The data for Valdoxan (agomelatine) were as follows:

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	5	2	3	2	67%	3	2	67%
Phase III	35	7	28	18	64%	29	24	83%
Phase IV	2	1	1	0	0%	1	1	100%
Other	4	4	0	0	0%	2	2	100%
<b>TOTAL</b>	<b>46</b>	<b>14</b>	<b>32</b>	<b>20</b>	<b>63%</b>	<b>35</b>	<b>29</b>	<b>83%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluable	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluable trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluable trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Servier, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Servier UK submitted that the objective of the ABPI study was to assess the timely disclosure in the public domain of the results of company-sponsored clinical trials carried out on 53 new products approved by the European Medicines Agency (EMA) between 2009 and 2011 inclusive, one of which was Servier's Valdoxan (agomelatine) which was approved for use in February 2009 by way of the centralised procedure.

This was a unique and politically-sensitive issue and the broader context could not be ignored. Therefore, Servier requested that the PMCPA adjudicated this matter without condemnation of Servier and closed the matter entirely.

Servier noted that the ABPI's research was undertaken in the context of the important on-going

debate and publicity regarding the transparency and disclosure of clinical trial information and in response to the call for evidence by the House of Commons Select Committee on Science and Technology (inquiry into clinical trials and disclosure of data). According to the ABPI press release of 11 November, the study was intended as a constructive contribution to the transparency debate. Indeed the study clearly highlighted a positive trend of increasing levels of disclosure for industry-sponsored clinical trials. In that same press release, the ABPI acknowledged that as part of a global industry it had actively engaged with stakeholders over several years to increase clinical trial transparency. The study itself was evidence of such engagement which, according to the ABPI, was a 'catalyst for further change, leading to greater transparency across the pharmaceutical industry'. Servier was one such stakeholder and it was therefore incomprehensible that it was being investigated for a breach of the ABPI Code for assisting the ABPI in pursuance of its fundamental aims.

In undertaking the research, whilst the ABPI relied on publicly available information sources it also worked with the relevant companies in order to produce a comprehensive view of current levels of clinical trial results disclosure. Servier UK, along with its headquarters, worked together with the ABPI early in 2013 to ensure that all requests for further information, and verification of information already held by the ABPI, were responded to and confirmed respectively in a complete and timely manner. This collaborative approach reflected Servier's commitment to transparency and compliance, with current guidance and regulations. In view of the nature and purpose of the study, it was clear that it was never intended to be a trigger for raising compliance issues under the ABPI's own Code, rather it sought to produce a benchmark for industry on rates of public reporting of industry-sponsored trials within 12 months of market authorisation.

If there was a risk that companies participating in the study would be exposed to compliance issues, such companies would naturally have been reluctant to collaborate with the ABPI to the detriment of the fundamental aim of the study.

Servier noted that the ABPI did not necessarily expect a disclosure rate of 100% given the wide range of years over which trials included in its assessment were conducted (with some having been conducted more than ten years ago) together with the broad scope of inclusion for the study. Had the ABPI so wished, it could have reported relevant companies to the PMCPA which it did not do. Indeed, the ABPI had announced that for products launched in 2012 and 2013, it would take on the responsibility for reporting to the PMCPA non-compliance with trial registration and posting of summary results. This further confirmed that for the period prior to that (and relevant to the present complaint) it would not raise compliance issues.

Servier respected the PMCPA's remit to investigate complaints from whatever means and did not

dispute that it operated separately from the day to day management of the ABPI. However, the PMCPA was established by the ABPI to further the ABPI's aim of ensuring that the industry operated in a 'professional, ethical and transparent manner' (as set out in the introduction to the ABPI Code). As Servier had voluntarily assisted the ABPI in the pursuance of one of its fundamental aims, it should not be condemned by the PMCPA under the ABPI Code but rather be granted 'immunity' from the sanctions that would ordinarily be applicable for breaches of the Code – ie it should not be liable to pay any administrative charges, nor should it be subject to any other sanction. In the present circumstances, sanctioning a company under the ABPI Code would be counterproductive. It would undermine the industry's trust in the ABPI, because the ABPI Code was being used in a fashion that would constitute a misuse of self-regulation. It would be ironic and unfair if companies were condemned by the PMCPA under the ABPI Code, when the purpose of the ABPI undertaking the study and publishing was to support and encourage transparency. Indeed there was a greater risk that it would stifle any future exchange between pharmaceutical companies and the ABPI leading to less open dialogue between the ABPI and stakeholders. In any event, it was unnecessary to condemn companies under the Code because the study already revealed that there were lessons to be learnt – as the ABPI acknowledged in its press statements.

Industry as a whole was clearly engaged in this important debate and worked constructively on means to improve the transparency of clinical trial results disclosure. Servier was committed to such transparency and commended the ABPI's efforts in this area. Condemning companies in this way, under the ABPI Code, however, would unfortunately undermine this effort.

However, in so far as the PMCPA deemed that the ABPI Code applied and proceeded with the complaint, Servier responded to Clauses 1.8, 21, 2 and 9.

Servier provided the details for all the on-going and completed clinical trials examined by the ABPI for the purposes of the study and indicated which of those had a UK association. Whilst the ABPI Code did not apply to clinical trials which did not have a UK association, Servier had nevertheless provided details of those clinical trials if they were examined by the ABPI for the purposes of the study as per the PMCPA's request. Details of clinical trials conducted prior to 2008 were provided. Indeed, prior to 2008 there was no obligation on companies to disclose details relating to clinical trials under the ABPI Code. Companies were merely encouraged to disclose such information.

Therefore, in Servier's view, only those clinical trials that had a UK association and were conducted after 2008 fell within the scope of the present complaint. However, despite that fact, Servier nevertheless provided details of all trials examined by the ABPI for the purposes of its study, in the interests of co-operation.

Any broader request for information was not only outside the scope of the present complaint but would be burdensome and inappropriate. Servier was an international company with research facilities in different jurisdictions. Obtaining information concerning clinical trials which extended beyond those already examined by the ABPI, particularly where those clinical trials might have had no UK association, was a hugely burdensome exercise especially in the timeframe given and would result in an inefficient waste of resources.

#### **Clause 1.8**

The PMCPA had specifically asked Servier to comment on Clause 1.8 ie the jurisdictional aspect 'given the global nature of pharmaceutical research'.

Clause 1.8 stated: 'Pharmaceutical companies must comply with all applicable codes, laws and regulations to which they are subject'. It was clear from the supplementary information to Clause 1.8 that, if there was no UK link in terms of the activity, then the ABPI Code did not apply. As noted above, given the global nature of clinical research and in particular Servier's operations, it was clear that only a proportion of the clinical trials which were examined by the ABPI for the purposes of its study had any association with the UK. Servier provided information on those studies which had a UK association. The remainder were outside the scope of the present complaint and should be considered no further.

Depending on the clinical trial, different versions of the ABPI Code would apply. The current version of the ABPI Code referred both to the Joint Position on Disclosure and to the Joint Position on Publication, whereas the earlier versions of the Code referred only to the Joint Position on Disclosure (and even then, only in the supplementary information). In addition, and as developed below, earlier versions of the Code did not contain any obligation at all, but merely encouraged companies to disclose information relating to clinical trials. The obligation to disclose results of clinical trials only appeared therefore in the 2008 and subsequent codes of practice.

#### **Clause 21.3**

Servier had provided detailed information relating to all on-going and completed clinical trials examined by the ABPI for the purposes of the study. It was clear from the table in the study that only three studies carried out with UK involvement, completed after 2008, were found to be non-compliant with regards to disclosure. While Servier accepted that this was not necessarily in accordance with Clause 21.3, the broader context was relevant.

The first study (row 29 of Appendix 1) was completed in September 2011. This was a trial looking at a formulation different to the one authorised by the EMA and not on the market. The second trial (row 30) was completed in August 2011. A publication was currently in preparation. The third

trial (row 31) was completed in December 2008 and was due for imminent publication in early 2014.

In addition, Servier reminded the PMCPA of the rapidly changing environment (eg transparency was a live issue and the goal-posts changed as the debate moved forward) resulting in many changes and updates in both ABPI and international guidance over recent years. For example, the 2006 Code simply encouraged companies to comply with the Joint Position ie no requirement was incorporated into the ABPI Code as it was now. Whilst, the 2008, 2011 and 2012 Codes, required disclosure, they were less prescriptive than the current (Second 2012 Edition), merely stating in Clause 21.3 that 'Companies must disclose details of clinical trials' without stipulating how (although the supplementary information referred to the Joint Position on Disclosure of clinical trial results). The current ABPI Code set out important principles that Servier agreed should be adhered to, and as appreciated, this represented a challenge to industry as it raised issues of infrastructure and co-ordination for an international company, that Servier accepted must be addressed.

With reference to the Joint Position on Publication, the PMCPA should not ignore the difficulties associated with publication which were relevant to the public transparency debate. For example, it should be acknowledged that publication of a paper required a huge resource. There was also a certain element of publication bias which originated from journals and their editors: editors might also be reluctant to publish negative studies.

In conclusion, Servier submitted it explained the context of these instances of non-disclosure. In any event, as a result of the rapidly changing legal and self-regulatory environment Servier was currently in the process of considering its internal procedures and infrastructure and doing the utmost to implement this as soon as possible.

#### **Clause 9**

Clause 9 concerned the requirement to maintain high standards. Servier strongly refuted the alleged breach of Clause 9.

Servier was committed to achieving the highest standards with regards to the disclosure of clinical trial results. Reflective of the ever-changing environment as the debates moved forward in this area, Servier did not yet have comprehensive policies in place. In addition, to comply with the imminent update of EudraCT in 2014, Servier would take all necessary measures to ensure that all the regulatory requirements for clinical trial transparency would be met.

A breach of Clause 21.3 did not reflect a failure to maintain high standards; indeed it did not follow that every breach of the ABPI Code was a failure to maintain high standards. Servier had maintained high standards throughout: it had collaborated with the ABPI in relation to the study to provide

up-to-date information in order to help improve transparency. However, this was clearly a live issue and the goal-posts were changing as the transparency debate moved forward. It was not appropriate in the circumstances to hold Servier in breach of Clause 9 and as noted above, it would be counterproductive to any future transparency initiatives of the ABPI.

#### **Clause 2**

Servier submitted that Clause 2 was reserved for cases of particular censure. This was not such a case; it was not one of the breaches listed in the supplementary information to Clause 2, nor was it analogous. The arguments developed above explained why it would be counterintuitive to any future transparency initiatives to find Servier in breach of Clause 2 (and any other clauses). It would be highly ironic considering Servier's voluntary collaboration with the ABPI and unfair for a breach of Clause 2 to be ruled in circumstances where the ABPI did not intend to raise compliance issues. To condemn Servier would seriously deter companies from collaborating with the ABPI in the future and undermine the ABPI's efforts with regard to transparency, which was the very purpose of the study and article.

Servier respectfully requested that the PMCPA looked at the broader context of this complaint and the politically sensitive environment before taking any decision on this matter particularly in respect of Clauses 2 and 9.

#### **Conclusion**

Servier acknowledged at most a technical breach of Clause 21.3 if the PMCPA considered that the broader context of the complaint was not relevant and Servier's collaborative efforts with the ABPI were not taken into account. Servier strongly refuted a breach of either Clause 2 or 9 in any circumstances. However, in its view, the broader context of this matter could not be ignored and Servier requested that the PMCPA adjudicated this matter without condemnation of Servier and closed the matter entirely.

In a response to a request for further information, Servier confirmed that Valdoxan was first approved and commercially available in March 2009.

#### **GENERAL COMMENTS FROM THE PANEL**

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect,

agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superseded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

'Companies must disclose details of clinical trials.'

The relevant supplementary information stated:

**'Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superseded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'

The relevant supplementary information stated:

**'Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position

2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product

first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the





IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

#### **PANEL RULING IN CASE AUTH/2671/11/13**

The Panel noted the CMRO publication in that twelve evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 63%. Six studies completed before the end of 2012 had not been disclosed. The disclosure percentage at 31 January 2013 of trials completed before the end of January 2012 was 83%. A footnote stated that the undisclosed trials were in the process of being prepared for publication.

The Panel noted that Valdoxan was approved for use in Europe in February 2009. In response to a question whether this was when the product was first approved and commercially available anywhere in the world. Servier stated that the relevant date was March 2009. [See post consideration note].

The Panel was only concerned with studies which involved UK patients or involved the UK company. Two studies (25 and 26) which completed in September 2008 and April 2009 had, according to

Servier, not been disclosed within the timeframe. The Panel did not agree with Servier's submission that these studies had been disclosed very promptly thereafter. It appeared from the information provided by Servier that the abstracts for the studies were published in June 2010 and March 2011 with publication in 2011 and 2013 respectively.

The Panel noted that the relevant Code was 2008 and the Joint Position 2005. Servier should have disclosed the results for one study (Study 25) by March 2010 and the other study (Study 26) by April 2010. As the results were not disclosed within this timeframe Servier had not met the requirements of the Code. The Panel ruled a breach of Clause 21.3 of the 2008 Code as acknowledged by Servier. The Panel agreed with Servier that not every breach of Clause 21.3 would necessarily be a breach of other clauses of the Code, in particular Clauses 9.1 and 2. However, it considered that the delay in disclosure meant that high standards had not been maintained. A breach of Clause 9.1 was ruled. As the results had been disclosed the Panel considered that on balance there was no breach of Clause 2 and ruled accordingly.

The results of a further three studies (29, 30 and 31) which involved UK patients and completed in September 2011, August 2011 and December 2008 were still to be disclosed. The Panel considered that Servier, by not disclosing the results within 12 months of study completion (Study 30) or by one year after first approval (Study 31) ie by August 2012 and March 2010 respectively, the company had not met the requirements of the Code. The Panel ruled a breach of Clause 21.3 of the 2011 Code in relation to the study which completed in August 2011 (Study 30). The study which completed in December 2008 (Study 31) was ruled in breach of Clause 21.3 of the 2008 Code.

Study 29 completed in September 2011 and was carried out on a different formulation. The relevant Code was the 2011 Code and thus the Joint Position 2008 which stated that if trial results for an investigational product that had failed in development had significant medical importance, study sponsors were encouraged to post the results. The Panel was unsure whether the product had 'failed in development' or whether the results were of significant medical importance. Further companies were only encouraged to post results if possible. The complainant had not provided any details in this regard. The Panel considered that publication of such data was preferable, however failure to publish was not necessarily out of line with the Joint Position 2008. Thus the Panel ruled no breach of Clause 21.3 of the 2011 Code and consequently no breach of Clause 9.1 and 2.

The Panel noted that it now had to consider Clauses 9.1 and 2 with regard to Studies 30 and 31. It noted that the wording of Clauses 9.1 and 2 was the same in the 2008 Code as in the 2011 Code. The Panel noted that Servier knew from the CMRO publication that some of its trial data results had not been disclosed. The ABPI study was conducted between December 2012 and January 2013 but in the 9½

months that had elapsed between the end of the study and the receipt of this complaint, the company had not subsequently disclosed the missing data. Notwithstanding the company's submission that the missing data was being prepared for publication, the Panel considered that failure to disclose the data meant that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel also considered that failure to disclose meant that Servier had brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

The Panel noted there was no way of identifying from the list of 49 studies provided by Servier which were the remaining seven studies cited in the CMRO publication. If these studies had no UK involvement the matter did not come within the scope of the UK Code. If these studies had UK involvement but were completed before 5 January 2006 they would be exempted under the 2005 Joint Position. The Panel noted that the results from all studies, apart

from the three (29, 30, 31) considered above, had been disclosed. The Panel noted its dilemma and decided that the studies with no UK involvement did not come within the scope of the UK Code and therefore ruled no breach. The results of studies that completed before 5 January 2005 did not need to be disclosed. Thus the Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

[Post consideration note: Following notification of the Panel's rulings, Servier pointed out that Valdoxan was first approved and commercially available in the Ukraine in February 2007. The date of March 2009 related to its availability in the European Union. Servier decided not to appeal the Panel's rulings of breaches of Clauses 9.1 and 21.3 of the 2008 Code in relation to Study 25].

**Complaint received**                      **21 November 2013**

**Case completed**                         **11 April 2014**

# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v MERCK SHARP & DOHME

## Clinical trial disclosure (Brinavess, Victrelis and Sycrest)

An anonymous contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Brinavess (vernakalant hydrochloride), Sycrest (asenapine) and Victrelis (boceprevir).

The detailed response from Merck Sharp & Dohme is given below.

General detailed comments from the Panel are given below.

With regard to Sycrest, the Panel noted that eight of the evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 64%. The disclosure percentage at 31 January 2013 of trials completed before the end of January 2012 was 100%.

The Panel noted Merck Sharp & Dohme's submission that Sycrest was first approved and commercially available around 13 August 2009. For studies completed before that date the 2008 Code applied and hence the Joint Position 2005 was relevant.

The Panel noted that one study completed in 2005. It was not clear when the results were posted or whether there was UK involvement. The study was a preference study of flavouring. The Panel considered that this study could be considered an exploratory trial and thus the results did not need to be disclosed under the Joint Position 2005 unless they were deemed to have significant medical importance and might have an impact on product labelling. The Panel was unsure whether the results were of significant medical importance. The complainant had not provided any details in this regard. The Panel considered that publication of such data was preferable however on the information before it there appeared to be no need to disclose the trial results under the 2008 Code. The Panel ruled no breach of the 2008 Code including Clause 2.

The Panel noted Merck Sharp & Dohme's submission that the results of a study completed in December 2007 were presented at a meeting in June 2008 and posted in December 2009 immediately after the merger with Schering-Plough. The trial had UK sites. The Panel noted that the trial was on an indication unlicensed in the UK but schizophrenia was licensed in the US so the trial was covered by Joint Position 2005. The trial needed to be disclosed within one year of first approval and commercial availability of Sycrest ie before August 2010. On the information submitted by Merck Sharp & Dohme it appeared that this had been done as the study was posted in December 2009. The Panel therefore ruled no breach of the 2008 Code including Clause 2.

An anonymous contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration

and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for each product. The data for Brinavess (vernakalant hydrochloride), Sycrest (asenapine) and Victrelis (boceprevir) were as follows:

### Brinavess

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	2	0	2	1	50%	2	1	50%
Phase III	7	1	6	5	83%	6	6	100%
<b>TOTAL</b>	<b>9</b>	<b>1</b>	<b>8</b>	<b>6</b>	<b>75%</b>	<b>8</b>	<b>7</b>	<b>88%</b>

### Sycrest

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	10	7	3	1	33%	3	3	100%
Phase III	19	0	19	13	68%	19	19	100%
<b>TOTAL</b>	<b>29</b>	<b>7</b>	<b>22</b>	<b>14</b>	<b>64%</b>	<b>22</b>	<b>22</b>	<b>100%</b>

### Victrelis

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	4	1	3	2	67%	3	2	67%
Phase III	5	1	4	4	100%	4	4	100%
<b>TOTAL</b>	<b>9</b>	<b>2</b>	<b>7</b>	<b>6</b>	<b>86%</b>	<b>7</b>	<b>6</b>	<b>86%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluable	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluable trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluable trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Merck Sharp & Dohme.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Merck Sharp & Dohme, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Merck Sharp & Dohme stated that it interpreted the complaint as being based on the CMRO publication. The complaint did not address the registration of clinical trials but focused on alleged non-disclosure or non-timely disclosure of results. Merck Sharp & Dohme therefore confined its comments to that matter.

The objective of the CMRO publication was to produce a quantitative benchmark of disclosure rates for industry so that the ABPI and its member companies could better understand the current landscape. The ABPI used the study to highlight the positive trend of increasing levels of disclosure for

industry-sponsored clinical trials, and described the study as an important milestone in demonstrating the improvements in transparency made by the industry over many years.

Merck Sharp & Dohme further noted:

- The study did not limit assessment to a single registry or to prevailing laws or requirements in specific territories and counted either posting of summary results in a clinical trial registry or publication in the scientific literature as evidence of disclosure.
- The 12 month timeframe might not meet that set out in the IFPMA Joint Position as the latter started the clock at first global marketing authorisation which was not necessarily the US or EU marketing authorisation as in the CMRO publication.
- Disclosure as marked in CMRO publication might not meet that of prevailing laws or requirements in specific territories as the publication/disclosure might not contain all the necessary information on primary and secondary endpoints etc as the CMRO publication was binary - disclosed or not.

Merck Sharp & Dohme stated that as a company fully involved with the ABPI, it supported this initiative as part of the industry's journey to greater transparency. It submitted that the CMRO publication had applied standards that were generally accepted today, but it was important that its actions were judged by the standards applicable at the relevant time, not with hindsight.

### Merck Sharp & Dohme Publication Policy

Merck & Co Inc, the parent company had a publicly stated policy on publication of clinical trial data which indicated its commitment to transparency – this policy was introduced in 2008 and had been updated. Merck's policy for timely publication of clinical trial data was at <http://www.merck.com/research/discovery-and-development/clinical-development/Merck-Guidelines-for-Publication-of-Clinical-Trials-and-Related-Works.pdf>.

### Jurisdiction – Timing perspective

Merck Sharp & Dohme noted that the CMRO publication included studies on its products that were completed as long ago as 2002. The studies included in the complaint relating to Merck Sharp & Dohme products included studies completed as far back as 2005. Policies on clinical trial transparency and publication had evolved, for example the 2006 Code contained no mandatory provisions relating to the publication of clinical trials. Clause 21.3 of the Second 2012 Edition of the Code referred to the 2010 IFPMA Joint Position, Clause 21.3 of the 2011 Code referred to the 2008 Joint Position and Clause 21.3 of the 2008 Code referred to the 2005 Joint Position. The CMRO publication applied standards that were generally accepted today, but it was important that Merck Sharp & Dohme's actions be judged by the standards applicable at the relevant time and not by today's standards and with hindsight.

### Jurisdiction – International perspective

Merck Sharp & Dohme acknowledged that custom and practice in applying the Code had traditionally

extended to activities of the UK operating company (wherever those activities took place) or, in the case of a subsidiary company with its headquarters outside the UK, to activities of the company's global headquarters insofar as they were directed at UK health professionals. Application of this custom and practice would suggest that publication of studies that took place entirely outside the UK was not the responsibility of Merck Sharp & Dohme and therefore not subject to PMCPA jurisdiction. The only consideration in this regard was whether the granting of a pan-European marketing authorization amounted to directed at UK health professionals. Merck Sharp & Dohme submitted that the granting of a marketing authorisation to 26 countries was not specifically directed at any one of them and was insufficient to bring matters into scope of the Code, without specific UK involvement.

#### **Jurisdiction – Multi-company perspective**

Merck Sharp & Dohme stated finally, as noted below, it was often the case that several entities (in this case, up to five) had had responsibility for a product during the various stages of its development. The product moved from one company to another by licensing or by acquisition. Whilst each company must do due-diligence when it acquired a product, it was evidently impossible to correct a time-sensitive error retrospectively. For the criterion of publication within 12 months therefore, it is seemed inappropriate to hold a company responsible for something that took place prior to its involvement in the product's development and which could not be corrected post hoc.

#### **Response to the complaint**

The CMRO publication identified four products for which Merck Sharp & Dohme received a marketing authorisation in the time period studied, namely Elonva, Victrelis, Brinavess and Sycrest. Each product was given two scores, one relating to the ability to find publication within 12 months of study completion, the other relating to the ability to find publication at the arbitrary cut-off date of 31 January 2013.

Elonva scored 100% for each metric, and had not been included in the complaint.

For each of the remaining products, the authors provided Merck Sharp & Dohme with a list of 'missing' studies asking for comments. Many of those comments were subsequently provided as footnotes to the information in the electronic form of the publication.

#### **1 Brinavess**

The CMRO publication indicated that seven out of eight studies were published. The footnote in the CMRO publication indicated the company's response: The undisclosed Brinavess trial was not sponsored by Merck Sharp & Dohme. It was a Phase II study, carried out by Cardiome Pharma Corp Inc. There was no Merck Sharp & Dohme involvement nor UK involvement. The study completed in August 2006. The study pre-dated the licensing agreement

between Cardiome and Merck Sharp & Dohme in April 2009. Merck Sharp & Dohme stated that the results had been made public. This was dated June 2012.

The study was included in the dataset used by Merck Sharp & Dohme in the EU marketing authorization application, but the product was never launched in the UK, never made available to UK physicians and the marketing authorization had subsequently returned to Cardiome.

Merck Sharp & Dohme submitted that it had no case to answer under the ABPI Code. The responsibility for publishing data resided with Cardiome, the sponsor of the study. It therefore rejected the allegation of a breach of Clauses 21.3 and 9.

In response to a request for further information Merck Sharp & Dohme provided more information about the licensing agreement with Cardiome Pharma.

Secondly, the Panel requested data relating to the timeliness of publication of the Brinavess study portfolio. Data from the CMRO publication indicated that eight evaluable Brinavess studies were found of which two were identified as not published. The details were as follows:

#### **NCT00476112**

Merck Sharp & Dohme stated that this study was listed as having completed in March 2008, although the clinicaltrials.gov entry indicated a completion date of September 2004. The sponsors of the study were listed as Cardiome Pharma, with Astellas Inc as collaborators.

This study was completed long before Merck Sharp & Dohme's involvement with the product in 2009, and could not have been published by Merck Sharp & Dohme within one year of completion. Once Merck Sharp & Dohme had acquired rights to the product, publication was prompt. There was no involvement of Merck Sharp & Dohme in the UK, nor, according to the clinicaltrials.gov entry, any UK investigators.

Merck Sharp & Dohme submitted that it should not be held responsible for the actions of other companies five years prior to its involvement in a product and therefore refuted any accusation of a breach of the Code.

#### **NCT00267930**

Merck Sharp & Dohme stated that this study related to Brinavess tablets (not the injection), a product which was dropped from development. In that sense, it had been included in the CMRO publication in error.

This study was completed long before Merck Sharp & Dohme's involvement with the product in 2009, and could not have been published by Merck Sharp & Dohme within one year of completion. There was

no involvement of Merck Sharp & Dohme in the UK, nor, according to the clinicaltrials.gov entry, any UK investigators.

Merck Sharp & Dohme submitted that it should not be held responsible for the actions of other companies five years prior to its involvement in a product and therefore refuted any accusation of a breach of the Code.

## 2 Sycrest

The CMRO publication indicated that all 22 clinical trials of Sycrest included in the EPAR had been published. However, only 14 out of the 22 had been published within 12 months of study completion.

Sycrest (asenapine) was a product of collaborative research between Organon Laboratories NV and Pfizer Inc. Organon Biosciences BV (the parent company of Organon Laboratories NV) was acquired by the US company Schering Plough Corporation in 2007. Schering Plough Corporation

was subsequently acquired by means of a reverse takeover by Merck and Co. Inc. in 2009. Organon Laboratories Limited, the UK trading subsidiary of Organon Biosciences BV, remained an independent trading company until its assets were finally acquired by Merck Sharp & Dohme in August 2013.

Sycrest was studied for both bipolar depressive illness (manic depressive illness) and for schizophrenia. The European marketing authorization was only for bipolar illness (not for schizophrenia). The product had subsequently been licensed to Lundbeck.

All 22 studies had previously been disclosed publicly. Many of these were on the clinicaltrials.org web page which was hosted by PhARMA but discontinued when clinicaltrials.org was established by the FDA/NIH. The study reports were all available on the merck.com website. Merck Sharp & Dohme gave details of each of the 8 studies disclosed later than 12 months from study completion.

Number	Study Title	Comment
1	An Acceptability Study of Unflavored Asenapine Versus Raspberry Flavored Asenapine in Stable Patients With a Psychotic Disorder	This study completed in 2005, sponsored by Organon NV. It was not a safety or efficacy study of the product but a preference study of flavouring. Patients received only six doses of medication. The study pre-dated the IFPMA 2010 policy which only covered Phase III trials and trials of 'significant medical importance'. This study was in neither of those categories. It was publicly disclosed on merck.com
2	A Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Sublingual Asenapine in a Pediatric Population With Schizophrenia or Bipolar I Disorder	This study completed in 2011. It was a pharmacokinetic study in a paediatric population; asenapine was NOT licensed for use in paediatric patients but the data were included in the SPC. The results were also available on clinicaltrials.gov which was dated 20 November 2012 for first results received.
3	A Multicenter, Randomized, Double-Blind, Flexible-Dose, Long-Term Extension Trial of the Safety and Maintenance of Effect of Asenapine Using Olanzapine Positive Control in Subjects Who Complete Protocols 041021 or 041022.	This study completed in 2007. The trial results were initially posted on clinicaltrials.org which was subsequently discontinued. The results were then posted on the Merck & Co. company website.
4	A Phase 3, Randomized, Placebo-Controlled, Double-Blinded Trial Evaluating the Safety and Efficacy of Asenapine in Subjects Continuing Lithium or Valproic Acid/Divalproex Sodium for the Treatment of an Acute Manic or Mixed Episode	This study was initiated by Pfizer in 2005, transferred to Organon in 2007 and subsequently to Schering Plough in 2008. The study completed in 2007, prior to the acquisition of Schering Plough by Merck Sharp & Dohme. Ensuring publication within 12 months was therefore not possible for Merck Sharp & Dohme, but the publication was available at the cut off time used for the CMRO publication.
5 – 8		These studies were initiated by Organon NV or Organon in collaboration with Pfizer and completed in 2006 or 2007. They had been published in full and did not relate to the UK licensed indication. The results were posted on the Merck.com website.

In summary, Merck Sharp & Dohme submitted that Sycrest had had a complex gestation, with five companies involved in its development and launch. All studies used to support the marketing authorization had been published. Some of these, generally relating to different pharmaceutical preparations, pharmacokinetics in sub populations or in the UK unlicensed indication of schizophrenia (rather than bipolar disorder) were not published within 12 months of completion. These studies were

generally carried out in the 2005-2007 timeframe, prior to the Joint Position.

Following the acquisition of Schering Plough Corporation by Merck & Co Inc. all of the studies had been published prior to clinical availability of the product in the UK. For these reasons, Merck Sharp & Dohme rejected the alleged breach of Clauses 21.3 or 9.



In response to a request for further information, Merck Sharp & Dohme referred to the following:

### **Sycrest Study NCT01206517**

Merck Sharp & Dohme stated that this study was a phase I clinical pharmacology study in paediatric patients. It did not address efficacy or safety as its primary objective. This was only conducted in the US. Merck Sharp & Dohme in the UK had no involvement.

Sycrest was not licensed for use in paediatric patients, only in adults. The data did not therefore relate directly to the licensed indication. Nonetheless, the data were included in the SPC.

The completion date in the CMRO publication and in clinicaltrials.gov was August 2011. The results were published in clinicaltrials.gov, dated 20 November 2012, ie 15 months after completion.

Merck Sharp & Dohme submitted that this publication was consistent with the letter and the spirit of the 2010 Joint Position, when considering that the subject matter was not of high medical or scientific importance and the data were published within 18 months of the completion. The criteria used by the CMRO publication authors were different. Merck Sharp & Dohme did not believe that categorising this as a 'non-timely publication' using current day expectations retrospectively amounted to a breach of the Code when judged by the standards of the time.

In response to a further request for additional information Merck Sharp & Dohme reiterated that asenapine had had a complex gestation, it was a product of research by Organon NV initially in collaboration with Pfizer. Organon NV was acquired by Schering Plough Corp. Inc. in November 2007, which in turn merged with Merck & Co Inc. This was announced in principle in March 2009 but implementation in practice as the end of 2009. In Europe, the product was then licensed to Lundbeck for commercialisation. As such, a variety of sponsors had been responsible for the clinical development at different times.

Of the eight asenapine studies, the Panel asked for specific information on six. The dates of completion and the dates of disclosure according to the legacy Organon databases that Merck Sharp & Dohme had access to were provided. Merck Sharp & Dohme also obtained information from Lundbeck, the company which now promoted Sycrest. It was possible that disclosure might have taken place even earlier, for example as a conference presentation by the investigators, but Merck Sharp & Dohme was unable to confirm this from the data available.

Only one of the six studies had UK sites. This study recruited patients from May 2005 to June 2007 and completed in December 2007. Results were presented at the 1st Schizophrenia International Research Society Conference, Venice, Italy, June 21-25, 2008, and posted in December 2009 (immediately after the merger) to the (now defunct) PhRMA

clinicaltrialresults.com website. They were then transferred to the merck.com website following the discontinuation of the PhRMA website. Full peer reviewed publication details were also given.

As previously noted, Merck Sharp & Dohme's involvement in the product began in 2009 with the merger with Schering Plough. It was therefore not possible for Merck Sharp & Dohme to influence time-sensitive activities prior to this time.

As noted above, this schizophrenia study did not relate to the UK indication of bipolar disorder and that the one-year definition used in the CMRO publication to define 'timely publication' was not the standard of the day in 2007.

Copies of conference abstracts relating to each study, which represented the first disclosure were provided.

Other activities of Organon NV and to what extent Merck Sharp & Dohme in the UK should be held responsible was considered in a previous case, Case AUTH/2363/10/10, Merck Sharp & Dohme noted that in this case which related to educational websites and not to clinical research, the Appeal Board commented '...in the light of the exceptional circumstances of this case, arising from successive mergers and acquisitions, Merck Sharp & Dohme and Organon NV, although part of the same global company group, were not affiliates as referred to in Clause 24.2'.

Merck Sharp & Dohme stated that it had disclosed the results of the asenapine clinical trial program as soon as it was practical to do so post-merger, consistent with Merck Sharp Dohme's policies and commitment to clinical trial transparency. Merck Sharp & Dohme denied any breach of the Code.

### **3 Victrelis**

The CMRO publication indicated that one of the seven studies was not published at the time of the analysis. The Merck Sharp & Dohme response was given in the footnote.

'The trial report was submitted to the FDA within 12 month timeframe and was in the FDA review cycle. The trial results have now been made available on Clinicaltrials.gov by the FDA.'

The study was sponsored by Schering Plough and no UK involvement was known. The study completed in December 2011 and the results were published on 5 February 2013.

Merck Sharp & Dohme stated that this study showed a completion date of December 2011. Results were sent by Merck Sharp & Dohme to the US NIH [National Institutes of Health] for posting on 6 December 2012. The record was updated on 5 February 2013. In other words, Merck Sharp & Dohme had submitted the data for posting within 12 months but they were not posted by NIH until 5 days after the CMRO publication cut-off, and the trial was therefore classified as not disclosed.

In summary, this one study was submitted on time for disclosure within 12 months but because of delays in the validation process performed by NIH before posting, the publication was delayed by a few weeks. Merck Sharp & Dohme acted in good faith in submitting the data for disclosure and did not believe that this short administrative delay was sufficient to amount to a breach of Clauses 21.3 or 9.

### Summary

Merck Sharp & Dohme's submitted that its position on prompt publication was publicly stated and it strove to ensure that all activities were carried out consistent with these policies. The CMRO publication showed that the pharmaceutical industry has set itself targets, and was making great progress in achieving those targets.

Taking all four products in the CMRO publication 52 out of 54 studies had been publicly disclosed at the cut-off point. One had already been submitted and was disclosed a few weeks later. The second was a non-Merck Sharp & Dohme study and the responsibility lay elsewhere. These were the actions of a company committed to improved clinical trial transparency. Having considered all of the facts, the complex and changing nature of the data and pharmaceutical companies in control of the data, Merck Sharp & Dohme rejected the allegation of breaches of Clauses 21.3 and 9. It therefore followed that it rejected the accusation of a Clause 2 breach.

The data requested by PMCPA were extensive and Merck Sharp & Dohme believed it had provided sufficient supporting information to address the complaint. It had not provided all the data requested, such as a list of all countries worldwide in which each of the products was licenced. If PMCPA considered these essential, in reaching a decision Merck Sharp & Dohme suggested that it should be given opportunity to submit further information.

In response to a request for further information Merck Sharp & Dohme stated that the first regulatory authorisation for Sycrest was 13 August 2009 (US), Victrelis, 13 May 2011 (US) and Brinavess, 1 September 2010 (EU). The dates of commercial availability were shortly after the authorisation date in these markets.

### GENERAL COMMENTS FROM THE PANEL

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year

of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant

that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

*'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13.

In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For

trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

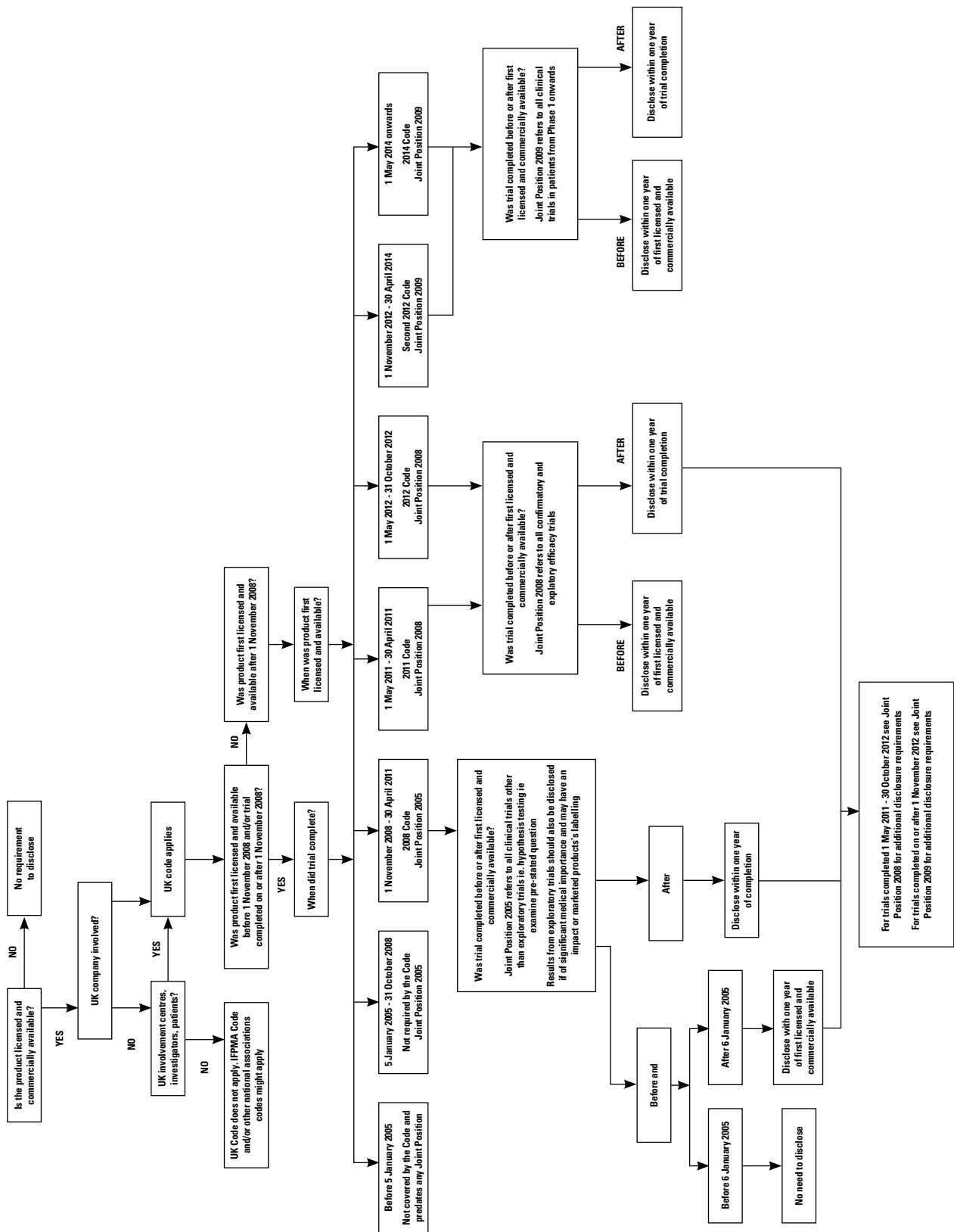
The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to

# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results



be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a

number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *de facto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

#### **PANEL RULING IN CASE AUTH/2672/11/13**

The Panel noted Merck Sharp & Dohme's submission regarding the industry's move to greater transparency. It considered that this was reflected in the establishment and development of the Joint Positions and the inclusion and development of requirements in the ABPI Code and other codes. In reaching any decision the Panel always took into account the dates of the codes and other relevant documents.

The Panel noted that Merck Sharp & Dohme submission that some studies published in 2005-2007 were prior to the first Joint Position (published on 6 January 2005) and was clear that the results of relevant clinical trials which completed after 6 January 2005 were to be disclosed. The Panel noted that as set out above the date a product was first approved and commercially available would determine which Joint Position applied and thus whether studies completed between 2005 and 2007 needed to be published.

The Panel noted Merck Sharp & Dohme's comments about marketing authorisations. It did not consider

that whether a product had a UK marketing authorization or not was relevant to the need to publish. As set out above the relevant factors were whether the trial was run by the UK company or had UK involvement.

The Panel considered each product separately.

## 1 Brinavess

The Panel noted that two of the evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 75%. One study completed before the end of January 2012 had not been disclosed. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 88%. A footnote explained that the undisclosed trial was not sponsored by Merck Sharp & Dohme; it was sponsored by Cardiome.

The Panel noted that both studies were sponsored by Cardiome and not Merck Sharp & Dohme. It appeared from the information provided by Merck Sharp & Dohme that the results for one study were disclosed in June 2012 and that the other was not on the licensed presentation. The Panel considered that as far as Merck Sharp & Dohme was concerned the matter did not come within the scope of the Code and therefore ruled no breach.

## 2 Sycrest

The Panel noted that eight of the evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 64%. The disclosure percentage at 31 January 2013 of trials completed before the end of January 2012 was 100%.

The Panel considered that Merck Sharp & Dohme was responsible under the Code for publication of Organon and Schering Plough studies.

The Panel noted Merck Sharp & Dohme's submission that Sycrest was first approved on 13 August 2009 and became commercially available shortly thereafter. For studies completed before that date the 2008 Code applied and hence the Joint Position 2005 was relevant.

The Panel noted that study one completed in 2005. It was not clear when the results were posted or whether there was UK involvement. The study was a preference study of flavouring, The Panel considered that this study could be considered an exploratory trial and thus the results did not need to be disclosed under the Joint Position 2005 unless they were deemed to have significant medical importance and might have an impact on product labelling. The Panel was unsure whether the results were of significant medical importance. The complainant had not provided any details in this regard. The Panel considered that publication of such data was preferable however on the information before it there appeared to be no need to disclose the trial results under the 2008 Code. The Panel ruled

no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

Another study completed in 2011 but was a pharmacokinetic study for an unlicensed indication. The Panel noted Merck Sharp & Dohme's submission that this study was on an unlicensed population and the data were included in the summary of product characteristics. In addition, it appeared the results were posted on clinical trials.gov in November 2012. Merck Sharp & Dohme submitted there was no UK involvement. The Panel considered that as there was no UK involvement the matter did not come within the scope of the Code and therefore ruled no breach.

The Panel noted Merck Sharp & Dohme's submission that five of the remaining six studies had no UK involvement identified and that the trial results had been disclosed. The Panel considered that as there had been no UK involvement the matter did not come within the scope of the Code and therefore ruled no breach.

The Panel noted Merck Sharp & Dohme's submission that the final study completed in December 2007. Results were presented at a meeting in June 2008 and posted in December 2009 immediately after the merger. The trial had UK sites. The Panel noted that the trial was on an indication unlicensed in the UK but schizophrenia was licensed in the US so the trial was covered by Joint Position 2005. The trial needed to be disclosed within one year of first approval and commercial availability of Sycrest ie before August 2010. On the information submitted by Merck Sharp & Dohme it appeared that this had been done as the study was posted in December 2009. The Panel therefore ruled no breach of Clause 21.3 and consequently Clauses 9.1 and 2 of the 2008 Code.

## 3 Victrelis

The Panel noted that one of the evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 86%. The disclosure percentage at 31 January of trials completed before the end of January 2012 was 100%. A footnote stated that the report was submitted to the FDA within the 12 month timeframe and was in its review cycle and that the trial results had been made available on clinical trials.gov by the FDA.

The Panel noted that Victrelis was first approved and commercially available in May 2011. It also noted Merck Sharp & Dohme's submission that it did not know of any UK involvement in the study. The study completed in December 2011 and the results disclosed in February 2013. The Panel considered that as there was no UK involvement the matter did not come within the scope of the UK Code and therefore ruled no breach.

**Complaint received**                      **21 November 2013**

**Case completed**                              **20 March 2014**

# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v RECORDATI

## Clinical trial disclosure (Silodyx)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Silogyx (silodosin).

The detailed response from Recordati is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that one evaluable study had not been disclosed in the timeframe. The disclosure percentage was 75%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 100%.

The Panel noted Recordati's submission that it sponsored two of the trials listed in the CMRO publication. With regard to one study which

completed in July 2013 (last patient, last visit), the Panel ruled no breach of the Second 2012 Edition of the Code including Clause 2 as the study results did not need to be disclosed until July 2014.

The Panel noted Recordati submitted data to show that the last patient, last visit, for the open label phase of a second study was 4 January 2008 and a synopsis of the clinical study report was submitted to various groups (competent authorities, ethics committees, investigators) between 22 September and 15 October 2008. An abstract was published in April 2010 and full publication (Chapple *et al*) was in November 2010.

The Panel noted Recordati's submission regarding the various dates of the various marketing authorizations. Silodosin twice daily was first approved for BPH in January 2006 (Kissei Pharmaceuticals in Japan). Silodosin once daily was first approved in October 2008 (Watson Pharmaceuticals, US). Recordati's version – Silodyx was approved for once daily use in January 2010 and first marketed in Germany in June 2010.

The Panel considered that it could be argued that the date a product was first approved and commercially available was not brand specific if there were a number of different brand names for the same product as for silodosin. The Panel noted, however, that the joint positions referred to maintaining protection for intellectual property rights. Further it was not clear whether the reference to first approved and commercially available was medicine specific or company specific.

The Panel considered that it could be argued that Recordati's second study completed after silodosin was first approved and commercially available (January 2006).

However, the Panel noted that the date of the last patient, last visit, 4 January 2008, and the date of the synopsis of the clinical study report, 22 September 2008 were both before there were any disclosure requirements in the Code. The matter was not covered by the 2006 Code and as such there could be no breach of it. Thus the Panel ruled no breach of the 2006 Code including Clause 2.

The Panel noted its ruling above. In addition it noted that if the relevant date of the first approval and commercial availability was company specific, ie the date of Recordati's product marketing authorization (June 2010), then the matter would be covered by the 2008 Code and the trial results would need to be disclosed by June 2011, which had happened.



An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European

Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

## COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for each product. The data for Silogyx (silodosin) were as follows:

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	2	2	0	0	0%	2	2	100%
Phase III	4	0	4	3	75%	4	4	100%
<b>TOTAL</b>	<b>6</b>	<b>2</b>	<b>4</b>	<b>3</b>	<b>75%</b>	<b>6</b>	<b>6</b>	<b>100%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluative	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluative trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluative trials which were fully disclosed

completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Recordati.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Recordati, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Recordati noted that the CMRO publication reviewed 53 new medicines authorised by the European Commission under the centralised procedure during the three years 2009 – 2011, and assessed whether all completed company-sponsored clinical trials conducted in relation to such products had been

published on a registry or in the scientific literature either (a) within 12 months of the later of the first regulatory approval or trial completion or (b) by 31 January 2013 (the end of the survey). The authors found that, of the studies considered, 77% had results disclosed by 12 months and by 31 January 2013, this figure had increased to 89%. The article did not name or otherwise identify the trials which comprised the 33% where results had not been disclosed within 12 months.

With respect to silodosin (Silodyx), the data provided to Recordati S.p.A. by the authors indicated that 13 clinical trials had been identified (three Phase II, four Phase III, four Phase IV and two observational prospective studies). Two of the identified studies had been sponsored by Recordati Industria Chimica e Farmaceutica S.p.A. (doing business also as Recordati S.p.A.): one of these studies had not yet been completed and was not therefore considered; the remaining study completed in 2008, but, according to the CMRO publication, was not published until after the 12 month period specified. The CMRO publication did not suggest that any of the studies relating to silodosin had been sponsored by Recordati Pharmaceuticals Ltd.

Silodosin was an  $\alpha$ -adrenoceptor antagonist originated by Kissei Pharmaceutical (Japan) for benign prostatic hyperplasia (BPH). It was first approved in Japan on 23 January 2006 (International Birth Date). Kissei was the marketing authorization holder of Urief in Japan, where it was administered twice daily.

As per contractual agreements with Kissei, other companies were responsible for the clinical development and subsequent marketing of silodosin in their territories, in particular:

- The US where silodosin had been developed for use once daily by Watson Pharmaceuticals (now Actavis Inc.), which marketed the product as Rapaflo (approved by the FDA in October 2008).
- In the Republic of Korea clinical trials had been performed by JW Pharmaceutical, which marketed silodosin as Thrupas.
- Recordati S.p.A had been responsible for the clinical development programme in Europe. Recordati Ireland Ltd had been granted two marketing authorizations for silodosin (Silodyx, Urorec) by the European Commission under the centralised procedure on 29 January 2010. Silodosin was first marketed in the EU (Germany) in June 2010. Other national marketing authorizations had been granted to Recordati or to Recordati licensees in other non EU countries. The list of countries where silodosin was presently authorised under the name of Recordati or under the name of a Recordati licensee was provided.
- Silodosin was not marketed in the UK by Recordati Pharmaceuticals Ltd, Recordati Ireland Ltd or Recordati S.p.A. or any other company of the Recordati group.

Details of the clinical trials conducted in relation to silodosin were provided.

As indicated to Recordati by the authors of the CMRO publication, only two of these trials were sponsored by Recordati (both by Recordati Industria Chimica e Farmaceutica S.p.A). Recordati stated that its response did not consider or comment on silodosin trials sponsored by companies outside the Recordati group.

With respect to the two studies sponsored by Recordati Industria Chimica e Farmaceutica S.p.A, the approach to publication was determined by the Recordati standard operating procedure (SOP) 06SC01R05 'Standard format of a Recordati clinical study protocol and procedures for its internal approval'. Accordingly, at the end of a study, results were communicated to investigators, ethics committees and competent authorities and, with the exception of Phase I studies, were published.

**Study KMD3213-IT-CL 0215 (EudraCT No 2005-005665-11; ClinicalTrials.gov Identifier: NCT00359905), an international, randomized, double-blind, placebo- and active-controlled Phase III clinical trial performed in Europe, with a 9 month open label extension period (completed)**

This trial was conducted at 72 sites in 11 European countries, of which 5 sites were located in the UK (2 additional UK sites did not recruit any patient). 1228 patients with benign prostatic hyperplasia were enrolled, of whom 18 were recruited in the UK. The trial was included on the public registry Clinicaltrials.gov in August 2006.

The results of the double-blind placebo and active controlled phase were first presented in abstract form at the EAU Congress 2010 (Eur Urol Suppl. 2010 April; 9 (2): 313) and then fully published (Eur Urol. 2011; 59 :342-52. Epub 2010 Nov 10).

Data related to the open label extension phase were included in a review on silodosin in 2011 (Curran MP. Silodosin. Treatment of the sign and symptoms of benign prostatic hyperplasia. Drugs 2011; 71: 897-907) and a full publication was in preparation.

**Study KMD 3213 IT-CL 0376 (EudraCT No 2011-000045-20; ClinicalTrials.gov Identifier: NCT01757769), an international, open-label, single-arm, Phase IV clinical trial (not yet completed)**

The trial, included in Clinicaltrialsregister.eu in March 2011, was not yet completed (Last Patient Last Visit on July 2013, clinical study report in preparation). In circumstances where this trial had not been completed and did not form part of the assessment by the authors. Recordati did not comment on it further.

**The complaint against Recordati Pharmaceuticals Ltd**

## **1 Applicability of the UK Code**

Recordati submitted that Recordati Pharmaceuticals UK did not appear to fall within the definition of 'company', provided by Clause 1.8 and its supplementary information:

'[...] Activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European country as well as the national code of the country in which the activities take place or the materials are used. [...]

By 'company' is meant any legal entity that organises or sponsors promotion which takes place within Europe, whether such entity be a parent company (e.g. the headquarters, principal office, or controlling company of a commercial enterprise), subsidiary company or any other form of enterprise or organisation.[...]

Recordati Pharmaceuticals UK was a subsidiary of Recordati S.p.A which was based in Milan (Italy). Recordati Pharmaceuticals UK did not have an active sales force and was not involved in the organisation or the sponsoring/promotion of medicines anywhere in Europe. In particular, Recordati Pharmaceutical Ltd did not participate in any of the promotional activities listed at Clause 1.2. The activities of Recordati Pharmaceuticals Ltd were limited to: regulatory activities (maintenance of current UK marketing authorizations), pharmacovigilance activities and product distribution activities. In these circumstances, the complaint directed towards Recordati Pharmaceuticals Ltd appeared inappropriate.

The only completed trial of silodosin sponsored by a company in the Recordati group was sponsored by Recordati Industria Chimica e Farmaceutica S.p.A, the parent company of Recordati Pharmaceuticals Ltd. Recordati Pharmaceuticals Ltd was not involved in the trial and had no control over publication of the data. While five study sites were located in the UK, the contribution of the UK to the number of trial participants was minimal.

Recordati submitted that it was significant that the ABPI's 'Best Practice Model for the Disclosure of Results and Transparent Information on Clinical Trials' was directed towards 'ABPI members and all industry sponsors of clinical trials who are required to publish their trial results ....' and did not suggest that the model applied to subsidiaries such as Recordati Pharmaceuticals Ltd, which did not sponsor the relevant trial.

In these circumstances, Recordati submitted that to impose responsibility for publication of trial data on the UK company was unreasonable and impractical. Trials were conducted on a global basis and many factors might influence the date of publication of the associated trial data. A local affiliate (particularly one, such as Recordati Pharmaceutical Ltd, that had played no part in the relevant trial) could have no control over publication of data or responsibility where there was delay.

### **Clause 21.3**

The complainant referred to the CMRO publication, as grounds for his/her complaint. This publication stated with regard to the assessment methodology that,

'Disclosure was assessed and recorded for two time points: firstly, within 12 months (of either the first regulatory approval by either the EMA or FDA [if applicable], or the date of completion of the trial if after the first approval); and secondly, at 31 January 2013, the end of the study period. While presentations at international conferences often represent the first public disclosure of results, there are no comprehensive and publicly available sources for reliably identifying all conference abstracts. Therefore we made no additional attempt to locate conference abstracts other than the routine search of PubMed, but if their existence was brought to our attention by the European marketing authorisation holder, abstracts published in journal supplements were accepted as valid evidence of disclosure of the trial and its results for the purely quantitative purpose of this study'.

Recordati submitted that the conclusions of the CMRO publication that the relevant Recordati study failed to comply with appropriate reporting requirements (whether in accordance with Clause 21.3 or with the joint position), were incorrect and that, in fact, Study KMD3213-IT-CL 0215 was properly reported.

Clause 21.3 of the 2008 Code provided no further details about what details should be disclosed and when; however the supplementary information to Clause 21.3 indicated that 'this clause requires the provision of details about ongoing clinical trials .... and completed trials for medicines licensed for use in at least one country'. Reference was made to the Joint Position 2005 as providing further information, but (in contrast to the Second 2012 Edition of the Code) there was no suggestion that compliance with the provisions of the Joint Position constituted a binding obligation and any construction of Clause 21.3 to impose such obligations in the absence of clear direction, would be unreasonable and unfair.

As described above, the results from Study KMD3213-IT-CL 0215 were published in abstract form at the EAU Congress 2010 and then in full in November 2010. The results of the open label extension phase were included in a review on silodosin in 2011 and a full publication was in preparation. It was Recordati's position that such publication satisfied the requirements of Clause 21.3.

However, whilst Recordati did not believe this was required under the 2008 Code, it believed that Recordati's actions were, in any event, also consistent with the principles underlying the joint position. On 29 November 2013, the ABPI, Clinical Development Manager, sent Recordati an email, on behalf of the authors, attaching an excel file, used for the purposes of the publication; this stated that the above Recordati study had missed compliance by 13 months. This conclusion was based on the Joint Position and arose from the use of 9 October 2008 as the first date of regulatory approval, which preceded publication of the results of Study KMD3213-IT-CL 0215 by more than 12 months. However, 9 October 2008 was the date of FDA approval obtained by Watson Pharmaceuticals, an independent company

unrelated to Recordati. Recordati Ireland Ltd in fact obtained its first approval for silodosin in the EU in January 2010; the publication of the abstract for the study was in April 2010 and the full publication of the double blind Phase occurred in November 2010 (well within 12 months of the date of approval). The publication of the open label extension was performed only later (2011); however these data were included in the EPAR from January 2010 and therefore in the public domain.

Recordati thus considered that reporting by Recordati Industria Chimica e Farmaceutica S.p.A was consistent with the Code and the principles of the joint position.

#### **Clause 2**

In the context of the submissions above, in particular the lack of any involvement by Recordati Pharmaceuticals Ltd in the relevant trial and that the trial was reported in accordance with the time limits under Clause 21.3 in any event, Recordati submitted that there had been no activity by Recordati Pharmaceuticals Ltd that warranted particular censure and that there had been no breach of Clause 2.

#### **Clause 9**

Recordati Pharmaceuticals UK maintained high standards at all times. Again, in the context of the above, Recordati submitted there had not been a breach of Clause 9.

In response to a query from the case preparation managing regarding trials sponsored by other companies mentioned in the analysis for CMRO publication but not included in Recordati's response, the company provided details of the six trials considered in the analysis for CMRO publication.

The following four Phase III clinical trials were considered because they were included in the dossier to obtain the EU marketing authorization:

EudraCT No 2005-005665-11 (NCT00359905), sponsored by Recordati in Europe  
S104009 (ClinicalTrials.gov Identifier: NCT00224107), sponsored by Watson in US  
S104010 (ClinicalTrials.gov Identifier: NCT00224120), sponsored by Watson in US  
S104011 (ClinicalTrials.gov Identifier: NCT00224133), sponsored by Watson in US.

In addition, for completeness Recordati also mentioned the Phase IV clinical study it sponsored after the approval in EU (EudraCT No 2011-000045-20, NCT01757769), that was excluded from the CMRO publication because it was ongoing at the time of the analysis.

The following studies were included in the CMRO publication but not in Recordati's response because they were Phase II studies performed in not yet approved indications of silodosin (neither in EU or in US):

Study S108001 (NCT00740779), a Phase II multicentre, double-blind, placebo-controlled study in patients with abacterial chronic prostatitis/chronic pelvic pain syndrome sponsored by Watson in US.

Study S108005 (NCT00793819), a Phase II double-blind, placebo-controlled Phase II study in patients with nocturia, sponsored by Watson in US.

In response to a request for further information Recordati submitted that the first marketing authorization was not granted to Recordati but to Kissei Pharmaceuticals in Japan on 23 January 2006 as Urief, which was first launched in May 2006. A second marketing authorization was granted to Kissei's licensee Watson Pharmaceuticals (now Actavis Inc) on 8 October 2008 (Rapaflo) which was launched in April 2009. Two marketing authorizations were granted to Recordati on 29 January 2010 (Silodyx and Urorec) first launch in June 2010.

Recordati was not the marketing authorization holder in Japan or US. Neither Urief nor Rapaflo were marketed in the EU.

#### **GENERAL COMMENTS FROM THE PANEL**

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of

clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the

first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly

introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

‘Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.’

The relevant supplementary information stated:

**‘Clause 21.3 Details of Clinical Trials**

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.’*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World

Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred

to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

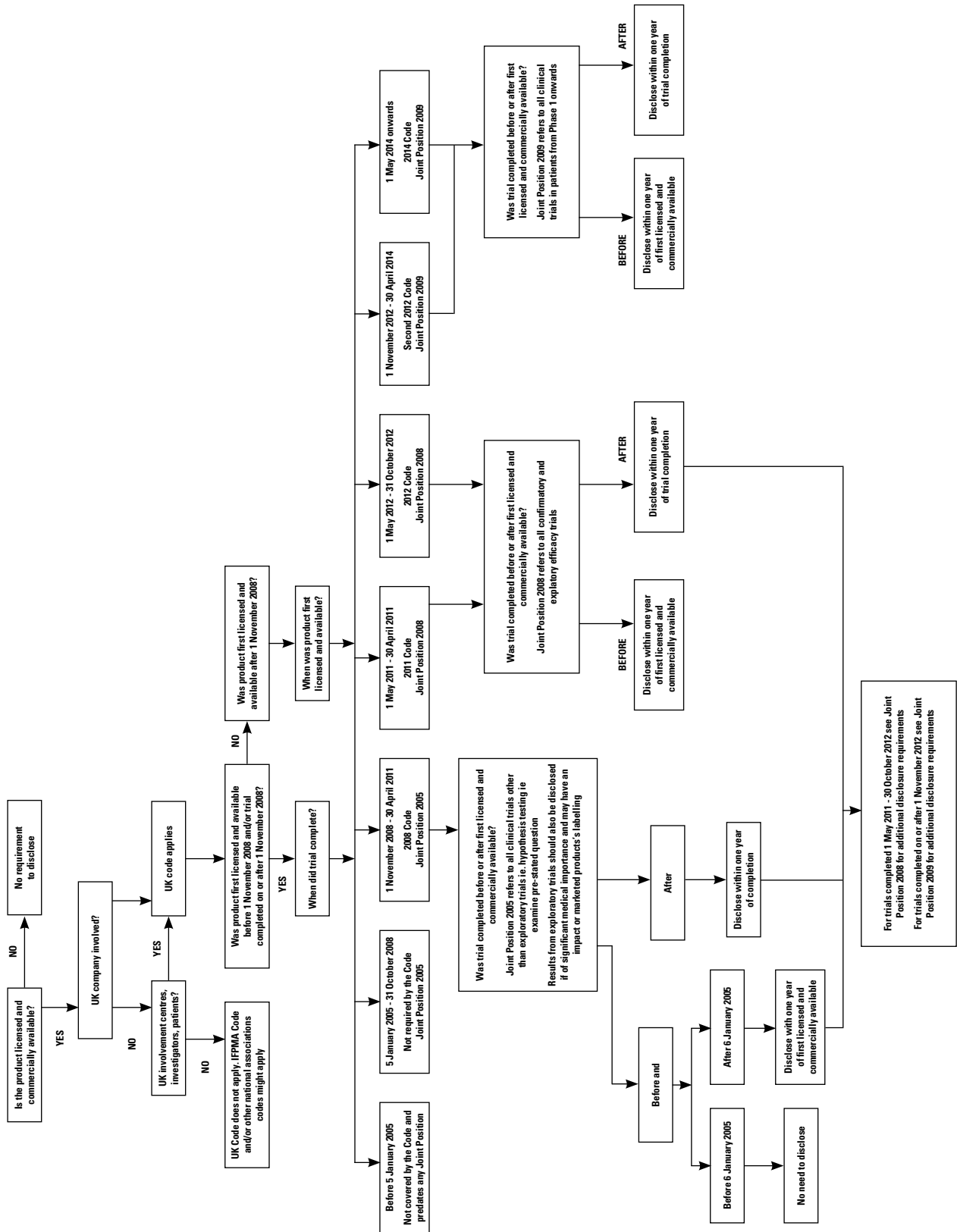
The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results





The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

#### **PANEL RULING IN CASE AUTH/2673/11/13**

The Panel noted the CMRO publication in that one evaluable study had not been disclosed in the timeframe. The disclosure percentage was 75%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 100%.

The Panel noted Recordati's submission that it sponsored two of the trials listed in the CMRO publication. With regard to Study NCT01757769 which completed in July 2013 (last patient, last visit), the Panel ruled no breach of Clauses 21.3, 2 and 9.1 of the Second 2012 Edition of the Code as the study results did not need to be disclosed until July 2014. The clinical study report was expected in March 2014.

The Panel noted Recordati submitted data to show that the last patient, last visit, for the open label phase of Study NCT00359905 was 4 January 2008 and a synopsis of the clinical study report was submitted to various groups (competent authorities, ethics committees, investigators) between 22 September and 15 October 2008. An abstract was published in April 2010 and full publication (Chapple *et al*) was in November 2010.

The Panel noted Recordati's submission regarding the various dates of the various marketing authorizations. Silodosin twice daily was first approved for BPH in January 2006 (Kissei Pharmaceuticals in Japan). Silodosin once daily was first approved in October 2008 (Watson Pharmaceuticals, US). Recordati's version – Silodyx was approved for once daily use in January 2010 and first marketed in Germany in June 2010.

The Panel considered that it could be argued that the date a product was first approved and commercially available was not brand specific if there were a number of different brand names for the same product as for silodosin. The Panel noted, however, that the joint positions referred to maintaining protection for intellectual property rights. Further it was not clear whether the reference to first approved and commercially available was medicine specific or company specific.

The Panel considered that it could be argued that Recordati's second study in question completed after silodosin was first approved and commercially available (January 2006).

However, the Panel noted that the date of the last patient, last visit, 4 January 2008, and the date of the synopsis of the clinical study report, 22 September 2008 were both before there were any disclosure requirements in the Code. The matter was not covered by the 2006 Code and as such there could no breach of it. Thus the Panel ruled no breach of Clauses 9.1 and 2 of the 2006 Code.

The Panel noted its ruling above. In addition it noted that if the relevant date of the first approval and commercial availability was company specific, ie the date of Recordati's product marketing authorization (June 2010), then the matter would be covered by the 2008 Code and the trial results would need to be disclosed by June 2011, which had happened.

<b>Complaint received</b>	<b>21 November 2013</b>
<b>Case completed</b>	<b>24 March 2014</b>

# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v GLAXOSMITHKLINE

## Clinical trial disclosure (Benlysta)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Benlysta (belimumab).

The detailed response from GlaxoSmithKline is given below.

General detailed comments from the Panel are given below.

The Panel noted that it appeared from the CMRO publication that one of the evaluable GlaxoSmithKline trials had not been disclosed. The disclosure percentage was 88%.

The Panel noted GlaxoSmithKline's submission that the one evaluable trial for which results had not

been disclosed was ongoing and the results would be disclosed in May 2017 (based on an expected completion date of May 2016). The disclosure percentage at 31 January 2013 of all trials completed before the end of January 2012 was 100%.

The Panel noted that as the study had not completed there was, as yet, no requirement to publish the results and no breach of the Second 2012 Edition including Clause 2 was ruled.

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### COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for each product. The data for Benlysta (belimumab) were as follows:

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	8	2	6	5	83%	7	7	100%
Phase III	4	2	2	2	100%	4	4	100%
Phase IV	1	1	0	0	0%	0	0	0%
<b>TOTAL</b>	<b>13</b>	<b>5</b>	<b>8</b>	<b>7</b>	<b>88%</b>	<b>11</b>	<b>11</b>	<b>100%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluative	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluative trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluative trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included GlaxoSmithKline.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to the companies, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

GlaxoSmithKline stated that the complaint was light on detail but noted that the complainant had referred to CMRO publication and alleged breaches of the Code with regard to ‘companies which have not disclosed their clinical trial results in line with the ABPI for licenced products’ (sic).

GlaxoSmithKline submitted that it was committed to reporting the results of clinical research that evaluated its medicines, irrespective of whether the outcomes were positive or negative. This was fundamental to the advancement of medical science. The company submitted that a full description of its policies on disclosing clinical trial information was provided in the company’s public policy and relevant confidential internal policy documents.

In summary, GlaxoSmithKline met its commitment to transparency by:

- Posting the results of its research on its publicly accessible clinical study register website (<http://www.GlaxoSmithKline-clinicalstudyregister.com/>). This received an average of almost 11,000 visitors a month, and by the end of 2012 contained almost 5,000 results summaries posted since it was launched in 2004.
- Seeking to publish all research results as full papers in peer reviewed scientific journals.

GlaxoSmithKline’s disclosure policy went beyond what was required by laws and regulations (Clause 1.8). For example, its commitment to post Phase I studies, observational studies and meta-analyses that evaluated its medicines, went beyond what was required by US and EU regulations.

GlaxoSmithKline submitted that new commitments delivered in 2013 built on its long standing focus to share the results of its research and help ensure the important contribution made by people who took part in research, was used to maximum effect in the creation of scientific knowledge and understanding.

- In 2013, GlaxoSmithKline committed to expand the information made publicly available on the Register to include Clinical Study Reports (CSRs) CSRs would be available, with personal information removed, once the trial had been published and the medicines approved or

terminated from development. This commitment included publishing CSRs for all approved medicines dating back to the formation of GlaxoSmithKline in 2000. Given the volume of studies, this work would be completed in a step-wise manner over the next few years, with priority given to the most commonly prescribed medicines.

- In May 2013, GlaxoSmithKline also launched a system to enable researchers to request access to the detailed anonymised patient-level data that sat behind the results of clinical trials. This would enable researchers to examine data more closely and to conduct further research. The system was a first step from which GlaxoSmithKline and others could learn. GlaxoSmithKline worked with others in industry and the public sector to encourage the development of a broader, independent system where data from studies conducted by multiple organisations were made available for further research.

GlaxoSmithKline submitted that these ongoing and new initiatives demonstrated its commitments to provide greater access to clinical trial information and commitment to the highest standards.

GlaxoSmithKline submitted that the CMRO publication did not review compliance with the ABPI Code or legal requirements. The authors were best placed to explain their methodology.

It appeared, however, that although all the Code requirements for disclosure of trial results related to completed studies, an ongoing Benlysta study was included in the survey.

Clause 21.3 referred to the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Database requirement that:

- trials within scope were registered within 21 days after the initiation of patient enrolment and:
- results were posted no later than one year after the medicinal product was first approved and commercially available in any country; or for trials completed after this initial approval, results should be posted no later than one year after trial completion.

The trial in question was a Phase II extension study carried out exclusively in the US with an expected completion date of May 2016. The study was commenced by Human Genome Sciences (HGS) in 2004. HGS was fully owned by GlaxoSmithKline having been acquired in 2012. In line with the ABPI Code, the results would not be in scope for disclosure until one year after trial completion (ie May 2017 based on the expected completion date). A result summary would then be added to relevant public registers.

In summary, GlaxoSmithKline submitted it was committed to the highest standards (Clause 9.1) and did not accept that any breaches to the Code had occurred, thus maintaining confidence in the industry (Clause 2).

## GENERAL COMMENTS FROM THE PANEL

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers

of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant

to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

In the 2011 Code (which superceded the 2008 Code and came into operation on 1 January 2011 with a transition period until 30 April 2011 for newly introduced requirements), the supplementary information to Clause 21.3 was updated to refer to the 2008 IFPMA Joint Position.

In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

*'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information*

*can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by



Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the

studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

### **PANEL RULING IN CASE AUTH/2674/11/13**

The Panel noted that it appeared from the CMRO publication that one of the evaluable GlaxoSmithKline trials had not been disclosed. The disclosure percentage was 88%.

The Panel noted GlaxoSmithKline's submission that the one evaluable trial for which results had not been disclosed was ongoing and the results would



be disclosed in May 2017 (based on an expected completion date of May 2016). The disclosure percentage at 31 January 2013 of all trials completed before the end of January 2012 was 100%.

The Panel noted that as the study had not completed there was, as yet, no requirement to publish the results and no breach of Clause 21.3 of the current Code ie the Second 2012 Edition was ruled. Consequently, there could be no breach of Clauses 9.1 and 2 and thus the Panel ruled accordingly.

**Complaint received**      **21 November 2013**

**Case completed**        **20 March 2014**

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# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v JANSSEN

## Clinical trial disclosure (Incivo)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Incivo (telaprevir).

The detailed response from Janssen is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that eight evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 56%. The disclosure percentage at 31 January 2013 for trials completed by end of January 2012 was 78%. A footnote stated that the Tibotec BVBA trials had been disclosed and were publicly available but were not captured by the methodology. They had been submitted to clinicaltrials.gov. The remaining trials were not sponsored by Johnson & Johnson.

The Panel noted Janssen's submission that only two of the eight trials had been sponsored by a Johnson & Johnson company (Tibotec BVBA). The first approval for Incivo/Incivek was granted in May 2011. The one study with UK involvement finished in May 2009 and was published in September 2011 which was within the timeframe given the product was first approved in May 2011. Thus the Panel ruled no breach of the 2011 Code including Clause 2.

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

### COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

The summary output for each medicine set out the sources for all trials found, irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for the products. The data for Incivo (telaprevir) were as follows:

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	13	1	12	6	50%	12	8	67%
Phase III	9	3	6	4	67%	6	6	100%
<b>TOTAL</b>	<b>22</b>	<b>4</b>	<b>18</b>	<b>10</b>	<b>56%</b>	<b>18</b>	<b>14</b>	<b>78%</b>

The explanation of terms given in the documentation was as follows:

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluative	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluative trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluative trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Janssen.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Janssen, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

## RESPONSE

Janssen stated that the complainant appeared to have accused a large number of pharmaceutical companies and included in his/her list of companies and pharmaceutical products 'J&J for Incivo'. A breach of Clauses 21, 9 and 2 of the Code was alleged. As Clauses 21.1 and 21.2 did not appear to be relevant to the complaint, Janssen assumed the complainant was only alleging a breach of Clause 21.3. The PMCPA also indicated that Janssen should consider Clause 1.8.

Janssen responded to the complaint in relation to the clinical trials for Incivo (telaprevir) that Johnson & Johnson companies had sponsored.

Janssen understood from one of the authors of the CMRO publication that two clinical trials sponsored by Tibotec BVBA (part of the Johnson & Johnson family of companies) contributed to the finding of 'non-disclosed' clinical trials in relation to Incivo (telaprevir) using the authors' methodology. Janssen submitted that this methodology was not necessarily definitive with regard to disclosure in relation to clinical trials.

The studies in question were VX-950-TIDP24-C209 ('C209') and VX-950-TIDP24-C210 ('C210') which appeared as the first two of the 10 clinical trials identified. The list of clinical trials so identified and sent to Janssen on 27 February 2013 was provided. The other eight telaprevir clinical trials listed were sponsored either by Mitsubishi Tanabe Pharma or Vertex Pharmaceuticals.

A footnote to the summary table included in the CMRO publication stated, 'Information from Johnson and Johnson: The results of the Tibotec BVBA trials have been disclosed and are publicly available, but were not captured by the methodology. They have been submitted to clinicaltrials.gov. The remaining trials were not sponsored by Johnson and Johnson'.

Janssen responded to the complaint only in relation to these two clinical trials as it could not take responsibility for disclosure of trials sponsored by other pharmaceutical companies.

Janssen provided the following information on the two Johnson & Johnson-sponsored studies:

### C209

Clinicaltrials.gov Identifier: NCT00561015A  
Title: A Phase 2a Study to Evaluate Viral Kinetics and

Safety of Telaprevir in Participants with Genotype 2 or 3 Hepatitis C Infection

The study included UK-based sites and the sponsor was based in Belgium.

First received in clinicaltrials.gov: 19 November 2007

Study start (first patient in): 6 December 2007

End of study: 28 May 2009

Results: *Gastroenterology*, September 2011; 141:881-889

#### **C210**

Clinicaltrials.gov Identifier: NCT00580801

Title: An Exploratory Study of Telaprevir in Treatment-Naïve Participants with Chronic Genotype 4 Hepatitis C Virus Infection

The study did not involve UK-based sites, subjects or investigators and was conducted in France. The sponsor was based in Belgium.

First received in clinicaltrials.gov: 20 December 2007

Study start (first patient in): 3 January 2008

End of study: 11 January 2010

Results: Manuscript initially submitted to *Gastroenterology* on 31 May 2012. Published eventually in *Journal of Infectious Diseases* 2013;208:1000-7.

Janssen submitted that the results of C210 were also presented:

1. As an oral presentation at the European Association for the Study of the Liver (EASL) Meeting in 2009, abstract (Benhamou Y, *et al.* Results of a Proof of Concept Study (C210) of Telaprevir Monotherapy and in Combination with Peginterferon Alfa-2a and Ribavirin in Treatment-naïve Genotype 4 HCV Patients. *J Hepatol* 2009;50(Suppl. 1):S6 (Abstract 10).
2. As a poster at the American Association for Study of Liver Diseases (AASLD) Meeting in 2010 (Benhamou Y, *et al.* Activity of Telaprevir Monotherapy or in Combination with Peginterferon Alfa-2a and Ribavirin in Treatment-naïve Genotype 4 Hepatitis C Patients: Final Results of Study C210. *Hepatology* 2010;52(Suppl. 1):719A (Abstract #828).

The first licence for Incivo/Incivek (telaprevir) globally was granted by the FDA in May 2011.

Thus, given the timings of the submission to a recognised clinical trial registry and dissemination of the results in relation to the date of first licence, Janssen submitted that both C209 and C210 were disclosed in accordance with Clause 21.3 and were compliant with the recommendations of the Joint Position 2009, and the Joint Position on the Publication of Clinical Trial Results in the *Scientific Literature* 2010. Janssen therefore maintained that it had complied with all applicable codes, laws and regulations and had not breached Clause 1.8.

Janssen submitted that Johnson & Johnson, and by default, Janssen had maintained high standards in relation to the disclosure and thus had not breached Clause 9. It had not brought the pharmaceutical industry into disrepute and thus Janssen also denied a breach of Clause 2.

Standard operating procedures (SOPs) and policy documents were provided these being: SOP-10376 Public Results Disclosure of Company-sponsored Clinical Trials, SOP-10377 Public Registration of Company-sponsored Clinical Trials and POL-06204 Public registration and Results Disclosure of Company-sponsored Clinical Trials.

Since Janssen believed the complaint was without merit and it had provided evidence to support this view above, the company did not need to supply the additional information requested. This being details of all ongoing and completed trials in relation to telaprevir, such as dates of commencement, date of completion, the study type, and the nature and extent of any UK involvement etc.

In Janssen's view the complaint was clearly based only on the clinical trials considered by the methodology of the CMRO publication, it was not appropriate to supply extensive information on various other clinical trials, for which there was no reason to believe that disclosure, compliant with the two Joint Positions, had not occurred.

Companies other than Johnson & Johnson had sponsored clinical trials with telaprevir and details were given. Neither Johnson & Johnson, nor Janssen-Cilag Ltd in the UK could take responsibility for the obligations of other sponsors in this regard and therefore no evidence in relation to clinical trials sponsored by these companies was offered.

In summary, Janssen submitted that the disclosure of the telaprevir trials sponsored by Johnson & Johnson, referred to in the CMRO publication complied with the joint positions and Clause 21.3.

Janssen stated that it took its obligations under the Code very seriously and it specifically refuted breaches of Clauses 1.8, 21, 9 and 2.

#### **GENERAL COMMENTS FROM THE PANEL**

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

The Panel considered that the first issue to be determined was whether the matter was covered by the ABPI Code. If the research was conducted on behalf of a UK pharmaceutical company (whether directly or via a third party) then it would be covered

by the ABPI Code. If a study was run by a non UK company but had UK involvement such as centres, investigators, patients etc it was likely that the Code would apply. The Panel appreciated the global nature of much pharmaceutical company sponsored clinical research and a company located in the UK might not be involved in research that came within the ABPI Code. It was a well established principle that UK pharmaceutical companies were responsible for the activities of overseas affiliates if such activities related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 Edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.

The Panel noted that the first Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was agreed in 2005 by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). The announcement was dated 6 January 2005.

The Panel noted that Article 9, Clinical Research and Transparency, of the most recent update of the IFPMA Code of Practice (which came into operation on 1 September 2012) included a statement that companies disclose clinical trial information as set out in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2009) and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (2010). As companies had, in effect, agreed the joint positions their inclusion in the IFPMA Code should not have made a difference in practice to IFPMA member companies but meant that IFPMA member associations had to amend their codes to reflect Article 9. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. Pharmaceutical companies that were members of national associations but

not of IFPMA would have additional disclosure obligations once the national association amended its code to meet IFPMA requirements. The disclosures set out in the joint positions were not required by the EFPIA Codes.

The Panel noted that even if the UK Code did not apply many of the companies listed by the complainant were members of IFPMA and/or EFPIA.

The Panel considered that it was good practice for clinical trial results to be disclosed for medicines which were first approved and commercially available after 6 January 2005 (the date of the first joint position). This was not necessarily a requirement of the ABPI Codes from that date as set out below.

As far as the ABPI Code was concerned, the Panel noted that the first relevant mention of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 was in the supplementary information to Clause 7.5 of the 2006 Code:

***'Clause 7.5 Data from Clinical Trials***

*Companies must provide substantiation following a request for it, as set out in Clause 7.5. In addition, when data from clinical trials is used companies must ensure that where necessary that data has been registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.'*

Clause 7.5 of the 2006 Code required that substantiation be provided at the request of health professionals or appropriate administrative staff. Substantiation of the validity of indications approved in the marketing authorization was not required. The Panel considered this was not relevant to the complaint being considered which was about disclosure of clinical trial results. The Joint Position 2005 was mentioned in the supplementary information to Clause 21.5 but this did not relate to any Code requirement to disclose clinical trial results.

In the 2008 ABPI Code (which superceded the 2006 Code and came into operation on 1 July 2008 with a transition period until 31 October 2008 for newly introduced requirements), Clause 21 referred to scientific services and Clause 21.3 stated:

*'Companies must disclose details of clinical trials.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position*

*on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (<http://clinicaltrials.ifpma.org>).*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

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In the Second 2012 Edition (which came into operation on 1 July 2012 with a transition period until 31 October 2012 for newly introduced requirements), changes were made to update the references to the joint position and to include the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. Clause 21.3 now stated:

*'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.'*

The relevant supplementary information stated:

***'Clause 21.3 Details of Clinical Trials***

*This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2009 and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature 2010, both at <http://clinicaltrials.ifpma.org>.*

*Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'*

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

The Panel examined the Joint Position on the Disclosure of Clinical Trial Information which was

updated on 10 November 2009 and superseded the Joint Position 2008. With regard to clinical trial registries the document stated that all trials involving human subjects for Phase I and beyond at a minimum should be listed. The details should be posted no later than 21 days after the initiation of enrolment. The details should be posted on a free publicly accessible internet-based registry. Examples were given. Each trial should be given a unique identifier to assist in tracking. The Joint Position 2009 provided a list of information that should be provided and referred to the minimum Trial Registration Data Set published by the World Health Organisation (WHO). The Joint Position 2009 referred to possible competitive sensitivity in relation to certain data elements and that, in exceptional circumstances, this could delay disclosure at the latest until after the medicinal product was first approved in any country for the indication being studied. Examples were given.

The Panel noted that the complaint related to the disclosure of clinical trial results.

With regard to the disclosure of clinical trial results the Joint Position 2009 stated that the results for a medicine that had been approved for marketing and was commercially available in at least one country should be publicly disclosed. The results should be posted no later than one year after the medicine was first approved and commercially available. The results for trials completed after approval should be posted one year after trial completion – an adjustment to this schedule was possible to comply with national laws or regulations or to avoid compromising publication in a peer-reviewed medical journal.

The Joint Position 2009 included a section on implementation dates and the need for companies to establish a verification process.

The Joint Position 2005 stated that the results should be disclosed of all clinical trials other than exploratory trials conducted on a medicine that was approved for marketing and was commercially available in at least one country. The results generally should be posted within one year after the medicine was first approved and commercially available unless such posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. The Joint Position 2008 was dated 18 November 2008 and stated that it superseded the Joint Position 2005 (6 January and 5 September). The Joint Position 2008 stated that results should be posted no later than one year after the product was first approved and commercially available in any country. For trials completed after initial approval these results should be posted no later than one year after trial completion. These schedules would be subject to adjustment to comply with national laws or regulations or to avoid compromising publication in a peer reviewed medical journal.

The Joint Position on the Publication of Clinical Trial Results in the Scientific Literature was announced on 10 June 2010. It stated that all industry

sponsored clinical trials should be considered for publication and at a minimum results from all Phase III clinical trials and any clinical trials results of significant medical importance should be submitted for publication. The results of completed trials should be submitted for publication wherever possible within 12 months and no later than 18 months of the completion of clinical trials for already marketed medicines and in the case of investigational medicines the regulatory approval of the new medicine or the decision to discontinue development.

Having examined the various codes and joint positions, the Panel noted that the Joint Position 2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

The Panel noted that deciding which Code applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account the transition period, came into operation on 1 May 2011 was the first edition of the Code to refer to the Joint Position 2008.

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the Joint Position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 Code). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

For medicines first licensed and commercially available in any country from 1 November 2008 until 30 April 2011 the results of clinical trials completed before 6 January 2005 would not have to be posted.

From 1 May 2011 there was no exclusion of trials based solely on completion date and so for a product first licensed and commercially available anywhere in the world after 1 May 2011 the applicable joint positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available.

Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version

of the Code (and joint position) applied for trials completed prior to first approval. The next consideration was whether the trial completed before or after this date. For trials completing after the date of first approval, the completion date of the trial would determine which Code applied. The Panel considered that the joint positions encouraged disclosure as soon as possible and by no later than 1 year after first availability or trial completion as explained above. The Panel thus considered that its approach was a fair one. In this regard, it noted that the complaint was about whether or not trial results had been disclosed, all the joint positions referred to disclosure within a one year timeframe and companies needed time to prepare for disclosure of results. The Panel considered that the position concerning unlicensed indications or presentations of otherwise licensed medicines etc would have to be considered on a case by case basis bearing in mind the requirements of the relevant joint position and the legitimate need for companies to protect intellectual property rights. The Panel followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

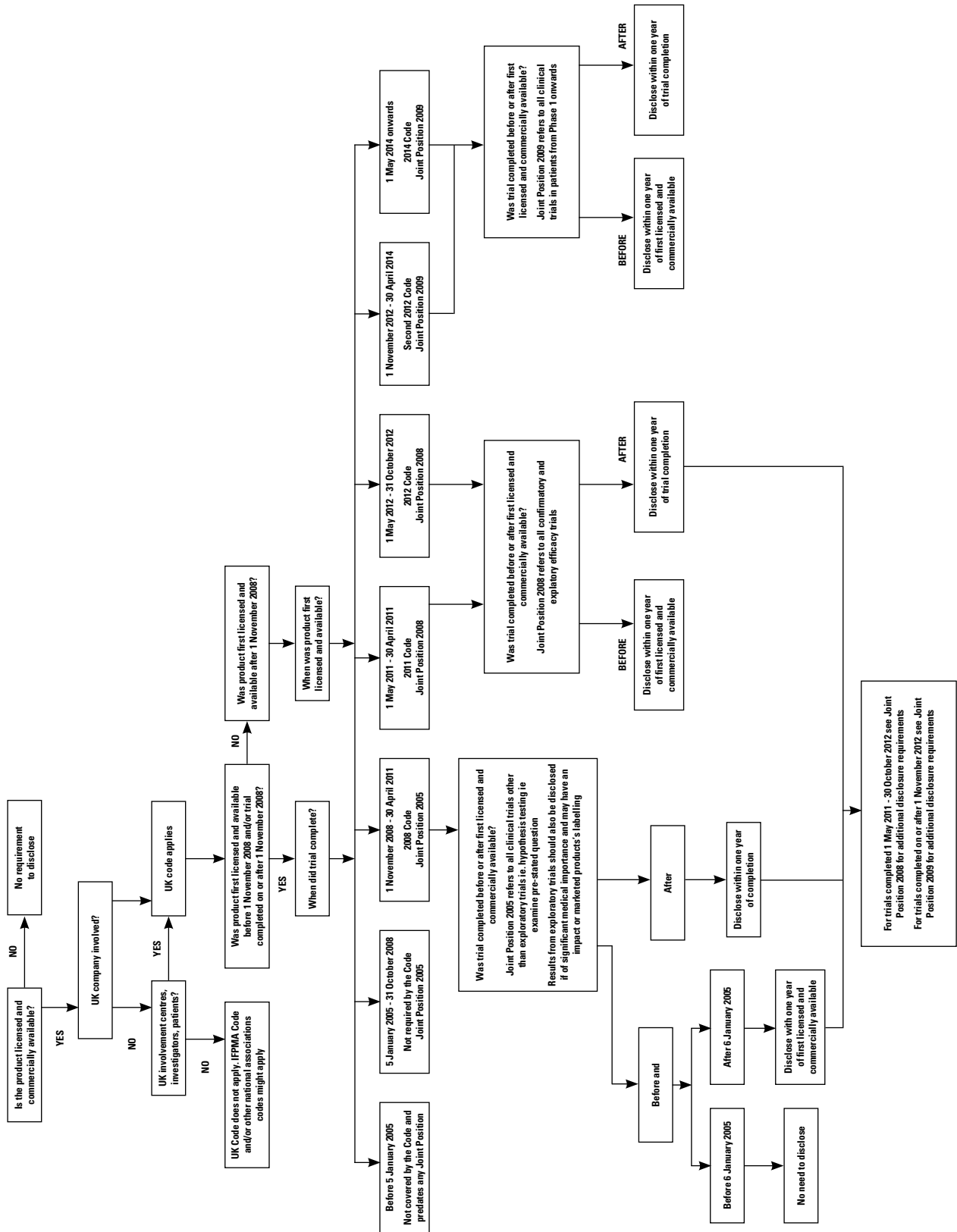
The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. Companies would be well advised to ensure that all the clinical trial results were disclosed as required by the Codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did

# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results





not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, *Applicability of Codes, inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

#### **PANEL RULING IN CASE AUTH/2676/11/13**

The Panel noted the CMRO publication in that eight evaluable studies had not been disclosed within the

timeframe. The disclosure percentage was 56%. The disclosure percentage at 31 January 2013 for trials completed by end of January 2012 was 78%. A footnote stated that the Tibotec BVBA trials had been disclosed and were publicly available but were not captured by the methodology. They had been submitted to clinicaltrials.gov. The remaining trials were not sponsored by Johnson & Johnson.

The Panel noted Janssen's submission that only two of the eight trials had been sponsored by a Johnson & Johnson company (Tibotec BVBA). The first approval for Incivo/Incivek was granted in May 2011. The two studies in question (C209 and C210) had been published. Study C209 finished in May 2009 and was published in September 2011 which was within the timeframe given the product was first approved in May 2011. Thus the Panel ruled no breach of Clause 21.3 of the 2011 Code and consequently no breach of Clauses 9.1 and 2.

With regard to Study C210, the Panel noted Janssen's submission that it had been conducted outside the UK with no UK involvement (be that UK company or UK centres). The Panel considered as there was no UK involvement, the matter did not come within the scope of the UK Code and therefore ruled no breach.

**Complaint received            21 November 2013**

**Case completed                20 March 2014**

# ANONYMOUS, NON CONTACTABLE HEALTH PROFESSIONAL v MERCK SHARP & DOHME

## Promotion of ezetimibe and sitagliptin

An anonymous, non-contactable complainant who described him/herself as a practicing clinician with an advisory role at a clinical commissioning group (CCG) complained about a meeting with two representatives from Merck Sharp & Dohme. The complainant stated that the representatives asked him/her to look at a computer programme (MIRROR) in his/her CCG capacity. The complainant stated that the computer programme purported to hold information about hospital admissions; the representatives focussed in particular on non-elective hospital admissions in patients with heart disease and diabetes. Merck Sharp & Dohme marketed Ezetrol (ezetimibe) as adjunctive therapy to reduce cholesterol levels in patients with, *inter alia*, primary hypercholesterolaemia and Januvia (sitagliptin) for use in adults with type 2 diabetes to improve glycaemic control.

The complainant stated that with regard to heart disease the representatives used MIRROR to discuss non-elective admissions for a variety of coronary events and focussed on the number of these events that occurred in patients with cholesterol levels above the quality outcome framework (QOF) targets. They claimed that the coronary event had been as a result of cholesterol levels being too high and that if the complainant treated his/her patients better and reached not only the QOF target but even lower, he/she could help to save money. The complainant explained that his/her practice achieved as close to target as possible. The complainant was then told that if he/she used Ezetrol then more patients would reach a lower cholesterol level and stop the coronary events. The complainant was unaware of any data that showed that Ezetrol reduced coronary events or death and when challenged the representatives conceded that there was no data available but there soon would be. The complainant stated that the representatives insisted on selling Ezetrol as a medicine that would stop coronary events just because it lowered cholesterol and that studies had shown the lower the level the better the outcome; but they could not provide any outcome data. The complainant alleged this was misleading and potentially dangerous.

The complainant was similarly concerned about the representatives' discussion on diabetes, which focussed on hypoglycaemia and that such attacks precipitated even more serious issues including fractures. The blame for these events was placed on sulphonylureas as a class despite the complainant's challenge that poor insulin control was more likely the problem. The complainant was told that if he/she used Januvia then he/she would stop patients having hypoglycaemic events and needing hospital treatment and was referred to a couple of clinical trials that showed a lower incidence

of hypoglycaemia with Januvia compared with a number of sulphonylureas. The complainant asked to see the effect of reducing hospital admissions from these data and was told the studies did not look at that and they covered all grades of severity of hypoglycaemia. The representatives conceded that only severe events would need hospital attendance but could not quantify how Januvia did against comparative medicines. However the representatives asserted there would be a reduction in urgent admissions if Januvia was used instead of sulphonylurea but were not able to provide clinical trial data to support it. Again the representative dismissed the importance of insulin related hypoglycaemia.

The complainant stated he/she was alarmed at the way in which this information was presented to health professionals. As the information could be presented to practices with their specific practice information the complainant was even more concerned that this presentation or programme was being used widely and alleged it was misleading. The use of such material brought the pharmaceutical industry into disrepute. Presenting data and making false claims was a disgrace.

The complainant alleged that there was disguised promotion of Ezetrol and Januvia in the presentation and that claims for the medicines could not be substantiated. The linking of the medicines to this computer data made a clear link between the perceived problem and that the Merck Sharp & Dohme medicines could prevent or reduce the problem, which was not so. The programme included prescribing information but the products had no data or licences for the prevention of the issues that the programme purported to identify. The complainant stated that this must be wrong. The complainant alleged that the Merck Sharp & Dohme representatives had promoted the medicines for unlicensed uses.

The detailed response from Merck Sharp & Dohme is given below.

The Panel noted that the complainant was anonymous and non-contactable. Such complaints were accepted and like all complaints judged on the evidence provided by the parties. The complainant bore the burden of proof. It was not possible to contact the complainant for further information.

The Panel noted that point 1 of the information which Merck Sharp & Dohme stated representatives had to read through and discuss with customers before they proceeded further with the MIRROR tool stated, 'Merck Sharp & Dohme ("MERCK SHARP & DOHME") has developed this MIRROR tool for

the purpose of promoting its products. Prescribing information for relevant MERCK SHARP & DOHME products can be found at the prescribing information tab found at the top of each page'. The Panel noted that it had not been provided with the complete MIRROR tool. Screenshots all included a link to prescribing information and reports generated at a customer's request would have prescribing information attached. The Panel did not know in what context the meeting in question had been set up but as the complainant had clearly considered that Ezetrol and Januvia had been promoted it did not consider that the use of MIRROR amounted to disguised promotion. No breach of the Code was ruled.

The Panel noted that both Ezetrol and Januvia had been promoted within the context of a conversation about data held within the MIRROR tool. It appeared that field-based staff used the MIRROR tool to examine local health economy data and, within that context, promote a medicine. With regard to Ezetrol, the complainant had submitted that the representatives had discussed non-elective admissions for a number of coronary events and had focussed on the number of these events which had occurred in patients with cholesterol levels above the QOF targets. Merck Sharp & Dohme submitted that the MIRROR tool could conceivably be used to highlight the incidence of hospital admissions for ischaemic heart disease but that it would not be possible to attribute this to hypercholesterolaemia or to assert that the use of Ezetrol would result in fewer hospital admissions. In the Panel's view however, to promote Ezetrol, a lipid lowering agent, following a conversation about non-elective cardiovascular hospital admissions in patients with cholesterol levels above QOF targets, invited the customer to link the two conversations and assume that Ezetrol had a role in reducing such admissions. Although MIRROR briefing material stated that Merck Sharp & Dohme products must be portrayed accurately, fairly and objectively, and always within their licence, the Panel noted the MIRROR briefing document stated that:

'MIRROR can and should also be used with a customer(s) to highlight local performance gaps or disease management issues and to facilitate discussions to progress towards potential solutions.

It is important to ensure that we maintain balance in these discussions. We may, where appropriate, suggest that our products might help to address an issue highlighted by the MIRROR tool but we cannot guarantee what the impact of our products will be and we should not suggest that use of our products will solve an issue completely.'

An earlier briefing document stated:

'MIRROR can be used in calls with healthcare professionals to raise specific disease management issues and it is acceptable in that same call to then discuss how a treatment/disease management strategy, involving therapy

classes that involve 1 or more MSD products, could produce benefits for the patient and local health economy.'

The Panel noted that the summary of product characteristics (SPC) for Ezetrol stated that a beneficial effect on cardiovascular morbidity and mortality has not yet been demonstrated. The Panel considered, given the statements above from the briefing documents, that on the balance of probabilities, concurrent use of the MIRROR tool and promotion of Ezetrol had given a misleading impression, which could not be substantiated, that use of the medicine would decrease non-elective hospital admissions due to coronary events. A breach of the Code was ruled. Further, the Panel considered that such an impression, given the statement in the SPC that a beneficial effect on cardiovascular morbidity had not been demonstrated, was inconsistent with the Ezetrol SPC. A breach of the Code was ruled. The Panel considered that Ezetrol had, in effect, been promoted for an unlicensed indication. A breach of the Code was ruled. The Panel considered that the representatives had not promoted the rational use of Ezetrol. A breach of the Code was ruled.

The Panel noted that although the complainant stated that he/she had asked for outcome data, as the claim for reduced hospital admissions could not be substantiated, none could be provided. In that regard the Panel ruled no breach of the Code, noting its ruling above of a breach of the Code.

The Panel noted the complainant's allegation that the representatives had suggested that use of Januvia instead of sulphonylureas would reduce urgent hospital admissions due to hypoglycaemia. The representatives had not been able to produce any data to support this claim. The Panel noted Merck Sharp & Dohme's submission that Januvia was associated with a lower incidence of hypoglycaemia than sulphonylureas and that to highlight this in a promotional call was acceptable, as was highlighting the scale of hypoglycaemia-related hospital admissions through tools such as MIRROR. The Panel noted its comments above and considered that to promote Januvia within the context of a conversation about hypoglycaemia-related hospital admissions would imply that the medicine had a role in reducing such admissions. The Panel considered that such an implication was misleading and could not be substantiated. Breaches of the Code were ruled. The Panel did not consider that such an impression was inconsistent with the Januvia SPC. No breach of the Code was ruled. The Panel considered, however, that Januvia had, in effect, been promoted for an unlicensed indication. A breach of the Code was ruled. The Panel considered that the representatives had not promoted the rational use of Januvia. A breach of the Code was ruled.

The Panel noted that although the complainant stated that he/she had asked the representatives to substantiate the claim that Januvia would reduce hospital admissions, as the claim could not be substantiated no data could be provided. In that

regard the Panel ruled no breach of the Code, noting its ruling above of a breach of the Code.

The Panel was very concerned about the wording of the MIRROR briefing documents quoted above. In the Panel's view, to suggest that a medicine might help to address an issue or could produce benefits usually resulted in the impression that the medicine would definitely do so. MIRROR was used to establish a local health economy need or gap which, when followed by a promotional discussion, invited the customer to link the two and assume that the medicine would address that need or fill the gap. In the Panel's view the briefing material positively encouraged representatives to discuss medicines in relation to the local health economy data provided by MIRROR. The Panel considered that the use of the MIRROR tool to discuss healthcare issues was incompatible with the concurrent promotion of medicines unless those medicines were appropriately licensed or had relevant outcome data (eg reduced hospital admissions). In the Panel's view the MIRROR briefing material advocated a course of action which was likely to breach the Code. A breach of the Code was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained and a breach of the Code was ruled. The Panel further considered that the use of MIRROR in conjunction with the promotion of medicines, and to brief representatives that it was acceptable to suggest that Merck Sharp & Dohme's products might help to address an issue highlighted by the tool, was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Upon appeal by Merck Sharp & Dohme the Appeal Board noted that the company had raised points about the veracity of the complaint, conduct of the meeting and use of the MIRROR tool that had not previously been submitted to the Panel.

The Appeal Board noted from Merck Sharp & Dohme's submission at the appeal that the company's field based area access leads (AALs) who used the MIRROR tool were separate from its sales representatives. The AALs had a promotional and non promotional role. Each AAL was experienced and had received specialist training. A call by an AAL to use the MIRROR tool would only be in response to a request from a health professional (payers, commissioners etc) usually elicited by a sales representative at a prior call. The way in which the AAL would use the MIRROR tool in each meeting was led by the health professional choosing which information he/she wanted to view in a chosen disease area and region. The discussion and extraction of data in just one disease area could take up to 2 hours. The Appeal Board noted Merck Sharp & Dohme's submission that the MIRROR tool examined the burden of illness and despite its description as a promotional tool, it was not designed to lead to a product discussion although this might happen.

The Appeal Board noted Merck Sharp & Dohme's submission that a call detailing the MIRROR tool

concerning two different disease areas did not occur but if it had, it would take up to 4 hours to complete which would be impractical for most health professionals. The Appeal Board also noted that Merck Sharp & Dohme could find no record of an AAL detailing the MIRROR tool with another Merck Sharp & Dohme employee as described by the complainant.

At the end of detailing the MIRROR tool a report was generated for the health professional to keep. The Appeal Board noted that the complainant had not provided any additional evidence such as this report to support his/her allegations.

The Appeal Board noted its comments above and as, on the balance of probabilities, it was not satisfied that the alleged meeting took place it ruled no breaches of the Code in relation to the claims allegedly made about Ezetrol and Januvia. The appeal on these points was successful.

The Appeal Board noted that in the information which preceded the MIRROR tool, it was clearly stated that Merck Sharp & Dohme had developed the tool to promote its medicines. The company representatives at the appeal stated, however, that it was for use in a non promotional/health inequality/service improvement discussion but that if that discussion led into a promotional discussion the tool would nonetheless meet the requirements of the Code. The Appeal Board was concerned that the MIRROR tool thus appeared to have both a non promotional and a promotional purpose and in that regard it queried whether all of the Code requirements for each could truly be met.

The Appeal Board noted that the MIRROR tool launch materials, part of the briefing material provided by Merck Sharp & Dohme, referred to the core campaigns for both Januvia and Ezetrol. In the Appeal Board's view some of the slides appeared to positively encourage AALs to promote Merck Sharp & Dohme's products (eg the slide headed 'Value Proposition for key stakeholders'). This slide stated that Ezetrol should be an *essential* part of the management of patients with type 2 diabetes and CVD to reduce cholesterol and CV risk' (emphasis added). In the Appeal Board's view to describe Ezetrol as essential was exaggerated; it was indicated only as add-on therapy when patients had been inadequately controlled with a statin alone. A slide which detailed the payer proposition for Januvia stated that '...sitagliptin improves patient experience by reducing the complications of type 2 diabetes'. In that regard the Appeal Board noted from the Merck Sharp & Dohme representatives that there was no outcome data to show that Januvia reduced cardiovascular disease, skin conditions etc (ie the 'complications' of diabetes) and although it had a low incidence of hypoglycaemia, hypoglycaemic episodes were acute events/side effects of therapy, not complications of the disease.

The Appeal Board considered that the MIRROR tool briefing materials were likely to encourage AALs to discuss Merck Sharp & Dohme products in relation to data generated by the MIRROR tool. It noted its comments above about the briefing material

**and the absence of patient outcome data. The Appeal Board considered that the briefing materials advocated a course of action that was likely to lead to a breach of the Code and consequently it upheld the Panel's ruling of a breach of the Code. High standards had not been maintained and the Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on these points was unsuccessful. The Appeal Board did not consider that the circumstances warranted a ruling of a breach of Clause 2 and no breach was ruled. The appeal on that point was successful.**

An anonymous, non-contactable complainant who described him/herself as a practicing clinician with an advisory role with a clinical commissioning group (CCG) complained about a meeting with two representatives from Merck Sharp & Dohme Limited. The complainant stated that the representatives asked him/her to look at a computer programme (MIRROR) in his/her CCG capacity. Merck Sharp & Dohme marketed Ezetrol (ezetimibe) as adjunctive therapy to reduce cholesterol levels in patients with, *inter alia*, primary hypercholesterolaemia and Januvia (sitagliptin) for use in adults with type 2 diabetes to improve glycaemic control.

## COMPLAINT

The complainant stated that the computer programme purported to hold information about hospital admissions; the representatives focussed in particular on non-elective hospital admissions in patients with heart disease and diabetes.

The complainant stated that he/she had reflected on the meeting and was disturbed by what the representatives had said and he/she now considered that claims about Merck Sharp & Dohme's medicines had no substance. If this was standard practice by Merck Sharp & Dohme then the complainant was convinced that the company had breached the Code.

The complainant stated that with regard to heart disease the representatives showed a number of slides that looked at non-elective admissions for a variety of coronary events. They then focussed on the number of these events that occurred in patients with cholesterol levels above the quality outcome framework (QOF) targets. They claimed that the coronary event had been as a result of cholesterol levels being too high and that if the complainant treated his/her patients better and reached not only the QOF target but even lower, he/she could 'do his/her bit' to save money. The complainant stated that he/she explained that his/her practice had a very robust protocol for reaching targets as evidence of best clinical practice and achieved as close to target as possible with the medicines it used. The complainant was then told that if he/she used Ezetrol then more patients would reach a lower cholesterol level and stop the coronary events. The complainant was unaware of any data that showed that Ezetrol was proven to reduce coronary events and that there was no evidence for reducing events or death. In response to the complainant's challenge the representatives conceded that there was no data available but there soon would be. In the complainant's view this was odd. The complainant

stated that the representatives insisted on selling Ezetrol as a medicine that would stop coronary events just because it lowered cholesterol and that studies had shown the lower the level the better the outcome; but they could not provide any outcome data. The complainant alleged this was very misleading and potentially dangerous.

The complainant considered that the representatives' slides on diabetes, which focussed on hypoglycaemia, were disconcerting. Figures were picked out to show that hypoglycaemic attacks precipitated even more serious issues including fractures. The blame for these events was placed on sulphonylureas as a class. The complainant challenged back with the view that poor insulin control was more likely the problem. The representatives pressed on with their assertion that it was only a problem of sulphonylureas. The representatives then told the complainant that if he/she used Januvia then he/she would stop patients having hypoglycaemic events and needing hospital treatment. The complainant stated that he/she again asked again for evidence and was briefly referred to a couple of clinical trials that showed a lower incidence of hypoglycaemia with Januvia compared with a number of sulphonylureas. The complainant asked to see the effect of reducing hospital admissions from these data and was told the studies did not look at that and they covered all grades of severity of hypoglycaemia. The representatives conceded that only severe events would need hospital attendance but could not quantify how Januvia did against comparative medicines. However the representatives asserted there would be a reduction in urgent admissions if Januvia was used instead of sulphonylurea but were not able to provide clinical trial data to support it. Again the representative dismissed the importance of insulin related hypoglycaemia.

The complainant stated he/she was alarmed at the way in which this information was presented to health professionals. As the information could be presented to practices with their specific practice information the complainant was even more concerned that this presentation or programme was being used widely and alleged it was misleading.

The use of such material brought the pharmaceutical industry into disrepute. Presenting data and making false claims was a disgrace.

The complainant alleged that there was clear disguised promotion of Ezetrol and Januvia in the presentation and that claims for the medicines could not be substantiated with any clinical trial data.

The linking of the medicines to this computer data made a clear link between the perceived problem and that the Merck Sharp & Dohme medicines could prevent or reduce the problem, which was not so in everyday practice.

The programme included prescribing information but the products had no data or licenses for the prevention of the issues that the programme purported to identify. The complainant stated that this must be wrong.

The complainant alleged that the Merck Sharp & Dohme representatives had promoted the medicines outside of the products' licences and for unlicensed uses.

When writing to Merck Sharp & Dohme, the Authority asked it to bear in mind Clauses 3.1, 3.2, 7.2, 7.4, 7.5, 7.10, 9.1, 12.1, 15.9 and 2 of the second edition of the 2012 Code of Practice.

## RESPONSE

Merck Sharp & Dohme refuted the allegations and strongly believed that it had not breached the Code by the use of the MIRROR tool generally and/or by any individual specific interaction between any Merck Sharp & Dohme employees and a practising clinician.

The MIRROR tool, which because it relied on highly interactive access to a very extensive database, could not be provided electronically, in full, to the Panel. However, Merck Sharp & Dohme provided representative screenshots of the most recent active version of the tool which demonstrated the variety of information that could be accessed, together with screenshots of information about the tool itself that must mandatorily be presented to health professionals each time it was used. These were the screenshots used in training the Merck Sharp & Dohme market access leads who used the tool in the field. Merck Sharp & Dohme also provided the relevant approval certificates.

Merck Sharp & Dohme explained that the MIRROR tool was an interactive database of information derived from Health Episode Statistics (HES) data, supplied to the company via a commercial reuse licence by the NHS Information Centre (NHSIC). The tool was used by specifically trained health access leads with NHS personnel who might be interested in the data contained within it.

The tool brought together various categories of information, including local hospital admission data; out-patient data; attainment of QOF targets and practice-level prescribing information. All data was anonymised at the patient level. The tool was used to enable better understanding of the use of local resources for specific disease entities, to help identify areas of concern and to map healthcare needs and usages geographically. At the customer's request, reports could be generated and printed for their use, subject to various compliance restrictions detailed below. By the terms of the licence with the NHSIC, access to the tool could not be provided independently to health professionals; it could only be used in conjunction with a trained market access lead.

Merck Sharp & Dohme stated that careful examination of its customer relations database, which recorded all interactions between company personnel and health professionals, did not identify any call which would fit the parameters outlined in the complaint. Merck Sharp & Dohme was confident in the credibility and integrity of its field-based employees, and did not accept that any of them would deviate from the training and briefing related

to the use of MIRROR. Without precise information from the complainant about where the alleged call had taken place and/or the Merck Sharp & Dohme employees concerned, the company could not investigate any specific employees and/or specific activity. Accordingly, its response focussed on the training and briefing information provided to employees who used the MIRROR tool (certified copies of the original and subsequent MIRROR tool briefing documents and copies of the slides used in training sessions on the tool were provided).

Merck Sharp & Dohme noted that the first screen following the log-on screen contained a summary of important information about the tool. The briefing document stated, under 'Important information': 'Prior to demonstrating the MIRROR tool, the important information shown below should be read through and discussed with customers'. In the same document, under 'What can I do and what can I not do...' was the statement: 'The first page contains important information about the tool. It highlights that MIRROR has been designed as a promotional tool; sets out an overview of the sources data used in the tool; and stipulates limitations on the use of data outputs. Customers need to be made aware of this important information at the outset'. The first paragraph of the 'Important information' screen within the tool itself stated that Merck Sharp & Dohme 'has developed this MIRROR tool for the purpose of promoting its products. Prescribing information for relevant MERCK SHARP & DOHME products can be found at the prescribing information tab found at the top of each page'.

Further users were instructed that 'When generating local reports to send to or leave with customers, MIRROR will attach the important information section and the appropriate prescribing information and these must be included when the reports are sent to or left with a customer'.

Merck Sharp & Dohme submitted that it was thus clear that its personnel were trained and briefed specifically to ensure that health professionals knew from the outset that the tool was intended for promotional use, and the tool itself complied with all relevant clauses of the Code for promotional materials. Merck Sharp & Dohme did not accept the complainant's allegation that use of the tool represented disguised promotion and it denied a breach of Clause 12.1.

With regard to more general compliance briefing, Merck Sharp & Dohme noted that the original briefing document stated that 'MIRROR is a flexible and interactive tool and it is extremely important that you ensure it is used in line with the core principles of the Code, ie it must be used in a manner that portrays Merck Sharp & Dohme products accurately, fairly and objectively. As always we must also ensure that discussions of Merck Sharp & Dohme products are always within their licence indications'. A subsequent briefing document, issued following updates to the tool, and which supplemented but did not supplant the original briefing, additionally stated that 'It is important to ensure that we maintain balance in these discussions. We may, where

appropriate, suggest that our products might help to address an issue highlighted by the MIRROR tool, but we cannot guarantee what the impact of our products will be and we should not suggest that use of our products will solve an issue completely’.

Additionally, the MIRROR training slides reinforced these points; and, in particular, stated that ‘As with all interactions, we must be fair and balanced in these discussions and ensure that they are within the terms of our product licence’.

Merck Sharp & Dohme considered that it had thus taken sufficient opportunity in its briefing and training materials to remind MIRROR users that all conversations relating to the tool must be undertaken in compliance with the principles of the Code, and, especially, that any promotion of Merck Sharp & Dohme products must be in accordance with their respective licences.

### **Ezetrol**

Merck Sharp & Dohme noted the complainant’s allegation that Ezetrol was promoted to him/her, in conjunction with use of the MIRROR tool, as a treatment that would ‘stop the coronary events’ highlighted by the in-patient data. He/she further alleged that the Merck Sharp & Dohme personnel insisted on selling Ezetrol as a medicine that would stop coronary events just because it lowered cholesterol and that, whilst they acknowledged that no cardiovascular outcome data was available for Ezetrol, ‘there soon would be’.

Merck Sharp & Dohme submitted that it was difficult to respond to a one-sided report of a conversation from an anonymous complainant. However, it found it extremely unlikely that the employees concerned would have made the alleged statements, as they would directly contravene explicit training and briefing instructions. In the case of Ezetrol, not only would they contravene the principles referred to above, but they would go against a clear reminder in the training slides that Ezetrol was not licensed for reduction in cardiovascular outcomes. Furthermore, all Merck Sharp & Dohme sales personnel knew from general training that they were not allowed to proactively raise ongoing outcome studies, and that any enquiries about such studies from health professionals should be referred to the medical or medical information department (see below).

In this context, the MIRROR tool could conceivably be used to highlight the incidence of hospital admissions for ischaemic heart disease, but it would not be possible to attribute underlying causation (eg to hypercholesterolaemia), nor to ascertain (or assert) that lowering cholesterol with Ezetrol would necessarily lead to a reduction in hospital admissions or, indeed, the incidence of heart disease. Merck Sharp & Dohme reiterated that personnel were clearly instructed not to make or suggest such inferences. It would be a matter for the individual health professional’s clinical judgement as to the weight to give to these various considerations.

Merck Sharp & Dohme was confident in the credibility and integrity of its employees in relation to this point and, as such, it strongly refuted the allegation that it had used the MIRROR tool to promote Ezetrol for cardiovascular outcomes, outwith its licensed indications.

Merck Sharp & Dohme explained that the forthcoming data about Ezetrol and reduction of coronary events was from the IMPROVE-IT trial, a cardiovascular outcome study set up to evaluate any reduction in risk of occurrence of a composite endpoint of cardiovascular death, major coronary event or stroke in subjects with stabilised high-risk acute coronary syndrome treated with an Ezetrol/simvastatin combination, compared with statin alone. The study was close to completion, and was expected to report at the end of 2014 or early in 2015. The sales force was instructed not to raise the existence of the trial proactively. If asked about it by a customer, it was instructed to respond ‘It is an ongoing clinical trial, and I am not able to discuss it with you. If you have questions about this study, I can submit a medical information request for you, or arrange a meeting with one of our MSLs’.

### **Januvia**

Merck Sharp & Dohme noted the complainant’s allegation that unwarranted assumptions were made concerning the potential reduction in hypoglycaemia-related hospital admissions if Januvia was used instead of sulphonylureas. Again, the company found it difficult to credit that the conversation took place in the manner alleged.

The MIRROR tool would provide information on the incidence of such admissions. Clearly, it was likely that a majority of these would be insulin-related, but equally some would result from sulphonylurea use. As noted in a recent review (Barnett *et al*, 2013), one study found that ‘the proportion of individuals treated with sulphonylureas or insulin for less than 2 years experiencing at least one severe (requiring external medical assistance) episode of hypoglycaemia was similar: 7% versus 7%’. Likewise: ‘Individuals most at risk of hypoglycaemia are those treated with insulin or sulphonylureas’. The authors also summarised the relative risks of Januvia and a sulphonylurea with respect to hypoglycaemia as follows: ‘For example, in a study comparing the efficacy and safety of Januvia versus glipizide in people with type 2 diabetes and inadequate glycaemic control on metformin monotherapy, the sulphonylurea was associated with a significantly greater risk of hypoglycaemic events regardless of the most recent HbA<sub>1c</sub> value’. Finally: ‘In a recent UK study, the total costs of severe hypoglycaemia were estimated as ... £16.4 million for type 2 diabetes’ (which the authors took to be a ‘gross underestimate’). Again, while some of this was undoubtedly insulin-related, it was a reasonable inference that a proportion of this figure was related to sulphonylurea administration.

It was well accepted that the class of medicines to which Januvia belonged (the dipeptidyl peptidase

(DPP)-4 inhibitors) was associated with a significantly lower risk of hypoglycaemia than the sulphonylureas (Nauck *et al*, 2007). Noting this in a promotional call was acceptable, as was highlighting the scale of hypoglycaemia-related hospital admissions through tools such as MIRROR. As noted above, employees were briefed that 'We may, where appropriate, suggest that our products might help to address an issue highlighted by the MIRROR tool, but we cannot guarantee what the impact of our products will be and we should not suggest that use of our products will solve an issue completely'. Merck Sharp & Dohme considered that use of Januvia might indeed help to address the issue of sulphonylurea-induced hypoglycaemia, and that noting this would be valid under the Code. However, as per the briefing and training materials, the company expected this to be presented in a balanced way, and without undue emphasis on possible beneficial outcomes. In particular, it would be foolish to deny the role that insulin might play in a proportion of admissions for hypoglycaemia, and there would be no potential benefit to the company if it did so. Merck Sharp & Dohme did not believe that the conversation reported by the complainant took place in the manner alleged.

### Summary

Merck Sharp & Dohme noted that it had been asked to consider the requirements of a number of clauses of the Code. As noted above, in the absence of direct evidence other than the complainant's letter as to what was or was not said at the alleged call, the company relied on its internal briefing and training materials.

With regard to Clauses 3.1 and 3.2, there was clear evidence that representatives were instructed and expected to promote only in accordance with the respective marketing authorizations. In particular, they were specifically reminded in training that Ezetrol was not licensed for improvement in cardiovascular outcomes. Merck Sharp & Dohme strongly refuted the allegation that it had breached Clauses 3.1 and 3.2, and had every confidence that its employees would follow the training and briefing.

With regard to Clauses 7.2, 7.4, 7.5 and 7.10, the MIRROR tool itself was based on validated datasets supplied by the NHS, and could not itself be misleading or require further substantiation. Whether the data had been used to make misleading, inaccurate, unbalanced or non-substantiable verbal statements was the point at issue. In the absence of further information, Merck Sharp & Dohme referred to its briefing and training materials, in which the standards it expected from its representatives who used the tool were explicitly made. The company reiterated that it had great difficulty in accepting the version of events alleged by the complainant. Again, it strongly refuted the allegations, and denied any breach of Clause 7.

It was made abundantly clear to users from the outset that MIRROR was a promotional resource, and therefore the issue of disguised promotion covered by Clause 12.1 did not arise.

Merck Sharp & Dohme submitted that its detailed briefing material complied with Clause 15.9 and that it had maintained the highest standards in the use of the tool. It denied breaches of Clauses 2 or 9.1.

### PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. Such complaints were accepted and like all complaints judged on the evidence provided by the parties. The complainant bore the burden of proof. It was not possible to contact the complainant for further information.

The Panel noted Merck Sharp & Dohme's clear acknowledgement that MIRROR had been designed as a promotional tool. Point 1 of the information which Merck Sharp & Dohme stated representatives had to read through and discuss with customers before they proceeded further with the MIRROR tool stated, 'Merck Sharp & Dohme ("MERCK SHARP & DOHME") has developed this MIRROR tool for the purpose of promoting its products. Prescribing information for relevant MERCK SHARP & DOHME products can be found at the prescribing information tab found at the top of each page'. The Panel noted that it had not been provided with the complete MIRROR tool. Screenshots showed that the pages of MIRROR provided, which Merck Sharp & Dohme submitted were representative of the most recent active version of the tool, all included a link to prescribing information. Merck Sharp & Dohme had further submitted that reports generated at a customer's request would have prescribing information attached. The Panel did not know in what context the meeting in question had been set up but it noted that the complainant had clearly considered that Ezetrol and Januvia had been promoted during the course of the conversation. In that regard the Panel did not consider that the use of MIRROR amounted to disguised promotion. No breach of Clause 12.1 was ruled.

The Panel noted that both Ezetrol and Januvia had been promoted within the context of a conversation about data held within the MIRROR tool. It appeared that field-based staff used the MIRROR tool to examine data from the local health economy and, within that context, promote a medicine. With regard to Ezetrol, the complainant had submitted that the representatives had shown a number of slides that looked at non-elective admissions for a number of coronary events and had focussed on the number of these events which had occurred in patients with cholesterol levels above the QOF targets. As the complainant was anonymous and non-contactable, Merck Sharp & Dohme could not identify which of its field-based staff were involved but it did submit that the MIRROR tool could conceivably be used to highlight the incidence of hospital admissions for ischaemic heart disease but that it would not be possible to attribute this to hypercholesterolaemia or to assert that the use of Ezetrol would result in fewer hospital admissions. In the Panel's view however, to promote Ezetrol, a lipid lowering agent, following a conversation about non-elective cardiovascular hospital admissions in patients with cholesterol levels above QOF targets,



invited the customer to link the two conversations and assume that Ezetrol had a role in reducing such admissions. Although MIRROR briefing material stated that Merck Sharp & Dohme products must be portrayed accurately, fairly and objectively, and always within their licence, the Panel noted the following statement from the MIRROR briefing document (ref NOND-1034256-0020):

‘MIRROR can and should also be used with a customer(s) to highlight local performance gaps or disease management issues and to facilitate discussions to progress towards potential solutions.

It is important to ensure that we maintain balance in these discussions. We may, where appropriate, suggest that our products might help to address an issue highlighted by the MIRROR tool but we cannot guarantee what the impact of our products will be and we should not suggest that use of our products will solve an issue completely.’

An earlier briefing document (ref NOND-1034256-0007) stated:

‘MIRROR can be used in calls with healthcare professionals to raise specific disease management issues and it is acceptable in that same call to then discuss how a treatment/disease management strategy, involving therapy classes that involve 1 or more MSD products, could produce benefits for the patient and local health economy.’

The Panel noted that the summary of product characteristics for Ezetrol stated that ‘A beneficial effect of Ezetrol on cardiovascular morbidity and mortality has not yet been demonstrated’. The Panel considered, given the statements above from the briefing documents, that on the balance of probabilities, concurrent use of the MIRROR tool and promotion of Ezetrol had given a misleading impression, which could not be substantiated, that use of the medicine would decrease non-elective hospital admissions due to coronary events. A breach of Clauses 7.2 and 7.4 was ruled. Further, the Panel considered that such an impression, given the statement in the SPC that a beneficial effect on cardiovascular morbidity had not been demonstrated, was inconsistent with the particulars listed in the Ezetrol SPC. A breach of Clause 3.2 was ruled. The Panel considered that Ezetrol had, in effect, been promoted for an unlicensed indication. A breach of Clause 3.1 was ruled. The Panel considered that the representatives had not promoted the rational use of Ezetrol. A breach of Clause 7.10 was ruled.

The Panel noted that although the complainant stated that he/she had asked for outcome data, as the claim for reduced hospital admissions could not be substantiated, none could be provided. In that regard the Panel ruled no breach of Clause 7.5, noting its ruling above of a breach of Clause 7.4.

The Panel noted the complainant’s allegation that the representatives had suggested that use of

Januvia instead of sulphonylureas would reduce urgent hospital admissions due to hypoglycaemia. The representatives had not been able to produce any data to support this claim. The Panel noted Merck Sharp & Dohme’s submission that Januvia belonged to a class of medicines which was associated with a lower incidence of hypoglycaemia than the sulphonylureas and that to highlight this in a promotional call was acceptable, as was highlighting the scale of hypoglycaemia-related hospital admissions through tools such as MIRROR. The Panel noted its comments above and considered that to promote Januvia within the context of a conversation about hypoglycaemia-related hospital admissions would imply that the medicine had a role in reducing such admissions. The Panel considered that such an implication was misleading and could not be substantiated. A breach of Clauses 7.2 and 7.4 was ruled. The Panel did not consider that such an impression was inconsistent with the particulars listed in the Januvia SPC given that the SPC did not refer to hypoglycaemia complications or morbidity. No breach of Clause 3.2 was ruled. The Panel considered, however, that Januvia had, in effect, been promoted for an unlicensed indication. A breach of Clause 3.1 was ruled. The Panel considered that the representatives had not promoted the rational use of Januvia. A breach of Clause 7.10 was ruled.

The Panel noted that although the complainant stated that he/she had asked the representatives to substantiate the claim that Januvia would reduce hospital admissions, as the claim could not be substantiated no data could be provided. In that regard the Panel ruled no breach of Clause 7.5, noting its ruling above of a breach of Clause 7.4.

The Panel was very concerned about the wording of the MIRROR briefing documents quoted above. In the Panel’s view, to suggest that a medicine might help to address an issue or could produce benefits usually resulted in the impression that the medicine would definitely do so. MIRROR was used to establish a local health economy need or gap which, when followed by a promotional discussion, invited the customer to link the two and assume that the medicine would address that need or fill the gap. In the Panel’s view the briefing material positively encouraged representatives to discuss medicines in relation to the local health economy data provided by MIRROR. The Panel considered that the use of the MIRROR tool to discuss healthcare issues was incompatible with the concurrent promotion of medicines unless those medicines were appropriately licensed or had relevant outcome data (eg reduced hospital admissions). In the Panel’s view the MIRROR briefing material advocated a course of action which was likely to breach the Code. A breach of Clause 15.9 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel further considered that the use of MIRROR in conjunction with the promotion of medicines, and to brief representatives that it was acceptable to suggest that Merck Sharp & Dohme’s products might help to

address an issue highlighted by the tool, was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

During its consideration of this case, the Panel was concerned to note that in briefing material prepared for the MIRROR launch, (ref NOND-1040876-0005), it was stated that 'Therefore Ezetrol should be an essential part of the management of patients with type 2 diabetes and CVD [cardiovascular disease] to reduce cholesterol and CV risk'. The Panel queried whether describing Ezetrol as an 'essential' part of management met the requirements of the Code. The Panel also queried whether stating that it reduced CV risk was consistent with the particulars listed in the Ezetrol SPC given that the medicine was licensed to reduce cholesterol and that no beneficial effect of the medicine on cardiovascular morbidity or mortality had yet been demonstrated. Similar concerns applied to the statement that Januvia 'improves patient experience by reducing the complications of type 2 diabetes'. The Panel requested that Merck Sharp & Dohme be advised of its concerns.

## APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme based its appeal on four key points:

- 1 There was reason to believe that the complaint which purported to come from a health professional was, in fact, from an ex-employee with a grudge following redundancy. As such, it might be a complete fabrication and could not be taken at face value.
- 2 The complainant had described a series of interactions that Merck Sharp & Dohme did not recognize as likely to have occurred and could not verify from its records.
- 3 It was entirely appropriate to use the MIRROR tool in the context of the promotion of medicines.
- 4 The interactions described in the complaint were inconsistent with everything the company had put in place to ensure appropriate use of the MIRROR tool.

Merck Sharp & Dohme was extremely concerned about the potentially far-reaching implications of the Panel's ruling for the industry as a whole and the manner in which it interacted with the NHS and health professionals. Merck Sharp & Dohme submitted that companies should work with the NHS and NHS health professionals to help them achieve their strategic objectives. One of the NHS's strategic objectives and priorities was to improve the nation's cardiovascular health and the Government had made it clear that key to this was the early diagnosis and management of diabetes and hypercholesterolemia. It was entirely appropriate for a company to help doctors understand the burden of specific diseases within their geographical area, identify unmet needs and inequalities in access to care based on geographical location and identify common risk factors such as type 2 diabetes and elevated cholesterol levels. A company must then be able to explain how its products could help improve glycaemic control in patients with type 2 diabetes

(eg Januvia) and address hypercholesterolaemia that was not appropriately controlled with a statin alone (eg Ezetrol).

Merck Sharp & Dohme submitted that if the Panel was correct, companies would not be able to discuss the efficacy of their products for the approved indications in the context of the NHS's strategic priorities and that could not possibly be the right outcome. For the Panel to have found Merck Sharp & Dohme in breach for off-label promotion, it needed to identify an off-label product claim. The Panel had not provided any evidence that Merck Sharp & Dohme had made such a claim. Rather, the Panel had raised a hypothesis that a broad, contextual discussion of cardiovascular health in a doctor's area followed by a discussion of a product's efficacy for its approved indications must constitute off-label promotion.

Merck Sharp & Dohme asked the Appeal Board to identify a single piece of evidence that it had promoted either Januvia or Ezetrol off-label.

## 1 The complaint

Merck Sharp & Dohme appreciated the need for the PMCPA to be able to consider anonymous complaints as there would undoubtedly be cases where a genuine 'whistle blower' felt unable to identify him/herself when he/she nonetheless raised important matters. However, the acceptance of anonymous complaints at face value, as seemed to have taken place here, without a critical appraisal of the veracity of the allegations, left open the possibility that vindictive allegations were assumed to be true and Merck Sharp & Dohme was left to defend itself against an unverifiable 'he said, she said' situation. Historically in such situations, where versions of events differed between complainant and respondent, the PMCPA had generally concluded that the level of proof required to rule a breach had not been reached. This was also reflected in fundamental concepts of procedural fairness and the right to a fair hearing. On this occasion, however, the unverified accusations of the complainant seemed to have been taken as true, despite extensive evidence from Merck Sharp & Dohme that the described events were unlikely to have occurred.

Merck Sharp & Dohme noted that over the past few months, it had been the subject of three complaints from anonymous, non-contactable complainants – the current case (Case AUTH/2699/2/14), and Cases AUTH/2651/11/13 and AUTH/2646/10/13. Historically, this was very much out of character. The timing fitted with a significant downsizing and restructuring of the company's primary care division.

Merck Sharp & Dohme had examined the complaint submitted in the current case alongside that of Case AUTH/2646/10/13, which purported to come from a health professional, and noted unusual structure (eg subject matter line being placed above the salutation line) and phraseology ('the drug firm Merck Sharp & Dohme') which raised significant doubt about whether they truly came from two independent health professionals. If there was doubt about the

complaint's true provenance, then there must be doubt about the truthfulness of the content.

## 2 The described interaction

Merck Sharp & Dohme submitted that since the complainant was anonymous and non-contactable, it was not possible to be certain of some information, eg the location of alleged activities. The complainant had alleged that he/she had met two Merck Sharp & Dohme representatives. Merck Sharp & Dohme representatives did not usually call on health professionals in pairs. A manager sometimes accompanied a more junior representative, but the MIRROR tool was used only by more experienced representatives, so this was unlikely to have occurred in this case. In any event, had two representatives visited a single health professional together, this would have been documented in Merck Sharp & Dohme's customer relationship management (CRM) tool in which representatives had to record details of all interactions with health professionals, including the names of other representatives present. Merck Sharp & Dohme had not found any record that a meeting involving two representatives using the MIRROR tool had taken place.

Merck Sharp & Dohme submitted the complainant had provided no evidence to show that this meeting took place (representative names, for example, or copies of print-outs that might have been left) and no evidence to support that the alleged claims were made by its representatives. This was not a description of an event that Merck Sharp & Dohme recognised, and it submitted that this was unlikely to be a true record of a meeting between Merck Sharp & Dohme and a health professional.

Merck Sharp & Dohme submitted that even if the Appeal Board concluded that the interaction did take place as described, it did not accept that there was any clear evidence that the alleged claims were made by its representatives.

## 3 Use of the MIRROR tool

Merck Sharp & Dohme submitted that the MIRROR tool was essentially a 'front end' computer programme that displayed data from NHS databases, specifically hospital episode statistics. As such, it allowed prescribers and purchasers to understand the burden of illness in their own locality, and by implication draw conclusions about the relative position with neighbouring areas, national averages, achievement of NHS targets, strategies and outcomes, volume of events, etc.

Merck Sharp & Dohme submitted that the MIRROR tool was used to help health professionals understand the burden of specific diseases within their geographical area and to identify unmet needs. In particular, the MIRROR tool could highlight the real world implications of particular conditions or health risks, such as cardiovascular risk, and the size of the problem in the health professional's locality. Educating health professionals about this was entirely appropriate and consistent with the

Government's health strategy. The UK had a high rate of cardiovascular disease with significant cost implications that placed a huge financial burden on the NHS. As a result, in 2013 the Department of Health (DoH) developed a specific cardiovascular disease outcomes strategy for the prevention, diagnosis and treatment of cardiovascular disease to improve outcomes ('Cardiovascular Disease Outcomes Strategy: Improving outcomes for people with or at risk of cardiovascular disease'). This document specifically recognized inequalities in access to care, including inequalities based on geographical location, and identified common risk factors, such as diabetes and elevated cholesterol levels. The MIRROR tool allowed Merck Sharp & Dohme representatives to establish a context, namely that it was important for health professionals to identify, and where appropriate treat, patients with a particular condition or health risk. Merck Sharp & Dohme representatives could then discuss the use of the company's products, within their licensed indications, as part of the NHS's overall treatment strategies.

Merck Sharp & Dohme submitted that this did not involve off-label product claims. Nor did it explore the 'what if....' type of question – 'What if I prescribed more Ezetrol?' or 'What if I prescribed more Januvia?'. These questions could not be addressed because the impact of Ezetrol on cardiovascular-related hospital admissions, or Januvia on diabetes-related hospital admissions, was unknown. Whilst the software was clever and attractive, there was nothing unique about the data, only about how they were presented.

Merck Sharp & Dohme was confident that its comprehensive and thorough training programme, which it discussed below, meant that no Merck Sharp & Dohme representative would make inappropriate claims as alleged.

Merck Sharp & Dohme submitted that during the development of the MIRROR tool there were extensive discussions about whether or not to use it for promotional purposes, because the data contained within it – effectively local demographics and health resource data – were unrelated to specific products. The data did not represent or purport to represent the impact of any particular medicine. It was also anticipated that in demonstrating the tool, the customer might ask for a 'cut' of the data that identified patients who were outside the licensed indication for Merck Sharp & Dohme's products. Unlike a printed detail aid, where epidemiological data could be presented that matched the licensed patient population, with an interactive system it was not possible to prescribe what data were explored.

On balance, Merck Sharp & Dohme submitted that given the value of the data and the surrounding discussions, it decided that the tool could be used in association with a promotional call, to establish the size of the problem in the locality, before detailing Ezetrol and/or Januvia.

Merck Sharp & Dohme noted that the Panel, however, had concluded that '... to suggest

a medicine might help to address an issue or could produce benefits usually resulted in the impression that the medicine would definitely do so'. It stated that using MIRROR to identify a local health economy need or gap followed by a promotional discussion '... invited the customer to link the two and assume that the medicine would address that need or fill the gap'. Finally, the Panel considered that 'the use of the MIRROR tool to discuss healthcare issues was incompatible with the concurrent promotion of medicines unless those medicines were appropriately licensed or had relevant outcome data (eg reduced hospital admissions)'.

Merck Sharp & Dohme strongly disagreed with the Panel's unfounded conclusions. Indeed, if the Panel's ruling was maintained, it would negatively impact not just Merck Sharp & Dohme but the entire British pharmaceutical industry. The Panel's position meant that representatives could never draw attention to the burden of specific diseases on the NHS, educate health professionals about DoH strategy or clinical guidelines from the National Institute for Health and Care Excellence (NICE) or even discuss general disease areas. In particular, pharmaceutical companies could not explain how their products fitted into the overall treatment priorities of the NHS. Essentially, the Panel's position would prohibit pharmaceutical companies from giving any sort of context to their discussions about the licensed uses of their medicines. This could not be a correct interpretation of the Code.

Further, Merck Sharp & Dohme submitted that there was no justification for the Panel's assertion that to suggest a medicine might play a distinct role in addressing a broader public health issue usually resulted in the impression that the medicine would definitely do so. If that assertion were true, any claim that a medicine could treat a particular condition that played a role in a wider public health concern, in this case cardiovascular health and/or diabetic complications, would be interpreted as a guarantee of its efficacy in the broader context. Such a conclusion was illogical and did not reflect the many years of experience of promotional interactions between pharmaceutical representatives and sophisticated prescribers.

To illustrate this, Merck Sharp & Dohme noted the following quotation from the DoH's 2013 'Cardiovascular Disease Outcomes Strategy: Improving outcomes for people with or at risk of cardiovascular disease.'

Excerpt from executive summary, page 5:

'... CVD [cardiovascular disease] in practice represents a single family of diseases and conditions linked by common risk factors and the direct effect they have on CVD mortality and morbidity. These include coronary heart disease, stroke, hypertension, hypercholesterolemia, diabetes, chronic kidney disease, peripheral arterial disease and vascular dementia. Many people who have one CVD condition commonly suffer from another and yet opportunities to

identify and manage these are often missed. Patients often receive care from multiple different teams in a disjointed way. This results in uncoordinated care, multiple different hospital visits and, in some cases, confusing or contradictory information. This happens both in hospitals and in the community. A more co-ordinated and integrated approach is needed to assessment, treatment and care to improve outcomes, including patient experience and patient safety.'

Paragraph 1.3-1.4:

'CVD is an overarching term that describes a family of diseases sharing a common set of risk factors. This outcomes strategy largely focuses on conditions causing, or resulting from, atherosclerosis (furring or stiffening of the walls of arteries), particularly coronary heart disease, stroke and peripheral arterial disease (PAD).

It also covers other conditions such as vascular dementia, chronic kidney disease (CKD), arrhythmias, sudden cardiac death and heart failure, because they share common risk factors or have a significant impact on CVD mortality or morbidity. The complications of diabetes also share the same modifiable risk factors as CVD and having diabetes increases individuals' risk of CVD. This strategy considers the implications of diabetes on CVD risk rather than its detailed management.'

Paragraph 1.6

'A number of common risk factors are recognised as increasing the likelihood of individuals developing atherosclerosis. [...]

- hypertension/raised blood pressure;
- raised cholesterol/disordered lipids;
- impaired glucose tolerance/diabetes; and
- chronic kidney disease (CKD).'

Merck Sharp & Dohme submitted that if the Panel was correct, no representative would be able to discuss the importance of managing diabetes and elevated cholesterol levels using products approved for those purposes, given their importance as common risk factors linked to cardiovascular disease (CVD). In the Panel's view, to 'suggest a medicine might help to address [CVD] or could produce benefits usually resulted in the impression that the medicine would definitely do so'.

Merck Sharp & Dohme submitted that that was simply not what MIRROR or its representatives did and the Panel had produced no evidence that this had occurred. Merck Sharp & Dohme and its representatives had helped doctors understand cardiovascular health issues and inequalities in treatment between areas, before discussing use of Ezetrol and Januvia for their approved indications. There was no claim that the products were efficacious against CVD. If clinicians stated that 'patients with elevated cholesterol levels and type 2 diabetes have a higher risk of CVD, so it was important that we do something about blood sugar

and LDL cholesterol levels', they were not stating medicines they prescribed for that purpose were efficacious against, for example, coronary heart disease, stroke and peripheral arterial disease; they were merely stating that the patients needed to lower their blood sugar and cholesterol levels because elevated levels put them at risk of heart disease. There was no claim of efficacy against CVD. Nor did it follow that just because MIRROR allowed the presentation of data relating to the significance of cardiovascular health issues in a particular locality, that any subsequent discussion of the efficacy of Merck Sharp & Dohme's products must necessarily be off-label.

#### 4 Training and briefing materials

Merck Sharp & Dohme submitted that its representatives had been rigorously trained on the use of the MIRROR tool and the types of statements that were acceptable. This training was delivered at a full day, face-to-face, training session attended by the medical and compliance teams. A significant part of the training was role play scenarios where the representatives were thoroughly trained on how to present the MIRROR data, and to make sure that they discussed only the licensed indications for both Ezetrol and Januvia.

Merck Sharp & Dohme submitted that representatives were made fully aware of the source of the data in MIRROR and what the data represented (and what they did not represent). The representatives were clearly instructed that the data should not be used to make product-related claims that either could not be substantiated, or that might recommend, directly or indirectly, the use of either Ezetrol and/or Januvia in patients outside the respective licensed indications.

Merck Sharp & Dohme submitted that with a comprehensive and thorough training programme in place, it was confident that none of its representatives would make inappropriate claims as alleged.

Merck Sharp & Dohme noted that the Panel appeared to have focused on three paragraphs from MIRROR briefing documents. Two of these, from briefing document (ref NOND-1034256-0020) were:

'MIRROR can and should also be used with a customer(s) to highlight local performance gaps or disease management issues and to facilitate discussions to progress towards potential solutions.

It is important to ensure that we maintain balance in these discussions. We may, where appropriate, suggest that our products might help to address an issue highlighted by the MIRROR tool but we cannot guarantee what the impact of our products will be and we should not suggest that use of our products will solve an issue completely.'

The third paragraph, from briefing document (ref NOND-1034256-0007), stated:

'MIRROR can be used in calls with healthcare professionals to raise specific disease management issues and it is acceptable in that same call to then discuss how a treatment/disease management strategy, involving therapy classes that involve 1 or more MSD products, could produce benefits for the patient and local health economy.'

Merck Sharp & Dohme noted an additional statement from the briefing document ref NOND-1034256-0007, which the Panel appeared to have overlooked or ignored:

'MIRROR is a flexible and interactive tool and it is extremely important that you ensure it is used in line with the core principles of the Code i.e. it must be used in a manner that portrays MSD products accurately, fairly and objectively. **As always we must also ensure that discussions of MSD products are always within their licence indications'** (emphasis added by Merck Sharp & Dohme).

Contrary to the Panel's views, Merck Sharp & Dohme submitted that, in conjunction with the face-to-face training, the three paragraphs from the briefing material quoted by the Panel and the additional paragraph highlighted above, made it clear to representatives that they must be very careful not to claim, suggest or infer use of any Merck Sharp & Dohme product outside of their licensed indications, ie for a beneficial effect on health outcomes.

#### 5 Appeal

Merck Sharp & Dohme did not accept that there was any reliable evidence that its representatives had claimed a reduction in cardiovascular hospital admissions in patients treated with Ezetrol, or diabetes-related admissions in patients treated with Januvia. Consequently, Merck Sharp & Dohme appealed the Panel's rulings of breaches of Clauses 7.2, 7.4 and 7.10.

Merck Sharp & Dohme noted that the Panel had ruled breaches of Clause 3.1, which stated that a medicine must not be promoted prior to the grant of a marketing authorization. Merck Sharp & Dohme did not agree that this had occurred, nor was there evidence to suggest so. Both Ezetrol and Januvia had marketing authorizations. Consequently, Merck Sharp & Dohme appealed the Panel's ruling that there had been breaches of Clause 3.1.

Similarly, Clause 3.2 stated that the promotion of a medicine must not be inconsistent with the particulars listed in the SPC. Merck Sharp & Dohme submitted that as its representatives had only promoted Ezetrol to reduce cholesterol in patients with hypercholesterolaemia, and Januvia to improve glycaemic control, there had been no breach of Clause 3.2 and it appealed the Panel's ruling.

Contrary to the Panel's view, Merck Sharp & Dohme submitted that the representative's briefing materials and associated training made it clear when and where it was acceptable to suggest the use

of Ezetrol and/or Januvia. Merck Sharp & Dohme was confident that its representatives had not been inappropriately briefed to suggest, imply or claim that Merck Sharp & Dohme products reduced hospital admissions. As a result Merck Sharp & Dohme denied a breach of Clause 15.9 and it appealed the Panel's ruling.

Merck Sharp & Dohme strongly believed that high standards had been maintained at all times and that the reputation of, and confidence in, the pharmaceutical industry had not been compromised. Merck Sharp & Dohme therefore submitted that there had been no breach of either Clauses 9.1 or 2, and it appealed the Panel's rulings in this regard.

## 6 Summary

In summary, Merck Sharp & Dohme submitted that there was considerable doubt whether the meeting described by the anonymous, non-contactable complainant actually occurred. In Merck Sharp & Dohme's view, the meeting was highly unlikely to have taken place due to the robust, face-to-face, detailed training and briefing documents provided for representatives and the fact that it had been unable to find any evidence in the CRM system of a meeting between two Merck Sharp & Dohme representatives and a health professional involving the use of the MIRROR tool. Merck Sharp & Dohme suspected that the alleged incident had been fabricated.

Merck Sharp & Dohme was certain that, as a result of extensive training, its representatives who used MIRROR understood the difference between describing the local epidemiology, incidence, prevalence etc, and making a claim for Ezetrol and Januvia.

Merck Sharp & Dohme submitted that Code and compliance-related training provided to representatives had created a strong culture of Code awareness and compliance within the company. Merck Sharp & Dohme was confident and proud that all of its representatives were fully conversant with relevant areas of the Code and would never make claims that were misleading, incapable of substantiation, or outside the licensed indications for any of its products.

Merck Sharp & Dohme was greatly concerned that in the absence of any proof offered by the complainant, the Panel appeared to have taken the complaint at face value. The Panel's rulings also appeared to have been based on an interpretation that the representative's briefing and training material, as well as some content of the MIRROR tool, encouraged representatives to promote products outside their licensed indications, when in fact the briefing materials and the training made it absolutely clear that they must not do that. Further, the Panel seemed to have assumed that representatives would use the data displayed within MIRROR to promote Ezetrol and Januvia outside their licensed indications, contrary to the clear instructions given to them. There was no evidence that any of the alleged breaches actually occurred and Merck Sharp

& Dohme asked the Appeal Board to overturn all breaches ruled.

Merck Sharp & Dohme submitted that while it understood the importance of complying with its obligations under the Code, and it took any alleged breach very seriously indeed, it was particularly disappointed by the Panel's ruling of a breach of Clause 2. Rulings of breaches of Clause 2 were a sign of particular censure and were reserved for circumstances that brought discredit on the pharmaceutical industry. Merck Sharp & Dohme considered it was unjust and distinctly unfair to rule a breach of Clause 2 where the only 'evidence' was an unreliable complaint from an anonymous and non-contactable individual who claimed to be a health professional and for the Panel to take that complaint at face value, without questioning its accuracy or veracity.

Indeed, Merck Sharp & Dohme submitted that the Panel seemed to have ignored its own procedures, as it had described them in the ruling. The first paragraph of the Panel ruling stated:

'The Panel noted that the complainant was anonymous and non-contactable. Such complaints were accepted and like all complaints **judged on the evidence** provided by the parties. **The complainant bore the burden of proof** (emphasis added by Merck Sharp & Dohme).'

Merck Sharp & Dohme submitted that the anonymous complainant had not provided any evidence and as such it could not understand how, when the complaint was 'judged on the evidence' and that 'the complainant bore the burden of proof' the Panel could make any ruling against Merck Sharp & Dohme, and certainly not a ruling of a breach of Clause 2.

## APPEAL BOARD RULING

The Appeal Board noted that the Merck Sharp & Dohme had raised points about the veracity of the complaint, conduct of the meeting and use of the MIRROR tool that had not previously been submitted to the Panel.

Firstly the Appeal Board considered whether the meeting as described took place and consequently whether the alleged claims were made, bearing in mind that the complainant had to establish his/her case on the balance of probabilities.

The Appeal Board noted from the Merck Sharp & Dohme representatives at the appeal that the company's field based area access leads (AALs) who used the MIRROR tool were separate from its sales representatives. The AALs had a promotional and non promotional role. Each AAL was experienced and had received specialist training. A call by an AAL to use the MIRROR tool would only be in response to a request from a health professional (payers, commissioners etc) usually elicited by a sales representative at a prior call. The way in which the AAL would use the MIRROR tool in each meeting was led by the health professional choosing

which information he/she wanted to view in a chosen disease area and region. The discussion and extraction of data in just one disease area could take up to 2 hours. The Appeal Board noted from the Merck Sharp & Dohme representatives at the appeal that the MIRROR tool examined the burden of illness and despite its description as a promotional tool, it was not designed to funnel down to a product discussion although this might happen.

The Appeal Board noted that the complainant had alleged that two representatives had detailed the MIRROR tool for both Ezetrol and its effect on coronary events and Januvia and its effect on hypoglycaemic events. The Appeal Board noted from the Merck Sharp & Dohme representatives at the appeal that a call detailing the MIRROR tool concerning two different disease areas did not occur but if it had, it would take up to 4 hours to complete which would be impractical for most health professionals. The Appeal Board noted from the Merck Sharp & Dohme representatives at the appeal that it was standard practice for AALs to work alone and in that regard Merck Sharp & Dohme had checked previous AAL visits and it could find no record of an AAL detailing the MIRROR tool with another Merck Sharp & Dohme employee as described by the complainant. The company's CRM database required a dual call to be recorded.

The Appeal Board noted from the Merck Sharp & Dohme representatives at the appeal that at the end of detailing the MIRROR tool a report was generated for the health professional to keep. The Appeal Board noted that the complainant had not provided any additional evidence such as this report to support his/her allegations.

The Appeal Board noted that all complaints were judged on the evidence provided by the parties with the burden on the complainant to prove his/her case on the balance of probabilities. The Appeal Board noted its comments above and considered that, on the balance of probabilities, it was not satisfied that the alleged meeting took place. Consequently the Appeal Board ruled no breaches of Clauses 3.1, 3.2, 7.2, 7.4 and 7.10 in relation to the claims about Ezetrol allegedly made by Merck Sharp & Dohme's representatives. Similarly the Appeal Board also ruled no breaches of Clauses 3.1, 7.2, 7.4 and 7.10 in relation to the claims about Januvia allegedly made by Merck Sharp & Dohme's representatives. The appeal on these points was successful.

The Appeal Board noted that in the information which preceded the MIRROR tool, it was clearly stated that Merck Sharp & Dohme had developed the tool for the purpose of promoting its medicines. The company representatives at the appeal stated, however, that it was for use in a non promotional/

health inequality/service improvement discussion but that if that discussion led into a promotional discussion the tool would nonetheless meet the requirements of the Code. The Appeal Board was concerned that the MIRROR tool thus appeared to have both a non promotional and a promotional purpose and in that regard it queried whether all of the Code requirements for each could truly be met.

The Appeal Board noted that the MIRROR tool launch materials (ref NOND-1040876-0005), part of the briefing material provided by Merck Sharp & Dohme, referred to the core campaigns for both Januvia and Ezetrol. In the Appeal Board's view some of the slides appeared to positively encourage AALs to take opportunities to promote Merck Sharp & Dohme's products (eg the slide headed 'Value Proposition for key stakeholders'). This slide stated that Ezetrol should be an *essential* part of the management of patients with type 2 diabetes and CVD to reduce cholesterol and CV risk' (emphasis added). In the Appeal Board's view to describe Ezetrol as essential was exaggerated; it was indicated only as add-on therapy when patients had been inadequately controlled with a statin alone. A slide which detailed the payer proposition for Januvia stated that '... sitagliptin improves patient experience by reducing the complications of type 2 diabetes'. In that regard the Appeal Board noted from the Merck Sharp & Dohme representatives that there was no outcome data to show that Januvia reduced cardiovascular disease, skin conditions etc (ie the 'complications' of diabetes) and although it had a low incidence of hypoglycaemia, hypoglycaemic episodes were acute events/side effects of therapy, not complications of the disease.

The Appeal Board considered that the MIRROR tool briefing materials were likely to encourage AALs to discuss Merck Sharp & Dohme products in relation to data generated by the MIRROR tool. It noted its comments above about the briefing material and the absence of patient outcome data. The Appeal Board considered that the briefing materials advocated a course of action that was likely to lead to a breach of the Code and consequently it upheld the Panel's ruling of a breach of Clause 15.9. High standards had not been maintained and the Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on these points was unsuccessful. The Appeal Board did not consider that the circumstances warranted a ruling of a breach of Clause 2 and no breach was ruled. The appeal on that point was successful.

**Complaint received**                    **3 February 2014**

**Case completed**                        **8 July 2014**

# GENERAL PRACTITIONER v PFIZER

## Gaining access for remote detailing

A General Practitioner alleged that a representative from Pfizer had used underhand methods to speak to him in breach of the Code.

The complainant explained that the named representative had telephoned at least twice one morning (whilst he was seeing patients) and spoken to the receptionist, each time insisting that the complainant had arranged to speak to her and pressing to be put through urgently. The complainant called her back because he had previously had concerns about a medicine and wondered if it was a clinical scientist from Pfizer that had called. On returning the call, the complainant discovered that the caller was a representative trying to promote a medicine. The complainant stated that when challenged, the representative explained that the arrangements for the call had been made via a colleague. From his receptionist's report, the complainant did not think that that was so.

The detailed response from Pfizer is given below.

The Panel noted that the parties' accounts of whether the appointment was actually booked, the arrangements for the booking and what the representative had stated with regard to the urgency of the call differed. The complainant had not been party to any of these conversations. The Panel noted the difficulty in dealing with complaints based on one party's word against the other; it was often impossible in such circumstances to determine precisely what had happened. The introduction to the Constitution and Procedure stated that a complainant had the burden of proving their complaint on the balance of probabilities but the Panel noted the difficulty for complainants in cases such as this to provide any evidence to support their allegations. The Panel noted, however, that a high degree of dissatisfaction was usually required before an individual was moved to submit a formal complaint. The Panel noted that the complainant had been sent a copy of Pfizer's submission and stood by his version of events.

The Panel noted that arrangements for the call had been made via a call scheduling company whose call notes recorded that a named receptionist had suggested the date and time of the appointment. On the day, the representative had telephoned at the pre-arranged time and then, because the complainant was busy, had, at the receptionist's suggestion, called again fifteen minutes later. As the complainant was still busy, the representative had asked if he could return her call. In the Panel's view, this frequency of calls and the request for a return call, might have suggested to the complainant and receptionist that the matter was urgent even if as submitted by Pfizer, the representative had not stated it to be so. Although

it appeared that communication between the parties could have been better, the Panel noted that the representative had set out to fulfil a pre-arranged call at a time she had been told was convenient for the complainant. The Panel could understand the representative's desire to keep the appointment given that supplementary information to the Code stated that if, for unavoidable reasons, an appointment could not be kept, the longest possible notice must be given.

The Panel noted the differences between the parties but considered that, on balance, it had not been demonstrated that in contacting the complainant the representative had not maintained high standards of ethical conduct. Nor had it been established that, on the balance of probabilities, the representative had employed any inducement or subterfuge in order to speak to the complainant. The Panel thus ruled no breach of the Code.

A general practitioner complained that, a named Pfizer Limited medical representative had used subterfuge to gain an interview.

### COMPLAINT

The complainant explained that the named representative had called his practice at least twice on the morning in question and spoken to the receptionist. On both occasions the representative insisted that the complainant had made a prior arrangement to speak to her at 11am and pressed to be put through urgently. The complainant stated that he was seeing patients so called her back on the number taken by the receptionist. The complainant submitted that he had previously made enquiries through an independent pharmacist regarding concerns about a medicine and wondered if it was a clinical scientist from Pfizer that had called. On returning the call, the complainant discovered that the person who had called him was a representative attempting to market one of her products for the treatment of atrial fibrillation. The complainant stated that when challenged, the representative did not deny that the complainant had not made a prior arrangement to speak to her but claimed that it was a colleague who had called on her behalf. From his receptionist's report, the complainant did not think that that was so.

The complainant noted that Clause 15.3 stated that representatives must not employ any subterfuge to gain an interview and alleged that the representative in question had done just that. The complainant was annoyed that the representative had used underhand methods to try and obtain an interview.

When writing to Pfizer, the Authority asked it to respond in relation to Clauses 15.2 and 9.1 in addition to Clause 15.3 as cited by the complainant.



## RESPONSE

Pfizer submitted that the representative in question was a senior member of the remote detailing team having previously been a Pfizer primary care representative. The individual in question always conducted herself in a professional manner ensuring that she worked with the highest levels of integrity. She had passed the ABPI examination.

Pfizer worked with a call scheduling company which booked appointments with health professionals via surgery reception staff. This was the same practice as for any customer-facing representative going into the surgery except that the actual meeting was held via an online meeting room rather than face-to-face. Pfizer submitted that UK health professionals found this way of interacting convenient and flexible.

An agent from the call scheduling company contacted the complainant's surgery in late January 2014 and spoke to the receptionist who took down the details and suggested the time of the appointment. The call scheduling company's agent created an appointment for the representative to call the complainant on the day in question at 11am as recommended by the receptionist; the complainant would be there all day and could take the call after morning surgery. The receptionist stated that the telephone lines would be open and the complainant would have computer access for the online call.

The representative called the complainant, as arranged, and spoke to the receptionist on duty. The receptionist mentioned that the complainant was in surgery and suggested Wednesday afternoon would be a good time to call. However, the representative explained that she had an appointment to speak to the complainant at 11am and asked if she could call back when surgery had finished as she did not want him to think she had missed the appointment. In light of this explanation, the receptionist suggested that the representative call back at approximately 11.15am. Pfizer noted that the representative had acted on the advice given and called back at 11.15am. Given that surgery had not yet finished, she left a message with the receptionist to ask if the complainant could call her when convenient. This seemed to be the most reasonable course of action given that an appointment had been scheduled with the complainant for 11am but it was difficult to estimate when his surgery would finish. The representative therefore left her name, company, work number and stated that she had called to discuss a treatment for stroke prevention in non valvular atrial fibrillation. The representative did not state that the call was urgent.

The complainant called back at approximately 11.25am and the representative stated the purpose of her call. The complainant stated that the representative did not have an appointment to speak to him to which she replied that a colleague had made the appointment on her behalf and apologised for any misunderstanding.

Pfizer submitted that the appointment with the complainant was made in good faith with his

reception staff and therefore it refuted that it was in breach of Clause 15.3 nor did it consider that it was in breach of Clauses 9.1 or 15.2.

Pfizer provided evidence of the scheduling calls between the call scheduling company and the complainant's surgery. Pfizer noted that the call made by the call scheduling company to the surgery the day before was not answered. The call the next day was answered and led to the scheduling of the appointment with the representative in question.

**Further comments from the complainant** The complainant submitted that all of the receptionists were well trained and knew that none of the doctors from the practice routinely had appointments with pharmaceutical company representatives. The complainant thus found it very hard to believe that any of them would have offered an appointment on the day in question had the call scheduling company's agent been open about the purpose of the call. There was no evidence on the practice screen that any appointment was booked for any such purpose. Furthermore the complainant submitted that he always had a routine appointment with a patient for 11am so it would not be plausible that an appointment would be given at that time as all of his staff knew that he would still be consulting in surgery then.

The complainant stated that he would like to hear a recording of the conversation between the receptionist and call scheduling company. The complainant was surprised by the call scheduling company's claim that its telephone call in late January at lunch time was unanswered; telephones were automatically transferred through to an out-of-hours provider then so it would have been answered immediately. This led the complainant to wonder how reliable the evidence was. The complainant disputed the representative's claim that she did not state that the call was urgent as the receptionist clearly stressed this to him.

The complainant submitted that overall he was disappointed with Pfizer's response as all he wanted was a simple apology and an undertaking that this kind of behaviour would not persist. The complainant also requested that no-one from Pfizer, or from any third party contracted by the company, would telephone the surgery in this manner or try to arrange such appointments.

**Further comments from Pfizer** Pfizer submitted that the call scheduling company did not routinely record calls. A scheduling call was expected to take between one and two minutes so the telephone record previously provided was in line with call duration expectations.

The call notes including the appointment record provided showed that an agent from the call scheduling company contacted the complainant's surgery in late January and spoke to a named receptionist who recorded the appointment details and suggested the time. The call notes showed that the receptionist specifically commented that that day month and time would be a good time to telephone

as the complainant was in practice all day and could take the call after morning surgery. The call notes detailed that the receptionist had stated that the telephone lines would be open and the complainant would have access to a computer for the online call. Pfizer submitted that it was therefore clear to the receptionist that it would be a remote call. A follow up email from the agent to the receptionist was not sent but the receptionist did confirm that the appointment had been recorded and that she would pass on the information.

A copy of the script used by the call scheduling company when scheduling appointments was provided. Pfizer submitted that the call was originally scheduled to discuss Lyrica (pregabalin) for neuropathic pain but the Pfizer representative was also able to discuss a new indication for Eliquis (apixaban) to prevent stroke in patients with atrial fibrillation by the time of the actual call. Pfizer submitted that the representative chose to discuss the new information with the complainant rather than Lyrica and it was not unusual for a representative to focus on a different product in their portfolio than originally intended provided they were fully trained on that product.

Pfizer submitted that given the complainant's response to its previous letter, it assumed that the receptionist might not have written the appointment down in a place that was visible to practice staff on duty 5 weeks later when contacted by the Pfizer representative.

To address the complainant's final comments, Pfizer apologised for any inconvenience and distress this incident might have caused. Pfizer emphasized that the appointment was made in good faith by the call scheduling company via the receptionist and the Pfizer representative had the best intentions when she contacted the surgery at the scheduled time. Pfizer confirmed that it had noted and communicated the complainant's wish not to be contacted in the future by any Pfizer representative or third party call scheduling company working on Pfizer's behalf.

## **PANEL RULING**

The Panel noted the clauses cited by the complainant and the case preparation manager, Clauses 15.2, 15.3 and 9.1 of the Code. The 2014 Code came into operation on 1 January 2014 with a transition period for newly introduced requirements. The clauses cited in this case were the same in the 2014 and 2012 Second Edition (amended) Codes, thus the Panel used the 2014 Code.

The Panel noted that the parties' accounts of whether the appointment was actually booked, the arrangements for the booking and what the Pfizer representative had stated with regard to the urgency of the call differed. The complainant had not been party to any of these conversations. The Panel noted the difficulty in dealing with complaints based on one party's word against the other; it

was often impossible in such circumstances to determine precisely what had happened. The introduction to the Constitution and Procedure stated that a complainant had the burden of proving their complaint on the balance of probabilities but the Panel noted the difficulty for complainants in cases such as this to provide any evidence to support their allegations. The Panel noted, however, that a high degree of dissatisfaction was usually required before an individual was moved to submit a formal complaint. The Panel noted that the complainant had been sent a copy of Pfizer's submission and stood by his version of events.

The Panel noted that the call scheduling company's call notes recorded that a named receptionist had suggested the date and time of the appointment with the complainant. The call notes, however, clearly showed that the appointment had been made to discuss Lyrica (a treatment option for nerve pain) and in this regard the Panel was concerned to note Pfizer's submission that on the day the representative chose to discuss Eliquis for stroke prevention in patients with atrial fibrillation. The Panel considered that, although not the subject of the complaint, to specifically arrange an appointment to discuss one product but on the day to discuss another, in a completely different therapy area, was discourteous and potentially risked wasting a health professional's time. The Panel requested that Pfizer be advised of its concerns in this regard.

The Panel noted Pfizer's submission that on the day, the representative had telephoned at the pre-arranged time and then, because the complainant was busy, had, at the receptionist's suggestion, called again fifteen minutes later. As the complainant was still busy, the representative had asked if he could return her call. In the Panel's view, this frequency of calls and the request for a return call, might have suggested to the complainant and receptionist that the matter was urgent even if as submitted by Pfizer, the representative had not stated it to be so. Although it appeared that communication between the parties could have been better, the Panel noted that the representative had set out to fulfil a pre-arranged call at a time she had been told was convenient for the complainant. The Panel could understand the representative's desire to keep the appointment given that the supplementary information to Clause 15.4 stated that if, for unavoidable reasons, an appointment could not be kept, the longest possible notice must be given.

The Panel noted the differences between the parties in relation to the matter of complaint but considered that, on balance, it had not been demonstrated that in contacting the complainant the representative had not maintained high standards of ethical conduct. No breach of Clauses 9.1 and 15.2 were ruled.

With regard to the alleged breach of Clause 15.3 which stated, *inter alia*, that representatives must not employ any inducement or subterfuge to gain an interview, the Panel noted that it had not been

established that, on the balance of probabilities, the representative had employed any inducement or subterfuge in order to speak to the complainant. The Panel thus ruled no breach of Clause 15.3.

**Complaint received**      **6 March 2014**

**Case completed**        **19 May 2014**

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# WARNER CHILCOTT/DIRECTOR v TILLOTTS

## Alleged breach of undertaking

Warner Chilcott UK alleged that an Octasa (mesalazine, modified release (MR)) detail aid produced by Tillotts Pharma UK breached the undertaking given in Case AUTH/2610/6/13. Warner Chilcott marketed Asacol (mesalazine, modified release).

Warner Chilcott noted that in the previous case, Case AUTH/2610/6/13, a supplement produced by Tillotts was ruled in breach of the Code for, *inter alia*, the inclusion of a comparison of the dissolution profiles of Mesren and Asacol. The comparison was made in a section entitled 'Are there any significant differences between Asacol MR and Octasa MR?'; Octasa MR was a rebranded version of Mesren MR. The section contained a graph which demonstrated that the dissolution characteristics of Mesren MR and Asacol MR were very similar. Although the first sentence of the section at issue stated that there had been no clinical comparison of Asacol MR and Octasa MR, the Panel considered that most readers would read the rest of the section and assume that because the *in vitro* dissolution characteristics of Mesren and Asacol were similar, the clinical effects of Octasa MR and Asacol MR would also be similar. There was no clinical data to show that this was so. The Panel considered that the supplement was misleading in breach of the Code.

Turning to the detail aid now at issue, page 5 contained a graph which depicted the same dissolution profile of Asacol 400mg MR, Octasa 400mg MR and a reformulated Octasa 400mg MR (which contained the excipient triethyl citrate rather than dibutyl phthalate). The title of this section was 'Comparing Octasa 400mg MR and UK Asacol 400mg MR: Dissolution profiles'. The graph demonstrated that the dissolution profiles for all three were very similar. Warner Chilcott alleged that, similar to the previous case, despite the acknowledgement of absence of clinical data, the reader would assume that, because the dissolution characteristics of Octasa and Asacol were similar, the clinical effects of the two would also be similar. This impression was compounded by the statement immediately below the graph, 'Octasa 400mg MR with triethyl citrate has a comparable mesalazine release profile to Asacol 400mg MR'. There was no data to support a clinical equivalence comparison and Warner Chilcott alleged that this was misleading and contrary to the undertaking given in Case AUTH/2610/6/13. Warner Chilcott also alleged that the breach of undertaking amounted to a breach of Clause 2.

The detailed response from Tillotts is given below.

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very

important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the previous case, Case AUTH/2610/6/13, concerned, *inter alia*, a comparison of the dissolution profiles of Mesren MR and Asacol MR in a journal supplement. During its consideration of that case, the Panel had noted that the section of the supplement entitled 'Are there any significant differences between Asacol MR and Octasa MR?' clearly stated that 'Octasa MR has not been compared directly in a clinical study with Asacol MR'. The Panel considered that most readers would read the rest of the section and assume, even in the acknowledged absence of clinical data, that because the *in vitro* dissolution characteristics of Mesren and Asacol were similar, the clinical effects of Octasa MR and Asacol MR would also be similar. There was no clinical data to show that this was so. The Panel considered that the supplement was misleading and a breach of the Code was ruled.

The present case, Case AUTH/2706/3/14, concerned a page headed 'Comparing Octasa 400mg MR and UK Asacol 400mg MR: Dissolution profiles'. The first bullet point included a statement that a new excipient, triethyl citrate, had no effect on the dissolution profile. This was referenced to data on file. Beneath this was a graph which showed that the *in vitro* dissolution profiles of Octasa 400mg MR with triethyl citrate, Octasa 400mg MR with dibutyl phthalate and Asacol 400mg MR, were closely similar. A bullet point below noted that 'Octasa 400mg MR with triethyl citrate had a comparable mesalazine release profile to Asacol 400mg MR. Both products were resistant to dissolution at pH 6.4 and dissolved promptly at pH 7.2'. The final bullet point stated 'There are no direct clinical comparisons of Octasa 400mg MR and Asacol 400mg MR UK formulation'. The Panel noted Tillotts's submission that its market research supported its submission that the graph and text compared *in vitro* testing and made no clinical claim. The Panel noted that one key issue was whether even if readers were clear that the data derived from *in vitro* testing, the presentation of the data was such that, on the balance of probabilities, readers would assume that the results were, nonetheless, relevant to the clinical situation.

The Panel noted that the previous page stated that Octasa 400mg MR was a branded generic version of Asacol 400mg MR. Turning to the page at issue, the Panel noted that the only reference to 'in vitro dissolution profiles' appeared in a small typeface in the heading to the graph; the heading referred only to 'Dissolution profiles'. The Panel considered the reference to *in vitro* dissolution profiles was not sufficiently prominent to qualify the primary impression of the page; that there was clinical data to support the comparison. The fourth bullet

point which stated there were no direct clinical comparisons of Octasa 400mg MR and Asacol 400mg MR was insufficient, either alone or in combination with the heading to the graph, was not sufficiently prominent. Further, it was ambiguous as some readers might assume that there were indirect clinical comparisons of Octasa 400mg MR and Asacol 400mg MR and this was not so. The Panel considered that page 5 invited readers to compare the dissolution profiles of Octasa 400mg MR and Asacol 400mg MR and implied that the data presented was directly relevant to the clinical situation. There was no clinical data to support such an implication and the page was therefore misleading. A breach was ruled.

The Panel noted that whilst there were some similarities between the material presently at issue and that considered in Case AUTH/2610/6/13 there were differences in relation to the nature, content and context of the material. That previously considered was a journal supplement which had been used with health professionals involved in medicines budget management. The dissolution data were referred to in a section headed 'Are there any significant differences between Asacol MR and Octasa MR?'. The material presently at issue was a detail aid which, *inter alia*, discussed the use of a new excipient in Octasa 400mg MR, including its effect on the dissolution profile. On balance, the Panel did not consider that the detail aid was in breach of the undertaking previously given and ruled no breach including Clause 2.

Warner Chilcott UK Ltd alleged that an Octasa (mesalazine, modified release (MR)) detail aid (ref UK/OC/0002/0114) produced by Tillotts Pharma UK Limited breached the undertaking given in Case AUTH/2610/6/13. Warner Chilcott marketed Asacol (mesalazine, modified release).

## COMPLAINT

Warner Chilcott noted that in the previous case, Case AUTH/2610/6/13, a supplement produced by Tillotts was ruled in breach of the Code for, *inter alia*, the inclusion of a comparison of the dissolution profiles of Mesren and Asacol. The comparison was made in a section entitled 'Are there any significant differences between Asacol MR and Octasa MR?'; Octasa MR was a rebranded version of Mesren MR. The section focused on *in vitro* data and the Panel noted that the supplementary information to Clause 7.2 stated that care should be taken with the use of *in vitro* data and the like so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. The section contained a graph which demonstrated that the dissolution characteristics of Mesren MR and Asacol MR were very similar. Although the first sentence of the section at issue stated that there had been no clinical comparison of Asacol MR and Octasa MR, the Panel considered that most readers would read the rest of the section and assume that because the *in vitro* dissolution characteristics of Mesren and Asacol were similar, the clinical effects of Octasa MR and Asacol MR would also be similar. There was no clinical data to

show that this was so. The Panel considered that the supplement was misleading in that regard and a breach of Clause 7.2 was ruled.

Turning to the detail aid now at issue, page 5 contained a graph which depicted the same dissolution profile of Asacol 400mg MR, Octasa 400mg MR and a reformulated Octasa 400mg MR (which contained the excipient triethyl citrate rather than dibutyl phthalate). The title of this section was 'Comparing Octasa 400mg MR and UK Asacol 400mg MR: Dissolution profiles'. The graph demonstrated that the dissolution profiles for all three were very similar. As in the previous case, there was a statement under the graph that there were no direct clinical comparisons of Octasa 400mg MR and Asacol 400mg MR UK formulation. Warner Chilcott alleged that, similar to the previous case, despite the acknowledgement of absence of clinical data, the reader would assume that, because the dissolution characteristics of Octasa and Asacol were similar, the clinical effects of the two would also be similar. This impression was compounded by the statement immediately below the graph, 'Octasa 400mg MR with triethyl citrate has a comparable mesalazine release profile to Asacol 400mg MR'. There was no data to support a clinical equivalence comparison and Warner Chilcott alleged that this was misleading, in breach of Clause 7.2 and was contrary to the undertaking given in Case AUTH/2610/6/13, in breach of Clause 26. Given that an undertaking to the Authority was an important document and it was very important for the reputation of the industry that companies complied with undertakings; Warner Chilcott alleged a breach of Clause 2.

## RESPONSE

Tillotts noted that Paragraph 2.2 of the Constitution and Procedure stated that a complainant had the burden of proving their complaint on the balance of probabilities. Tillotts stated that Warner Chilcott did not come close to doing so in this case; the complaint was both spurious and speculative.

Tillotts stated that more broadly, the foundation of the complaint was that it was alleged that it was misleading to use *in vitro* data to make pharmacological claims about Asacol; in the absence of supporting clinical data, and that the use of *in vitro* data in this way breached the Code. This position was clearly unsustainable and alone showed that the complaint was ill founded.

Tillotts submitted that such an interpretation of the Code would prohibit manufacturers of generic medicines from making fully justified and clearly explained pharmacological claims about their medicines on the basis of *in vitro* data, without first carrying out clinical trials to support the claims. To be able to properly market their products, this would require manufacturers to expend significant financial and other resources on completely unnecessary clinical trials, trials which were not required by the Medicines and Healthcare Products Regulatory Agency (MHRA) as part of the licensing process. The additional costs would inevitably lead to price rises at great expense to consumers and to the taxpayer. It would, in essence, completely undermine the

benefits of generic medicines in the UK market. Tillotts submitted that this could not be the intention of the Code, which was aimed at preventing misleading advertising.

While this unsustainable position was the foundation of the complaint, it was not the complaint's underlying purpose. The complaint had been brought solely for commercial purposes as part of an on-going strategy by Warner Chilcott to inhibit and disrupt the activities of Tillotts; a much smaller competitor, which was successfully increasing its share of a market which Mesren was leading.

Tillotts stated that it treated compliance with the Code seriously in all respects, as was shown by the extensive precautions (detailed below) which it took to ensure that the detail aid was fully compliant before publication. It had given careful and detailed consideration to the allegations. However, Tillotts noted that the Authority was being asked to uphold the complaint solely to damage Tillotts' reputation and market share as part of a commercial strategy. The Authority should consider the complaint in its true context and not be misled into thinking that the complaint had been made to uphold the principles embodied in the Code.

Tillotts submitted that each allegation was without foundation and strongly contested the complaint, for the following reasons:

- a The detail aid used *in vitro* data to make a pharmacological comparison between two medicines, in a particular and relevant context and with sufficient clarification to ensure that the reader did not assume that any clinical claim was being made. A health professional would not be misled by this use of data and there had been no breach of Clause 7.2.
- b Tillotts had taken the undertaking very seriously and had taken all steps to comply with it. Since there had been no breach of Clause 7.2, there had been no breach of the undertaking. But, in any case, the complaint did not relate to a similar breach such that a breach of Clause 7.2 in this case would be a breach of the undertaking.
- c There had been no conduct which merited the allegation of a breach of Clause 2. Tillotts had acted only in accordance with best practice in pre-vetting materials to ensure Code compliance.

Tillotts set out its comments in further detail below.

With regard to Clause 7.2, Tillotts submitted that the detail aid was not misleading and the reader would not assume that because the dissolution characteristics of Octasa and Asacol were similar, the clinical effects of Octasa MR and Asacol MR would also be similar. Page 4 of the detail aid noted that Octasa 400mg MR was a branded generic version of Asacol (mesalazine) 400mg MR. It set out the respective excipients of Octasa and Asacol and noted that the two had comparable excipients (with the exception of triethyl citrate in Octasa and dibutyl phthalate in Asacol). The detail aid set out the rationale for the change in excipient.

Page 5 of the detail aid set out the effect of the change in excipient on the dissolution profiles of Octasa and Asacol. It would immediately be clear to a health professional that page 5 made no statement regarding clinical effects or clinical equivalence. Tillotts noted the following points in relation to page 5:

- a Health professionals reviewing the detail aid would be aware of the impracticality of testing dissolution *in vivo* due to the number of variables (colon pH varied according to the individual, food the individual had consumed, the individual's stress levels etc) and hence the pharmaceutical industry's consequent reliance on *in vitro* testing for dissolution profiles.
- b The heading expressly and clearly stated that it was the dissolution profiles of Octasa and Asacol which were being compared. Terminology such as 'Formulation/dissolution profiles' was used. Readers, based on this use of pharmacological terminology and their appreciation of the testing of dissolution profiles, would be clear from the outset that the content of the page related to *in vitro* testing.
- c The main feature on the page was a graph showing *in vitro* dissolution profiles – it was clear that this graph depicted the testing on which all of the conclusions on page 5 were based. It was expressly and clearly stated above the graph that the data was *in vitro* data.
- d The page made two points. Firstly, that the substitution of dibutyl phthalate with triethyl citrate in Octasa 400mg MR had no effect on the dissolution profiles; and (consequently) and secondly, that Octasa 400mg MR with triethyl citrate had a comparable mesalazine release profile to Asacol 400mg MR. Contrary to the complaint, it was clear to readers that these two points were taken directly from the *in vitro* data displayed on the graph.
- e Further, it was expressly noted in body copy, in font the same size and with no less prominence than the other key points made (and, again, clear to the readers), that there were no direct clinical comparisons of Octasa 400mg MR and Asacol 400mg MR. This ensured that readers could not form the impression that the detail aid made a clinical comparison between the two medicines.

The detail aid presented *in vitro* data and the conclusions which were readily apparent from that data to make a pharmacological comparison between Octasa and Asacol (in light of the different excipient). The *in vitro* data was not used to make any clinical claim. No express clinical claim was made and the detail aid gave sufficient context and clarification to ensure that readers did not assume that any such claim was made by implication. Consequently no clinical comparison was made.

Tillotts noted the allegation that readers, when presented with dissolution characteristics of Octasa and Asacol would assume that the clinical effects

of Octasa and Asacol would be similar. This was without foundation. In order for readers to assume this, they would need to: ignore the title of page 5, which set out what the purpose of the content was, ignore the broader context of the piece and their wider knowledge and expertise, ignore the prominent text which served to eliminate any possibility of doubt, and assume that the inclusion of similar dissolution profiles must have much broader significance (in absence of any such statement or suggestion in the detail aid).

Tillotts submitted that the intended audience would clearly not be misled by the detail aid in this way. In this context, it should be remembered that readers of the detail aid were clinicians; experienced health professionals with a good understanding of medicines and of the use and purpose of clinical and *in vitro* data. In this regard Tillotts noted that market research testing with health professionals conclusively demonstrated that they would not be misled by the *in vitro* data. The market testing concluded that health professionals would not consider that the detail aid made a clinical claim.

Tillotts submitted that the detail aid was developed in full knowledge of the supplementary information to Clause 7.2 which stated that *in vitro* data should only be extrapolated to the clinical situation where there was data to show that it was of direct relevance and significance. This was shown by the specific wording of the detail aid and by the steps Tillotts took when developing it. The detail aid made no claim that the *in vitro* data was of broader clinical significance, but simply stated the conclusions which could be drawn directly from the dissolution profile graph about the pharmacological similarities between Octasa and Asacol. Tillotts submitted that the detail aid did not extrapolate *in vitro* data to the clinical situation and noted that the Panel had previously considered advertisements where *in vitro* data was referred to and used to make claims relating to the clinical situation. This was not the case with the detail aid, which referred to a formulation change and appropriately presented the dissolution profiles and the pharmacological similarities between the two medicines by reference to their profiles. The title on page 5 clearly stated that any claims related to dissolution profiles (and not to the clinical situation).

Tillotts submitted that it was a misinterpretation of the Code to state, as Warner Chilcott had done, that the mere inclusion of *in vitro* data relating to the pharmacological properties of a medicine must (by implication) mean that such data was being '[extrapolated]... to the clinical situation'.

Tillotts submitted that even if the inclusion of *in vitro* data relating to the pharmacological properties of a medicine necessarily meant it was being extrapolated to the clinical situation, in this case there was ample data to show that the dissolution profiles were of direct relevance and significance. In particular:

- a Octasa MR was a branded generic version of Asacol MR. The similarity of the two had been fully accepted by the MHRA and Tillotts had not

been required to carry out clinical trials in relation to Octasa MR. For this reason, it was unnecessary for promotional materials to make a clinical comparison between the two medicines as to their clinical effect generally.

- b The two medicines had comparable excipients, with the exception of triethyl citrate in Octasa vs dibutyl phthalate in Asacol. Dibutyl phthalate was also previously used in Octasa. The change was important because these excipients were plasticising agents which affected the integrity of the coating of the medicine. The change could legitimately lead to the question of whether the dissolution profile was different and the delivery of the medicine would be affected.
- c No clinical trial had been undertaken to compare Octasa MR and Asacol MR and the impact of the change in excipient (and this was clearly stated in the detail aid). Such a trial would be highly expensive and time intensive and the MHRA had not required such a trial to be undertaken.
- d However, the *in vitro* dissolution profiles of Octasa MR and Asacol MR could be readily compared and could show whether the change in excipient led to a change in pharmacological properties in this regard.
- e Since it was impractical to measure dissolution profiles *in vivo*, the use of *in vitro* dissolution profiles was accepted across the industry. Indeed, the MHRA required such data to be made available as part of the market authorization process, which provided the clearest possible indication of its relevance.
- f The *in vitro* data in this case showed that the change had no effect on the dissolution profiles.
- g The *in vitro* data had clearly addressed any concerns which the MHRA might have had in this regard since it had authorised Octasa on the basis of *in vitro* dissolution profiles. Clearly, the MHRA considered *in vitro* dissolution profiles to be of direct relevance and significance.

Tillotts submitted that for these reasons, the detail aid complied with the supplementary information to Clause 7.2.

Tillotts submitted that Warner Chilcott's interpretation of Clause 7.2 was that the use of any *in vitro* data to make a pharmacological comparison of two medicines was prohibited, in the absence of clinical data which supported it. This was clearly incorrect because the supplementary information to Clause 7.2 expressly envisaged *in vitro* data being used in certain situations and did not require it to be supported by clinical data and the purpose of Clause 7.2 was to prevent misleading advertising and the use of *in vitro* data in this context, not to indiscriminately prevent its use.

Tillotts noted that the manufacturers of generic medicines were not required to carry out clinical trials to obtain marketing authorisations. However, the implication of the complaint was such that

generics manufacturers would not be able to make pharmacological claims about their medicines in promotional materials based on *in vitro* data as this would breach the Code, even if the material did not mislead. Such manufacturers would then, effectively, be required to conduct clinical trials in order to make pharmacological claims about their medicines. To be able to properly market their products, manufacturers would be obliged to carry out completely unnecessary clinical trials, at considerable expense, leading to an inevitable increase in the prices of such generic medicines and potentially making the model economically unviable. This would ultimately compromise the value (and potentially the availability) of generic medicines, at significant expense to the consumer and to the taxpayer with a potentially highly significant impact on competition in the marketplace. Tillotts submitted that the Code could not possibly be intended to have such an effect.

Tillotts noted that Clause 26 provided that a company must ensure that it complied with an undertaking given in relation to a ruling under the Code. The undertaking stated that Tillotts would 'take all possible steps to avoid similar breaches of the Code occurring in the future'. Tillotts submitted that it had taken the undertaking very seriously and would continue to do so.

For the reasons set out above, the detail aid did not breach Clause 7.2 and so Tillotts submitted that there had been no breach of the undertaking. In any event, the breach alleged here was not a similar breach to that found in Case AUTH/2610/6/13. The presentation and purpose of *in vitro* data in the detail aid, which compared a changed excipient, was different to the material previously considered by the Panel. In Case AUTH/2610/6/13, the Panel made its ruling having considered a section of the supplement entitled 'Are there any significant differences between Asacol MR and Octasa MR'. The Panel considered that, in this context, the use of dissolution profiles would mislead readers. In contrast, the detail aid clearly stated that the data was being used to compare dissolution profiles, rather than to make any broader comparison. The detail aid clearly stated that Octasa MR was a branded generic version of Asacol MR with comparable excipients, with the exception of triethyl citrate used in Octasa. The dissolution profiles were then set out in this context. This was not the case with the supplement considered in Case AUTH/2610/6/13. The Panel's ruling in Case AUTH/2610/6/13 made no suggestion that, merely by including *in vitro* data to make a pharmacological comparison without supporting clinical data, material would breach the Code. Tillotts submitted that it could not have been reasonably expected to assume that this was the impact of the Panel's ruling, such that inclusion of data in future material would lead to a 'similar' breach.

Tillotts stated that it had taken considerable steps to avoid similar breaches (and these were set out further below).

Tillotts noted the wording of Clause 2 and its supplementary information and stated that for

the reasons set out above, it had not breached the undertaking and so no circumstances arose which merited an alleged breach of Clause 2 and the allegation was without foundation. Tillotts had provided readers of the detail aid with relevant and significant information to explain the purpose and effect of a different excipient in Octasa vs that used in Asacol. It could not be said that this discredited or reduced confidence in the pharmaceutical industry.

Tillotts also noted that it had taken extensive precautions to ensure compliance with the Code and the undertaking. The company was particularly concerned by this complaint and noted that it appeared to be nothing but an attempt to tarnish its reputation.

Tillotts stated that it took the following steps to ensure compliance with the undertaking:

- a In October 2013, before the detail aid was finalised, Tillotts raised the concept of its proposed promotional materials in a meeting with the MHRA. The MHRA representatives fully supported Tillotts setting out positive reasons about why it had changed an excipient in Octasa from that used in Asacol, even in the absence of clinical data comparing the two medicines.
- b Tillotts appointed an independent market research agency to test its proposal to include *in vitro* data in promotional materials for Octasa (as used in the detail aid). The purpose of the market testing was to confirm what conclusions health professionals would draw from the materials, including to confirm whether the use of *in vitro* data could be seen as being misleading. The market testing was carried out with 16 health professionals, whose responses confirmed that they had fully understood that the graph and text comparing dissolution profiles resulted from *in vitro* testing and made no clinical claim.
- c Throughout the development of the current promotional materials (including the detail aid), the draft materials were challenged against the Code, the ruling in Case AUTH/2610/6/13 and the undertaking and a number of changes were made to ensure compliance.
- d Tillotts appointed an additional external consultant, to review materials and provide advice on compliance with the Code, throughout the development of the current promotional materials (including the detail aid). Both the consultant and Tillotts' medical signatory, had considerable experience in working with and ensuring compliance with the Code.

Tillotts stated that in developing the detail aid, it used Zinc. This was an industry standard online review tool, which enabled Tillotts' compliance specialists to add comments to the documents. Even before being uploaded to Zinc, the draft detail aid was initially given consideration with regard to compliance with the undertaking and it went through a number of iterations. The draft detail aid was uploaded to Zinc in December 2013. It was subsequently interrogated for compliance with the



Code by both Tillotts' medical signatory and its external consultant and went through a number of iterations; both interrogated the detail aid in full knowledge of the ruling in Case AUTH/2610/6/13 and the undertaking (and particular terms contained within it). They both approved the detail aid as being compliant with the Code and the undertaking.

## PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the previous case, Case AUTH/2610/6/13, concerned, *inter alia*, a comparison of the dissolution profiles of Mesren MR and Asacol MR in a journal supplement published in the British Journal of Clinical Pharmacy. During its consideration of that case, the Panel had noted that the section of the supplement entitled 'Are there any significant differences between Asacol MR and Octasa MR?' clearly stated that 'Octasa MR has not been compared directly in a clinical study with Asacol MR'. The relevant section reported that Fadda and Basit (2005) had shown that Mesren and Asacol had similar dissolution profiles and that a more recent study carried out by Tillotts showed very little difference in the dissolution profiles of the two products. The Panel noted that the section at issue focussed on *in vitro* dissolution data. The supplementary information to Clause 7.2 stated that care should be taken with the use of *in vitro* data and the like so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. The Panel noted that the first sentence of the section at issue stated that there had been no clinical comparison of Asacol MR and Octasa MR. The Panel further considered that most readers would read the rest of the section and assume, even in the acknowledged absence of clinical data, that because the *in vitro* dissolution characteristics of Mesren and Asacol were similar, the clinical effects of Octasa MR and Asacol MR would also be similar. There was no clinical data to show that this was so. The Panel considered that the supplement was misleading in this regard. A breach of Clause 7.2 was ruled.

The present case, Case AUTH/2706/3/14, concerned page 5 of a detail aid. The page was headed 'Comparing Octasa 400mg MR and UK Asacol 400mg MR: Dissolution profiles'. The first bullet point included a statement that a new excipient, triethyl citrate, had no effect on the dissolution profile. This was referenced to data on file. Beneath this was a graph which showed that the *in vitro* dissolution profiles of Octasa 400mg MR with triethyl citrate, Octasa 400mg MR with dibutyl phthalate and Asacol 400mg MR, were closely similar. A bullet point below noted that 'Octasa 400mg MR with triethyl citrate had a comparable mesalazine release profile to Asacol 400mg MR. Both products were resistant to dissolution at pH 6.4 and dissolved promptly at

pH 7.2'. The final bullet point stated 'There are no direct clinical comparisons of Octasa 400mg MR and Asacol 400mg MR UK formulation'. The Panel noted Tillotts's submission that its market research supported its submission that the graph and text compared *in vitro* testing and made no clinical claim. The market research had not been provided and therefore the Panel did not know either the questions asked nor the material examined. The Panel noted that one key issue was whether even if readers were clear that the data derived from *in vitro* testing, the presentation of the data was such that, on the balance of probabilities, readers would assume that the results were, nonetheless, relevant to the clinical situation.

The Panel examined the context of the material on the page and the impression given to readers. The Panel noted that page 4 of the detail aid stated that Octasa 400mg MR was a branded generic version of Asacol 400mg MR. Turning to the page at issue, the Panel noted that the only reference to '*in vitro* dissolution profiles' appeared in a small typeface in the heading to the graph; the heading to page 5 referred only to 'Dissolution profiles'. The Panel considered the reference to *in vitro* dissolution profiles was not sufficiently prominent to qualify the primary impression of the page; that there was clinical data to support the comparison. The fourth bullet point which stated there were no direct clinical comparisons of Octasa 400mg MR and Asacol 400mg MR was insufficient, either alone or in combination with the heading to the graph. It was not sufficiently prominent to ensure readers were aware of the position. Further, it was ambiguous as some readers might assume that there were indirect clinical comparisons of Octasa 400mg MR and Asacol 400mg MR and this was not so. The Panel considered that page 5 invited readers to compare the dissolution profiles of Octasa 400mg MR and Asacol 400mg MR and implied that the data presented was directly relevant to the clinical situation. There was no clinical data to support such an implication and the page was therefore misleading. A breach of Clause 7.2 was ruled.

The Panel noted that whilst there were some similarities between the material presently at issue and that considered in Case AUTH/2610/6/13 there were differences in relation to the nature, content and context of the material. That previously considered was a journal supplement which had been used with health professionals involved in medicines budget management. The dissolution data were referred to in a section headed 'Are there any significant differences between Asacol MR and Octasa MR?'. The material presently at issue was a detail aid which, *inter alia*, discussed the use of a new excipient in Octasa 400mg MR, including its effect on the dissolution profile. On balance, the Panel did not consider that the detail aid was in breach of the undertaking previously given and ruled no breach of Clause 26 and consequently no breach of Clause 2.

**Complaint received**                      **25 March 2014**

**Case completed**                            **9 June 2014**

# NHS EMPLOYEE v PROSTRAKAN

## Osteoporosis review

An NHS employee complained that local practices had been misled to believe an osteoporosis therapy review service conducted by a third party service provider on behalf of ProStrakan was approved by the local clinical commissioning group (CCG) and was a continuation of the work done in 2009 when the CCG was a primary care trust (PCT). The complainant noted that the review appeared to be completely different to that done in 2009; the current review identified patients who had not ordered their calcium and vitamin D recently and switched them to non-formulary Adcal-D3 caplets.

The complainant remembered that ProStrakan had offered her another review via email but she had said no and it had gone ahead despite the complainant not replying to another letter from ProStrakan offering such support.

The complainant noted that the protocol provided by one practice contained numerous inaccuracies and would never have been supported by the CCG. The complainant was further concerned that a company had deceptively gained entry to practices and access to patient records. The complainant saw this as a serious information governance breach bordering on fraud.

The detailed response from ProStrakan is given below.

The Panel noted the parties' accounts differed with regard to whether ProStrakan had misled practices into believing that the therapy review had been approved by the local CCG. The complainant had not been party to any of the conversations between ProStrakan, the third party service provider and the individual practices. The Panel noted the difficulty in dealing with complaints based on one party's word against the other; it was often impossible in such circumstances to determine precisely what had happened. A complainant had the burden of proving their complaint on the balance of probabilities. The Panel noted, however, that a high degree of dissatisfaction was usually required before an individual was moved to submit a formal complaint.

The Panel noted that the complainant could not locate the email wherein she had declined ProStrakan's offer of a therapy review service and ProStrakan was unable to locate any such email or any other evidence that it had been informed that the CCG had adopted any position on the matter.

The Panel noted ProStrakan's submission that therapy reviews had only taken place after a detailed discussion with the practice concerned and with the written consent of two employees appropriately authorised to sign on the practice's behalf. The Panel noted ProStrakan's submission that local

guidelines were often unavailable to those outside of a CCG and it therefore relied upon the individual practices to ensure that participation in the service was appropriate and acceptable. The Panel considered that conducting therapy review services at individual practices despite the CCG not having made a decision regarding a proposal or not wishing to undertake a project, was not in itself prohibited by the Code provided that the way in which it was done complied with all relevant requirements of the Code. If however, a CCG or similar had clearly not sanctioned such a service then it would not be unreasonable to expect a pharmaceutical company to make that clear when discussing the matter with relevant practices. The Panel noted ProStrakan's submission that none of its employees covering the territory or their line managers had been told that the CCG(s) had taken either a positive or negative position on the matter.

The Panel noted that two separate practices had informed the complainant that they had been led to believe that the CCG approved the service offered by ProStrakan. This was denied by ProStrakan. The Panel considered that to have two practices with the same misunderstanding was concerning however as a similar service had been locally approved in 2009 it was possible that the practices might have thought this service was a continuation of the previous service. Overall, the Panel did not consider that on the balance of probabilities the complainant had proved that either Prostrakan or the third party service provider had employed any subterfuge to gain access to individual practices by suggesting that the therapy review service now on offer was supported by the local CCG. The Panel thus ruled no breach of the Code. The Panel did not consider that the representatives had failed to maintain a high standard of ethical conduct and ruled no breach of the Code.

The Panel considered that the complaint was about misleading practices about the CCG's views about the service and not about the actual service provided to one of the practices. If the complainant was concerned about the actual service then a further complaint could be made.

The Panel noted its rulings above and did not consider that ProStrakan or the third party service provider working on its behalf had failed to maintain high standards. No breach of the Code was ruled including no breach of Clause 2.

An NHS employee complained about an osteoporosis therapy review service conducted by a third party service provider on behalf of ProStrakan Ltd. ProStrakan marketed Adcal-D3 (calcium carbonate/colecalciferol) caplets and tablets which were indicated as an adjunct to specific therapy for

osteoporosis and in situations requiring therapeutic supplementation of malnutrition and the prevention and treatment of calcium deficiency/vitamin D deficiency especially in the housebound and institutionalised elderly subjects.

## COMPLAINT

The complainant explained that one of the local specialist pharmacy technicians informed her that a third party service provider had operated in local practices on behalf of ProStrakan. The practice manager from one surgery stated that the third party service provider had stated that the therapy review being offered was approved by the clinical commissioning group (CCG) and he/she had assumed that because the primary care trust (PCT) had done something similar in 2007-2009 it was OK and allowed them into the practice. A booking form provided showed that the activity had been going on since at least October 2013.

The complainant stated that the CCG had not supported the work and that any work would have had to go through its sponsorship panel and have, *inter alia*, a robust protocol, standard operating procedure, and letters to GPs introducing the project as it did in 2009, copies of which were provided. The complainant alleged that the company had misled practices into believing it was a continuation of the work done when it was a PCT whereas now it was a CCG.

The complainant provided a copy of the communication she sent to practices in the two CCG areas and posted on the pharmaceutical advisors group network. Following this communication, the practice manager at another centre, advised the complainant that it had been approached by the third party service provider which had stated that that it was a CCG supported project; a therapy review booked for May 2014 had since been cancelled.

A further practice notified the complainant that ProStrakan had approached it directly to offer the service like the one before.

The complainant contacted ProStrakan and the third party service provider. In response, ProStrakan stated that it and the third party service provider took such complaints very seriously; ProStrakan had made enquiries with the clinical director of the third party service provider and would speak to all of the relevant ProStrakan staff to seek clarity on what had been communicated with regard to the service. It was suggested that one of the senior managers meet with the complainant to have a more detailed discussion regarding her concerns. The complainant stated that she had responded and received a subsequent response from ProStrakan but did not wish to meet with ProStrakan at that stage.

The complainant reviewed her communication over the last year and found one letter from ProStrakan which she had not replied to. The complainant had asked ProStrakan for a comparison of Adcal-D3 with another named product which was the CCG's other choice on formulary. The complainant remembered

that ProStrakan had offered her another review via email but she had said no. The complainant could not find that email but stated that had she agreed, the usual steps through the sponsorship panel would have been taken. The complainant noted that it could be seen from the final paragraph of ProStrakan's letter that it had offered support and had gone ahead despite the complainant not replying.

The complainant stated that one practice had only allowed the third party service provider in because it had been led to believe that it was a CCG supported project. The complainant noted that a protocol such as the one received from one practice would never be allowed, because, in the complainants view, it contained a number of inaccuracies including references to a PCT when these no longer existed, reference to content which was not provided and reference to Adcal-D3 caplets which were not on formulary. The complainant noted from a letter provided by one of the practices, it appeared to be a completely different type of review to the one done in 2009.

The complainant stated that she did not plan to meet ProStrakan or the third party service provider and that her complaint was on behalf of both CCGs.

The complainant was further concerned that her practices had been misled and a company had gained entry to practices and access to patient records. The complainant saw this as a serious information governance breach bordering on fraud.

ProStrakan was asked to respond in relation to Clauses 2, 9.1, 15.2, 15.3, 18.1 and 18.4 of the Code.

## RESPONSE

ProStrakan submitted that it sponsored a therapy review service that was offered to all GP practices with computerised patient records and, as required by Clause 18, it was provided to any practice which expressed a desire to complete it. ProStrakan offered the service based on its current understanding of the new NHS structures; it could only be offered to, and authorised by, individual practices. ProStrakan encouraged CCGs to make recommendations with regard to the service but recognised that the decision and authority on such matters lay with each individual practice. Consequently its approach had always been based around invitations being issued to individual practices whilst seeking the approbation of other local authorities wherever possible. The third party provided the service to individual practices within the CCGs relevant to this complaint as a support to the local NHS. While the third party service provider was paid by ProStrakan, it was independent. The outcomes and documentation relating to the review belonged to the local NHS and were not shared with ProStrakan.

ProStrakan submitted that as GP practices were independent entities they might decide to undertake a review despite the CCG not having made a decision regarding a proposal or not wishing to undertake

a project. Reviews only took place following a detailed discussion of the protocol involved with the practice concerned and with written consent of two employees (either two GPs or a GP and practice manager). The protocol stipulated that the individuals signing on behalf of the practice must be appropriately authorised to do so. ProStrakan submitted that it was not aware that the CCG had decided not to conduct the project until it received the complaint. All interviewees were questioned at length regarding their discussions pertaining to the therapy review and the position of the CCG; all stated that they made no claims with respect to the views of the CCG neither did they believe that anything they said could have led to such a misunderstanding. The investigation uncovered no evidence to suggest that ProStrakan or the service provider had ever claimed that the service was CCG approved. Review of the documentation provided by the complainant and the additional documentation relating to the case found no evidence that such a claim had been made.

ProStrakan submitted that a key account team (KAT) worked principally in primary care and talked to health professionals such as GPs, practice managers and specialist nurses about three of ProStrakan's marketed products including Adcal. The KAT also discussed the ProStrakan therapy review service provided in accordance with Clause 18 at practice level. However, these discussions were conducted under strictly controlled conditions. KAT members were not permitted to discuss both promotional and non-promotional activities in the same call.

The detailed sales force briefing on the provision of the therapy review service was provided. ProStrakan summarised the key points.

The KAT was distinct from the clinical partnership team (CPT) which operated at a local health authority level (ie CCGs). The CPT might discuss therapy review services with appropriate members of a CCG with the view to encouraging participation in the interests of public health. The briefing document mentioned above also related to the CPT.

Only two ProStrakan employees were appointed to cover the aforementioned territory, a KAT and a CPT. Both were interviewed at length as were their line managers. None of the four had been told that the CCGs had taken either a positive or negative position on the matter.

Local discussions in relation to therapy review were practice-based and centred upon the protocol in order to ensure that all aspects of the service were open and transparent. ProStrakan was guided by the practice with respect to compliance with local procedures and policies. Local guidelines were often unavailable to those outside a CCG, ProStrakan therefore relied upon the individual practices to ensure that participation in the service was appropriate and acceptable.

The independent third party service provider was engaged by ProStrakan to undertake a therapy review service in line with Clause 18. The service aimed to facilitate the review of patients who might

be at risk of osteoporosis using a practice-agreed protocol specifically designed in conjunction with each participating practice. The service was reviewed and certified in line with the Code, and was supplied in compliance with detailed briefing documents agreed with both parties. Relevant documents including an osteoporosis patient information leaflet and letter templates were provided.

From April 2013 reviews had been conducted in a number of practices across both CCGs.

ProStrakan submitted that the response to the Authority's question regarding the normal outcome of such audits depended on the definition of 'outcome'. The output of the review service itself, as defined by the protocol, were lists of patients who had been identified as being likely to be at risk of having, or developing, osteoporosis according to pre-agreed criteria. These lists were only seen by the third party service provider pharmacist and practice employees undertaking the review. All copies were kept by the practice, and any advice/treatment decisions made on the clinical judgement of the lead GP. The therapy review protocol had been

developed to ensure that the practice was in full control of the review and any subsequent actions.

If 'outcome' was related to the advice/treatment decisions that might be taken as a consequence of the review, ProStrakan could not comment, as all treatment decisions were kept strictly confidential. ProStrakan was given no information whatsoever on what clinical decisions had been reached. For the avoidance of doubt, ProStrakan noted that it was provided with no information with regard to clinical interventions resulting from a review.

ProStrakan submitted that a therapy review was provided to one of the surgeries named by the complainant following the consent of its practice manager and one of the doctors as was evidenced by the signed protocol provided by the complainant.

The practice manager alleged that he/she undertook the review as the third party service provider had stated that it was a CCG approved piece of work. The third party service provider employees covering this area were extensively questioned on this issue, but none were identified as the caller to which the practice manager referred. The third party service provider was contacted to establish whether any other employees from the company could have made the call. No other individuals were identified and it was not possible to establish that the third party service provider had made such a call.

In addition, in order to establish whether it might have been the ProStrakan representative on territory who contacted the practice, the KAT was also asked to clarify any and all contact he/she had had with the practice manager.

The only telephone contact occurred in the week before the therapy review took place. This call was made to ensure that the appropriate arrangements

were in place for the review the following week and without further detail on the call it was not possible to progress any further with this line of enquiry.

As requested, the documentation provided to practices undertaking a review had been provided which included a blank copy of the protocol used which specifically mentioned the services' standing in relation to local guidance. The section about medicine selection included a list of all marketed products in the therapy area. It was provided to ensure that all therapeutic choices were available and was not necessarily equitable to local formulary. This was specifically stated where the text clarified that the list provided: 'does not replace local guidance or protocols'.

The complainant had specifically noted one point in the document, stating that: 'this was entirely a pharma project not supported by CCG'. ProStrakan suggested that this section of the protocol had been slightly misunderstood. The intent of this passage was to establish the third party service provider's position as an organisation independent of ProStrakan and was not intended to establish any link to, or support by, the NHS.

During its investigation ProStrakan noted that there were errors in the documentation provided in relation to the review completed at one practice. The errors related to isolated instances where its internal policies had not been followed. Details were provided including ProStrakan's view as to whether the errors were or might be breaches of the Code.

ProStrakan submitted that it did not offer a switch service; it supported a therapy review service to facilitate the review of patients who might be at risk of osteoporosis using a practice-agreed protocol specifically designed in conjunction with each participating practice. No review would be undertaken without the express permission of two individuals within any given practice. The practice was in complete control of the progress of the review at all times and decisions for any intervention, including medication, were based on the clinical judgement of the authorising lead clinician.

In the emails associated with a proposed review at a second practice which was subsequently cancelled, the practice manager, alleged, that 'this company' contacted him/her claiming that the review was CCG approved, and that 'they were one of the last practices to be done'. The email did not clarify whether 'this company' was ProStrakan or the third party service provider.

The KAT contacted the centre in March 2014 and discussed the therapy review service with the practice manager and an audit by the third party service provider was booked. Despite repeated questioning on this issue the KAT was clear that no CCG involvement was mentioned or implied.

ProStrakan noted that an email from the medicines management project lead at one CCG related to communications the KAT had with an NHS employee. The KAT stated that he/she had met the

NHS employee in April 2014 to discuss the therapy review service, and he/she expressed an interest in it. The KAT stated that he/she had mentioned that the project could be undertaken at CCG level, and that if the CCG was interested his/her colleague from the clinical partnership team would handle this.

The KAT denied that he/she had implied that the service was CCG authorised. Indeed, he/she recollected the NHS employee telling him to contact one of two individuals as he/she had not yet spoken to medicines management about it, neither of which had been contacted at the time of this response.

Having reviewed the letter provided by the complainant ProStrakan noted that the connection to the past project was made by the NHS employee, not the KAT. ProStrakan submitted that had the KAT already claimed that the project was CCG approved there would have been no need to establish to whom he/she should speak about having it signed off at this level.

ProStrakan wanted to address one of the medicine management employee's concerns that ProStrakan was trying to 'knobble the practices directly' by offering the service to individual practices. ProStrakan submitted that that was never its aim or intention and, as noted above, the Code required it to offer the service to any qualifying practice which wished to undertake it.

In conclusion ProStrakan submitted that despite having interviewed all ProStrakan and third party service provider employees covering the CCGs mentioned in the complaint it had identified no one who had claimed the project was CCG approved. ProStrakan had found no evidence that its representatives had acted in contravention to the Code in that regard and it denied a breach of Clause 15.3.

The therapy review service sponsored by ProStrakan was a medical and educational goods and service offered, and signed off, in line with the Code. ProStrakan provided the protocol, letters and briefing documents related to this service. It also interviewed all employees involved in the delivery of the service as identified by the complainant. ProStrakan submitted that it had identified no evidence that the service was offered in breach of the requirements of Clause 18.1.

Further to this, ProStrakan submitted that the documents supplied adequately clarified to the practices involved ProStrakan's involvement in the service and that of its provider.

ProStrakan submitted that it had found no evidence of ProStrakan or third party service provider employees acting in a manner that did not uphold the high standards expected of the industry. As it outlined above, ProStrakan had been unable to uncover any evidence that suggested either set of employees misrepresented the service with regards to CCG decisions. Indeed, it had not been possible to identify an employee of either company who was informed that a decision had been reached. The

service was offered to local practices in line with the guidance outlined by ProStrakan and the Code. ProStrakan did not consider that a breach of Clause 9.1 was warranted and consequently considered that a ruling of a breach of Clause 2 was not justified.

Regardless of the outcome of this complaint, ProStrakan apologised to the complainant for any inconvenience caused. ProStrakan submitted that it endeavoured to ensure that it worked with health professionals to improve patient care and to better the lives of patients treated with its products and was sorry that the complainant considered that it had not done so in this case.

In response to a request from the Panel for further information, ProStrakan submitted that a comprehensive review of the communications between the CPT and the complainant was conducted and only four emails were identified; three from the CPT to the complainant, and one from the complainant to the CPT, copies of which were provided. No communication informing ProStrakan of the CCG's position on the osteoporosis review service was identified during any of the documentation searches. Call reports from the customer record management (CRM) system provided no evidence which suggested that ProStrakan had claimed that the project was CCG approved.

ProStrakan submitted that following completion of the initial training program by the CPT, he/she started work on territory to contact key people within the CCG including the complainant. An email, sent to the complainant in July 2013, discussed how ProStrakan's osteoporosis therapy review service could assist CCGs to meet their local needs assessments. No response was received, and there was no further contact until the complainant emailed the CPT to ask about the price of products.

Following the complainant's email, the CPT tried a number of times to call and messages were left none of which were returned and the CPT was unable to secure a face-to-face meeting with the complainant.

Consequently the CPT replied to the complainant's email attaching the letter provided by the complainant in the original dossier which had been produced and certified for that purpose. Unfortunately, owing to the upcoming PPRS scheme he/she was unable to answer the complainant's question, so offered to get back in contact when able to fulfil the request.

As promised, the CPT sent a third email in February 2014. ProStrakan submitted that a meeting would have been preferred, but the complainant did not reply to the CPT's previous email.

During the week the complaint was received, the KAT told the CPT that he/she had received a voice message from the complainant who seemed to be displeased with ProStrakan and had concerns regarding the therapy review service.

As the complainant was at CCG level, the CPT took

the lead in attempting to telephone the complainant to clarify the situation but was unable to reach her. Both KAT and CPT escalated the matter to ProStrakan senior management, who by this time had already been directly informed of the issues by the complainant.

As the CPT was going on holiday he/she contacted the KAT to update him/her on what could potentially be discussed should the complainant get in touch. However no actions were taken by either party as all communication was suspended pending an investigation into the complainant's concerns.

The complainant referred to an email that she sent to the CPT stating that the CCG did not wish to take part in a project relating to an osteoporosis therapy review but was unable to locate this email.

Having reviewed the records and correspondence from the CPT and the other parties requested by the Authority, ProStrakan could not locate any such email or any other written indication that ProStrakan had been informed that either CCG mentioned in the complaint had adopted any position on the matter.

ProStrakan submitted that on assuming the role from his/her predecessor, the CPT tried to contact the complainant to ensure that she knew ProStrakan would continue to support the CCG in whatever manner it considered appropriate. Much of the communication provided demonstrated ProStrakan's desire to work with the CCG according to its needs. The CPT conducted a considerable amount of background research into the priorities and objectives in this locality. Osteoporosis and falls were clearly part of the CCG agenda, and the CPT was consequently keen to discuss this with the complainant.

Unfortunately the opportunity to do this was not forthcoming, and the CPT was unable to secure an appointment with the complainant. The email provided was the only direct communication received from the complainant.

A thorough review of call records was conducted and ProStrakan could find no evidence to suggest that the service was offered as CCG approved. ProStrakan submitted that the term 'CCG' was used only twice in the records as follows:

- to refer to the institution for which the complainant worked.
- Call record of meeting held by the KAT and a practice manager which read 'Likes TR [Therapy Review] and will discuss with practice. Will also discuss with named CCG member, for implementation throughout a named CCG'.

It was during this meeting that the practice manager contacted the NHS employee, who was a member of the CCG board, to look for approval for the project at this level. ProStrakan submitted that the meeting with the NHS employee was discussed at length in its original letter but noted that the CPT would have no need to look for CCG approval if he/she

believed that it was already in place. Indeed the NHS employee, as a member of the CCG board, would be well aware of the status of the project, had any decision been taken.

ProStrakan submitted in conclusion, given the complexity of the complaint it was important to evaluate the documents provided above in light of the original issues identified.

ProStrakan submitted that the documents demonstrated that both ProStrakan employees named in the complaint were looking to discuss a CCG project because they had not yet received an indication that a decision had been made.

ProStrakan submitted that what had been demonstrated was its desire to work with the CCG, and to align its program if necessary to help meet local objectives. ProStrakan submitted that the CPT had conducted a considerable degree of research into the CCG's needs, and intended to present this to the appropriate individuals if given the opportunity. Supporting improved patient outcomes was a key part of the osteoporosis review service that it offered. ProStrakan submitted that in its experience, this was best achieved when it worked together with the CCG. Unfortunately this was not possible in this case.

ProStrakan submitted that overall it identified no evidence that the service was offered in breach of the requirements of Clause 18.1 and denied that this clause had been breached.

ProStrakan submitted that its representatives had upheld the standards required of them, and had not breached Clause 15.2.

Consequently ProStrakan refuted that a breach of Clause 9.1 was warranted, and therefore asserted that a ruling of a breach of Clause 2 was not justified in this instance.

## PANEL RULING

The Panel noted the complainant's allegation that ProStrakan had misled practices into believing that the osteoporosis therapy review, offered by a third party service provider, had been approved by the local CCG. The Panel noted that the parties' accounts differed in this regard. The complainant had not been party to any of the conversations between ProStrakan, the third party service provider and the individual practices. The Panel noted the difficulty in dealing with complaints based on one party's word against the other; it was often impossible in such circumstances to determine precisely what had happened. The introduction to the Constitution and Procedure stated that a complainant had the burden of proving their complaint on the balance of probabilities. The Panel noted, however, that a high degree of dissatisfaction was usually required before an individual was moved to submit a formal complaint.

The Panel noted the complainant's submission that the CCG had not supported the work and that any work would have had to go through its sponsorship panel and have, *inter alia*, a robust protocol,

standard operating procedure, and letters to general practitioners introducing the project as it did in 2009 when a similar review was undertaken. The complainant could not locate the email wherein she had declined ProStrakan's offer of a therapy review service and ProStrakan was unable to locate any such email or any other evidence that it had been informed that the CCG had adopted any position on the matter.

The Panel noted ProStrakan's submission that therapy reviews had only taken place following a detailed discussion of the protocol involved with the practice concerned and with the written consent of two employees who were required by the protocol to be appropriately authorised to sign on the practice's behalf. The Panel noted ProStrakan's submission that local guidelines were often unavailable to those outside of a CCG and it therefore relied upon the individual practices to ensure that participation in the service was appropriate and acceptable. The Panel considered that conducting therapy review services at individual practices despite the CCG not having made a decision regarding a proposal or not wishing to undertake a project, was not in itself prohibited by the Code provided that the way in which it was done complied with all relevant requirements of the Code. If however, a CCG or similar had issued a clear statement that the CCG had not sanctioned such a service then it would not be unreasonable to expect a pharmaceutical company to make that clear when discussing the matter with relevant practices. The Panel noted ProStrakan's submission that none of its employees covering the territory or their line managers had been told that the CCG(s) had taken either a positive or negative position on the matter.

The Panel noted that two separate practices had informed the complainant that they had been led to believe by the third party service provider that the CCG approved the service offered by ProStrakan. This was denied by ProStrakan. The Panel considered that to have two practices with the same misunderstanding was concerning however it noted that a similar service had been locally approved in 2009; it was possible that the practices might have thought this service was a continuation of the previous service. Overall, the Panel did not consider that on the balance of probabilities the complainant had proved that either Prostrakan or the third party service provider had employed any subterfuge to gain access to individual practices by suggesting that the therapy review service now on offer was supported by the local CCG. The Panel thus ruled no breach of Clause 15.3. Given its ruling regarding Clause 15.3, the Panel did not consider that the representatives had failed to maintain a high standard of ethical conduct. The Panel thus ruled no breach of Clause 15.2.

The Panel noted that the complainant referred to a number of errors in the protocol. The Panel was unsure whether the documentation was provided to support the complainant's view that the CCG would not have endorsed the ProStrakan service because it had concerns about its implementation or because the complainant was concerned about the service. The Panel considered that the complaint was about misleading practices about the CCG's views about

the service and not about the actual service provided to one of the practices. The Panel therefore did not make any ruling under Clause 18 of the Code. If the complainant was concerned about the actual service then a further complaint could be made.

The Panel noted its rulings above and did not consider that ProStrakan or the third party service provider working on its behalf had failed to maintain high standards. No breach of Clause 9.1 was ruled. The Panel thus ruled no breach of Clause 2.

**Complaint received**      **9 April 2014**

**Case completed**        **24 June 2014**

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# GLAXOSMITHKLINE v ACTELION

## Presentation of composite endpoints

GlaxoSmithKline complained about the promotion of Opsumit (macitentan) by Actelion. Opsumit was indicated in the long-term treatment of certain patients with pulmonary arterial hypertension (PAH). The summary of product characteristics (SPC) stated that treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

GlaxoSmithKline was concerned about the presentation of endpoints from Pulido *et al* (2013) in a detail aid and leavepiece. GlaxoSmithKline did not refute that the composite primary end point of morbidity-mortality or the secondary composite endpoint of PAH related death or hospitalisation was achieved in Pulido *et al* or was mentioned in the Opsumit SPC. However, in GlaxoSmithKline's view, the promotional use of such composite endpoints must clearly show which components of that composite endpoint were statistically achieved, particularly as a mortality benefit had not been demonstrated. Claims which used arbitrarily titled endpoints (even if specified in clinical studies or the SPC) were misleading if they implied that all components of the endpoint had been achieved.

The detailed response from Actelion is given below.

GlaxoSmithKline alleged that use of 'reducing morbidity-mortality' in the claim in the detail aid that 'Opsumit helps redefine the future for patients with PAH by reducing morbidity – mortality', was misleading as it implied a mortality benefit whereas only the morbidity component of the endpoint was significant. GlaxoSmithKline was similarly concerned about the claim that Pulido *et al* had demonstrated morbidity-mortality in stable patients. The claim appeared on a graph which showed, over the course of three years, the percentage of placebo and Opsumit patients who were event free (49% vs 63% respectively).

The Panel noted that this was a specialist area. The composite endpoint was the time from initiation of treatment to the first event related to the worsening of PAH or death from any cause up to the end of treatment. Pulido *et al* reported that Opsumit significantly reduced morbidity and mortality but that the treatment effect for the primary outcome was driven mainly by differences in the rates of worsening PAH. When death was considered alone, there was a positive treatment effect for Opsumit but the difference compared with placebo was not statistically significant. Given that PAH was a progressive disease and clinical deterioration was likely to precede death the authors were not surprised that death from any cause or from PAH was rarely the first recorded event. The study was not powered to show an effect on mortality alone and concluded that Opsumit significantly reduced

morbidity and mortality and benefits were shown for patients with no previous treatment and for those receiving therapy for PAH at study entry. The SPC gave the outcome endpoints including data on the composite morbidity-mortality endpoint and estimates of the first morbidity-mortality event. The summary of outcome events showed that for the composite endpoint 53% of patients in the placebo group had an event vs 37% in the Opsumit 10mg treatment group ( $p < 0.0001$ ). However when this was broken down into its component parts the data showed that 7.6% of patients in the placebo group died vs 5.8% in the treatment group ( $p = 0.2$ ) and that 37.2% of patients in the placebo group experienced a worsening of their PAH vs 24.4% in the treatment group ( $p < 0.0001$ ).

The Panel noted that the detail aid was entitled 'Help her write future chapters'. The claim that 'Opsumit helps redefine the future for patients with PAH by reducing morbidity-mortality' appeared on page 2 under the heading 'It's time to challenge outcomes for your patients today and tomorrow'. The page in question did not include the additional data provided in either the study (to which it was referenced) or the SPC. The Panel considered that the meaning of the phrase morbidity-mortality was not necessarily clear in the detail aid. There was no reference to it being a composite endpoint ie the first occurrence of a morbidity or mortality event; given the references in the detail aid to the future and to tomorrow the Panel considered that it was not unreasonable that some readers would assume that Opsumit therapy significantly reduced not only morbidity but also mortality. This was not so. In the Panel's view insufficient information had been given about the primary endpoint results such that readers would not appreciate that the reduction in the primary outcome in the Opsumit treatment group was driven by a reduction in morbidity. The material was not sufficiently complete such that a health professional could form his/her own opinion about the full therapeutic value of the medicine. The Panel considered that the claim was misleading in that regard and ruled a breach of the Code. The Panel similarly ruled a breach with regard to the claim on the graph that Pulido *et al* had demonstrated morbidity-mortality in stable patients.

GlaxoSmithKline alleged that the risk reduction in the claim 'Sustained risk reduction from the start of therapy', which appeared within a graph, was not clear. As the title to the graph included 'reducing morbidity-mortality', it implied morbidity and mortality which was misleading as it was not clear that there was no significant effect on mortality.

The Panel noted its comments above and considered that they were relevant here. The Panel considered that the detail aid had not provided the reader

with sufficient information about the morbidity-mortality endpoint such that he/she would be able to readily appreciate the full therapeutic value of Opsumit. The Panel noted Actelion's submission that the graph had been taken from the SPC. In contrast with the SPC, however, readers were not provided with sufficient information such that they could appreciate that the reduction in the primary endpoint in the treatment group was driven by a reduction in morbidity. The Panel considered that, in that regard, the graph with its claim for a 'Sustained risk reduction from the start of therapy' was misleading. A breach of the Code was ruled. The Panel considered that in the context in which they were presented, the graph and the claim exaggerated the therapeutic value of Opsumit; a breach of the Code was ruled.

GlaxoSmithKline alleged that the claim 'Reduced risk of PAH-related death or hospitalisations' was misleading as it implied a reduction in death rates whilst the composite secondary endpoint was driven by reductions in hospitalisation with no significant reduction in mortality.

The Panel noted that Pulido *et al* included a secondary endpoint of death due to PAH or hospitalisation for PAH up to the end of treatment. A statistically significant treatment effect was observed with respect to this composite endpoint driven by lower rates of hospitalisation in the treatment group. There was no significant difference between the placebo group and the treatment group in the rates of death as a component of the composite endpoint. The Panel noted its comments about the context of the presentation of results relating to the composite endpoint above and considered that they were relevant here. The Panel considered that in the context of the detail aid the reader had not been presented with sufficient information such that he/she would appreciate that the reduction in the endpoint was driven by lower rates of hospitalisation. The Panel considered that in this regard the claim was misleading. A breach of the Code was ruled.

GlaxoSmithKline stated that substantiation was needed for the claims regarding the reduction of mortality, which it alleged were misleading and submitted that use of the terms morbidity-mortality and death or hospitalisation as quotations from Pulido *et al* had breached the Code.

The Panel considered that the impression of reduced mortality given by the claims at issue could not be substantiated and in that regard high standards had not been maintained. A breach of the Code was ruled. The Panel noted that in inter-company dialogue, Actelion had failed to provide substantiation for the implied mortality claims. A breach of the Code was ruled. The Panel noted that although the detail aid had featured the outcome of the study no actual quotations from the paper had been included. In that regard there could be no breach of the Code and the Panel ruled accordingly.

GlaxoSmithKline alleged that the claim 'In stable patients already receiving PAH-specific therapies, Opsumit offered a 38% reduction in relative risk reduction in morbidity-mortality at 3 years (p=0.009 [ARR 14%])' used within the leavepiece was misleading as there was no statistically significant mortality benefit shown in Pulido *et al* or in the Opsumit SPC.

The Panel noted its comments and rulings above with regard to the presentation of the composite endpoint. The Panel noted that the context in which the claim appeared in the leavepiece was different to the detail aid as it did not refer to 'tomorrow' or the 'future'. The Panel noted, however, that the claim appeared immediately after a claim about 'the first long-term event-driven outcome trial'. As above, the Panel considered that without the additional information provided in the study or in the SPC, it was not clear that the treatment effect for the primary event-driven outcome (morbidity-mortality) was driven by a decrease in morbidity, not mortality. In the Panel's view, the reader had not been given sufficient information upon which to make a fully informed decision about the therapeutic value of Opsumit. The Panel considered that the claim in the leavepiece was misleading. A breach of the Code was ruled.

GlaxoSmithKline UK Ltd complained about a detail aid (ref OPS 13/0038) and a leavepiece (ref OPS 13/0039) for Opsumit (macitentan) issued by Actelion Pharmaceuticals UK Ltd. Opsumit was indicated as monotherapy or in combination for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of world health organization (WHO) functional class (FC) II to III. Efficacy had been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease. Both pieces of material were for use with health professionals within specialist PAH centres and those who referred PAH patients to specialist centres.

GlaxoSmithKline marketed Volibris (ambrisentan) indicated for the treatment of adult patients with PAH classified as WHO functional class II and III, to improve exercise capacity. Efficacy had been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

#### General Comments from GlaxoSmithKline

At issue in this case was the way in which the primary and secondary composite endpoints from Pulido *et al* (2013) had been presented in the detail aid and leavepiece. GlaxoSmithKline did not refute that the composite primary end point of morbidity-mortality or the secondary endpoint of PAH related death or hospitalisation was achieved in Pulido *et al* or was mentioned in the Opsumit summary of product characteristics (SPC). However, in GlaxoSmithKline's view, the promotional use of such composite endpoints must clearly show what components of that composite endpoint were statistically achieved, particularly as a mortality

benefit had not been demonstrated. Claims which used arbitrarily titled endpoints (even if specified in clinical studies or the SPC) were misleading if they implied that all components of the endpoint had been achieved.

### Background from Actelion

Actelion noted that GlaxoSmithKline considered that its use of the phrase 'reducing morbidity-mortality' implied a mortality benefit claim. Actelion submitted however, that there was an underlying misinterpretation in GlaxoSmithKline's complaint and in that regard Actelion explained the origins of 'morbidity-mortality' to put into context how the phrase was used in the specialist literature, the SPC and the detail aid and leavepiece at issue.

Actelion stated that the traditional endpoints in PAH studies, and used for licensing, were short-term symptomatic measures such as the change in six minute walk distance (6MWD). Studies were typically conducted over 12-24 weeks. Bosentan (Tracleer), an Actelion medicine licensed for use in PAH in 2002, and ambrisentan, GlaxoSmithKline's Volibris licensed in 2008, were investigated using this endpoint. However, 6MWD did not correlate with long-term outcomes in PAH and offered limited information on disease progression. The world PAH community set up an expert task force in 2008 to look for better correlates of long-term outcomes which would more accurately measure disease progression. This task force focused on endpoints and clinical trial design and met at the 4<sup>th</sup> World Symposium on Pulmonary Hypertension (WSPH) in 2008. It recommended including a primary composite endpoint to accurately reflect clinical worsening and independent and blinded adjudication of events to minimize bias.

This primary endpoint should be a composite endpoint which reflected clinical worsening (morbidity or time to clinical worsening [TTCW]) and mortality. The adjudication of events by an independent and blinded panel would reduce the inconsistencies between event classification by sites and investigators.

The use of such a composite primary endpoint was subsequently recommended by the *European Medicines Agency* (EMA) as more relevant than change in 6MWD. The EMA recognized that measurement of mortality in such a rare disease in which effective therapies were already available would be challenging.

In 2009 the EMA published new guidelines for investigating medicines in PAH and recommended an event-driven design with mortality and morbidity as a composite endpoint. A 2009 review of the history and design of PAH studies by McLaughlin *et al* provided a summary of this recommendation. The Opsumit phase III study, (Pulido *et al*), the source of the data used in the materials at issue, provided a clear picture of disease progression by taking into account all of the events recommended by the task force and the EMA (a long-term, event-driven study with an adjudication of events). Pulido *et al* had time

to the first occurrence of a morbidity or mortality event as its composite primary endpoint.

The use of this event-driven morbidity-mortality endpoint directly and accurately reflected disease progression in PAH. The task force for the 5<sup>th</sup> WSPH in 2013 also recognised the robust nature of the evidence for only two products, Opsumit and epoprostenol. These were the only two treatments highlighted in the treatment algorithm for PAH with a level 1 recommendation based on the demonstration of morbidity and mortality as a primary endpoint or the reduction in all-cause mortality as a pre-specified endpoint.

Actelion noted that composite endpoints had been used in other studies and that its reference to morbidity-mortality was in line with such studies. Actelion cited in particular a number of cardiovascular studies.

Actelion submitted that in its view 'morbidity-mortality' referred to a composite endpoint with several components of mortality and morbidity. The approved wording in the SPC was carefully considered by national agencies. Section 5.1 of the Opsumit SPC used the hyphenated term 'morbidity-mortality' to describe the positive outcome of the composite primary endpoint of Pulido *et al* in figure 1 and table 1. In addition, all core materials had been pre-vetted by the Medicines and Healthcare Products Regulatory Agency (MHRA).

Actelion submitted that it had clarified the endpoints above and throughout inter-company dialogue with GlaxoSmithKline. It seemed that GlaxoSmithKline was reluctant to acknowledge that guidelines now supported event-driven studies with complex composite endpoints, the SPC described the positive outcome of the composite primary endpoint of Pulido *et al* as morbidity-mortality, and the scientific community discussed outcomes from these studies as morbidity-mortality with the understanding that this meant the combination of all-cause mortality plus PAH-related morbidity events.

In summary, Actelion submitted that morbidity-mortality was not a misleading term, it was widely understood to mean 'morbidity plus mortality events, together'. It did not imply reduction in both components individually. This was reflected in the SPC and was also in line with expert opinion.

### A Detail aid (ref OPS 13/0038)

The first page of the detail aid referred to the treatment of PAH and included the main claim 'Help her write future chapters' above an illustration of attending and graduating from university. Page two was headed 'It's time to challenge outcomes for your patients today and tomorrow' followed by a claim 'Opsumit helps redefine the future for patients with PAH by reducing morbidity-mortality' referenced to Pulido *et al*. A graph (adapted from Pulido *et al*) showed the sustained risk reduction from the start of therapy and referred to the percentage of patients that were event free. At three years 63% of Opsumit patients were without an event vs 47% of placebo

patients. A claim to the left of the graph stated 'Opsumit 10mg significantly reduced the overall risk of a morbidity-mortality event compared with placebo (63% versus 47%;  $p < 0.001$ ). The graph also included a claim '45%RRR 16% ARR  $p < 0.001$ '.

### **1 Claim 'Opsumit helps redefine the future for patients with PAH by reducing morbidity-mortality'**

This claim appeared as the sub-heading to page 2 and was referenced to Pulido *et al.*

#### **COMPLAINT**

GlaxoSmithKline alleged that use of 'reducing morbidity-mortality' was misleading in breach of Clause 7.2. The claim implied a mortality benefit whereas despite having a primary composite endpoint of time to first event of morbidity or mortality only the morbidity component was significant in table 2 of Pulido *et al* and table 1 of the Opsumit SPC. Pulido *et al* stated that the 'treatment effect for the primary endpoint was driven mainly by differences in the rates of worsening of pulmonary arterial hypertension'. GlaxoSmithKline stated that hyphenating morbidity-mortality into one word implied reductions in both components. Section 5.1 of the Opsumit SPC also stated 'The number of deaths of all causes up to [end of study] on macitentan 10mg was 35 versus 44 on placebo (HR 0.77; 97.5% CI: 0.46 to 1.28)', which was not statistically significant. GlaxoSmithKline alleged that using mortality as a claim in a promotional context was misleading in breach of Clause 7.2.

#### **RESPONSE**

Actelion submitted that the statement 'reducing morbidity-mortality' was widely understood to mean 'reducing mortality plus morbidity events' in the event-driven study. As discussed above, hyphenating the term did not imply a reduction in both components (in fact there were at least five components). There was no requirement in the Code to expand a composite primary endpoint into its components. Moreover, the hyphenated term was also used in the SPC. Actelion refuted that use of this term was in breach of Clause 7.2.

#### **PANEL RULING**

In considering all the allegations the Panel bore in mind that this was a specialist area. The SPC stated that treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

The Panel noted that Pulido *et al* was a long-term trial to assess the efficacy of Opsumit using a primary composite endpoint of morbidity and mortality. The composite endpoint was the time from initiation of treatment to the first event related to the worsening of PAH or death from any cause up to the end of treatment. All endpoints were independently adjudicated. The authors reported that Opsumit significantly reduced morbidity and mortality but that the treatment effect for the primary outcome was driven mainly by differences in the rates of worsening PAH. When death was

considered alone, there was a positive treatment effect for Opsumit but the difference compared with placebo was not statistically significant. Given that PAH was a progressive disease and clinical deterioration was likely to precede death the authors were not surprised that death from any cause or from PAH was rarely the first recorded event. The authors noted that the study was not powered to show an effect on mortality alone.

One of the limitations of the study was stated to be that it did not address the efficacy of Opsumit compared with other approved oral therapies for PAH. The study concluded that Opsumit significantly reduced morbidity and mortality and benefits were shown for patients with no previous treatment and for those receiving therapy for PAH at study entry.

The SPC provided details of the primary endpoint as the time to first occurrence of a morbidity event, up to the end of double-blind treatment, as defined as death, or atrial septostomy, or lung transplantation, or initiation of intravenous or subcutaneous prostanoids, or other worsening of PAH. Other worsening of PAH was further defined in the SPC. Following this information, Section 5.1 of the SPC gave the outcome endpoints including data on the composite morbidity-mortality endpoint and estimates of the first morbidity-mortality event. The summary of outcome events showed that for the composite endpoint 53% of patients in the placebo group had an event vs 37% in the Opsumit 10mg treatment group ( $p < 0.0001$ ). However when this was broken down into its component parts the data showed that 7.6% of patients in the placebo group died vs 5.8% in the treatment group ( $p = 0.2$ ) and that 37.2% of patients in the placebo group experienced a worsening of their PAH vs 24.4% in the treatment group ( $p < 0.0001$ ).

The Panel agreed with Actelion that there was no requirement in the Code to extend a composite primary endpoint into its components. The question to be considered was whether the claim for the composite endpoint in the context of the material at issue met the requirements of the Code.

The Panel noted that the detail aid was entitled 'Help her write future chapters'. The claim at issue that 'Opsumit helps redefine the future for patients with PAH by reducing morbidity-mortality' appeared on page 2 under the heading 'It's time to challenge outcomes for your patients today and tomorrow'. The page in question did not include the additional data provided in either Pulido *et al* (to which it was referenced) or the SPC. The Panel considered that the meaning of the phrase morbidity-mortality was not necessarily clear in the detail aid. There was no reference to it being a composite endpoint ie the first occurrence of a morbidity or mortality event; given the references in the detail aid to the future and to tomorrow the Panel considered that it was not unreasonable that some readers would assume that Opsumit therapy significantly reduced not only morbidity but also mortality. This was not so. In the Panel's view insufficient information had been given about the primary endpoint results such that readers would not appreciate that the reduction in the primary outcome in the Opsumit treatment group

was driven by a reduction in morbidity. The material was not sufficiently complete such that a health professional could form his/her own opinion about the full therapeutic value of the medicine. The Panel considered that the claim was misleading in that regard and ruled a breach of Clause 7.2 of the Code.

## **2 Claim 'Sustained risk reduction from the start of therapy'**

This claim appeared within the graph featured on page 2 which showed, over the course of three years, the percentage of patients taking either placebo or Opsumit 10mg who were event-free (47% vs 63% respectively  $p < 0.001$ ).

### **COMPLAINT**

GlaxoSmithKline alleged that it was not clear what the risk reduction related to, implying morbidity and mortality as the phrase 'reducing morbidity-mortality' was used in the title to the graph. No statistically significant reduction in mortality could be claimed, therefore the artwork was misleading in breach of Clause 7.8. GlaxoSmithKline noted that Section 5.1 of the Opsumit SPC mentioned a 45% relative risk reduction of the 'composite morbidity-mortality' endpoint which was 'established early and sustained', however in a promotional context it was not clear that there was no significant effect on mortality which remained misleading in breach of Clause 7.8.

GlaxoSmithKline alleged that the overall appearance of page 2 implied a morbidity and mortality benefit which was not so. The evidence in the study and the SPC showed no significant reduction in mortality. GlaxoSmithKline alleged that the claim exaggerated the properties of Opsumit and implied special merit which had not been shown in breach of Clause 7.10.

GlaxoSmithKline further alleged that the material claimed a mortality benefit which had not been substantiated by the evidence provided and was in breach of Clause 7.5.

### **RESPONSE**

Actelion submitted that the artwork was taken directly from Section 5.1 of the SPC. The company further submitted that morbidity-mortality was not a misleading term; it was widely understood to mean 'morbidity plus mortality events, together'. The term did not imply reduction in both components separately and Actelion did not claim mortality benefits in its promotional materials. In that regard the company denied a breach of Clause 7.8.

Actelion submitted that morbidity-mortality did not imply reduction in both components separately therefore there was no exaggerated claim. Mortality on its own was not suggested by Actelion. Expert, informed clinicians and scientists, who made up the prescribing and referring target group for this tertiary specialist area, understood that the graphics and data described the mortality plus morbidity events that were used to examine the efficacy of Opsumit in Pulido *et al*. Actelion submitted that

the claim reflected the SPC and was not a breach of Clause 7.10.

Actelion submitted that in its view the alleged breach of Clause 7.5 related to the previous points already covered under Clauses 7.2, 7.8 and 7.10 above regarding morbidity-mortality. Actelion did not consider that it had made a specific mortality claim and thus denied a breach of Clause 7.5.

### **PANEL RULING**

The Panel noted its comments and ruling in Point 1 above and considered that they were relevant here. The Panel considered that the detail aid had not provided the reader with sufficient information about the morbidity-mortality endpoint such that he/she would be able to readily appreciate the full therapeutic value of Opsumit. The Panel noted Actelion's submission that the graph had been taken from the SPC. In contrast with the SPC, however, readers were not provided with sufficient information such that they could appreciate that the reduction in the primary endpoint in the treatment group was driven by a reduction in morbidity. The Panel considered that, in that regard, the graph with its claim for a 'Sustained risk reduction from the start of therapy' was misleading. A breach of Clause 7.8 was ruled. The Panel considered that in the context in which they were presented, the graph and the claim exaggerated the therapeutic value of Opsumit; a breach of Clause 7.10 was ruled.

The Panel noted the alleged breach of Clause 7.5 which required that substantiation for any information, claim or comparison be provided as soon as possible, and certainly within ten working days, at the request of members of the health professions or appropriate administrative staff. The Panel noted that in inter-company dialogue, Actelion had failed to provide substantiation for the implied mortality claim. A breach of Clause 7.5 was ruled.

## **3 Claim '[Pulido *et al*] is the first study to demonstrate morbidity-mortality in stable PDE5i patients'**

This claim appeared within the graph featured on page 3 of the detail aid which showed, over the course of three years, the percentage of placebo and Opsumit 10mg patients who were event-free (49% vs 63% respectively).

### **COMPLAINT**

GlaxoSmithKline alleged that the claim was misleading, Pulido *et al* attempted to show a primary endpoint of reduction in morbidity or mortality. Whilst it met this endpoint it was driven exclusively by reductions in morbidity and not mortality which was not statistically significantly different between groups. A breach of Clause 7.2 was alleged.

### **RESPONSE**

Actelion submitted that GlaxoSmithKline might have misinterpreted Pulido *et al*. The primary endpoint of the study was not mortality or morbidity, but

mortality plus morbidity events together. As noted above, morbidity-mortality was widely understood to mean mortality plus morbidity events and in this context, the claims on page three regarding outcomes in the PDE5i subgroup were not misleading. The majority of patients in the study at baseline were on PDE5 inhibitors and this pre-planned subgroup analysis used the same primary endpoint. Actelion submitted that the data presented was not misleading and it denied a breach of Clause 7.2.

#### **PANEL RULING**

The Panel noted its comments and rulings above and considered that they were relevant here. The SPC did not include the data on page 3 of the detail aid. It was provided in a supplementary appendix to Pulido *et al* which was provided by Actelion upon request of the Panel. In the Panel's view, in the context of the detail aid the reader had not been provided with sufficient information such that he/she would appreciate that the reduction in the primary endpoint had been driven by reductions in morbidity. The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

#### **4 Claim 'Reduced risk of PAH-related death or hospitalisations'**

The claim, together with a prominent figure of 50%, appeared as a bullet point on page 4 of the Opsumit detail aid which was headed 'Plus improvements in other key patient parameters'. The claim related to the secondary outcome in Pulido *et al* and was referenced to Pulido *et al* and Channick *et al* (2013).

#### **COMPLAINT**

GlaxoSmithKline stated that the claim 'Reduced risk of PAH-related death or hospitalisations' was misleading as it implied a reduction in death rates. This composite secondary endpoint was driven by reductions in hospitalisation with no significant reduction in mortality. In the discussion of the results, Pulido *et al* stated that this 'was driven by lower rates of hospitalisation in the [Opsumit] groups'. A breach of Clause 7.2 was alleged.

#### **RESPONSE**

Actelion submitted that the word 'or' served the same purpose as the hyphen in the morbidity-mortality phrase. It did not mean PAH death or hospitalisation, separately. It was clearly a combined endpoint, again, consistent with other endpoints in the study. Importantly, use of 'or' in this context was exactly as used in the SPC: 'The risk of PAH related event or hospitalisation for PAH up to EOT [end of trial] was reduced by 50% ....'. Actelion refuted that the data presented was misleading and in breach of Clause 7.2.

#### **PANEL RULING**

The Panel noted that Pulido *et al* included a secondary endpoint of death due to PAH or hospitalisation for PAH up to the end of treatment. A

statistically significant treatment effect was observed with respect to this composite endpoint driven by lower rates of hospitalisation in the treatment group. There was no significant difference between the placebo group and the treatment group in the rates of death as a component of the composite endpoint. The Panel noted its comments about the context of the presentation of results relating to the composite endpoint above and considered that they were relevant here. The Panel considered that in the context of the detail aid the reader had not been presented with sufficient information such that he/she would appreciate that the reduction in the endpoint was driven by lower rates of hospitalisation. The Panel considered that in this regard the claim was misleading. A breach of Clause 7.2 was ruled.

#### **5 Overall**

#### **COMPLAINT**

GlaxoSmithKline stated that substantiation was needed for the claims regarding the reduction of mortality, which it alleged were misleading in breach of Clause 7.5. GlaxoSmithKline submitted that use of the terms morbidity-mortality and death or hospitalisation as quotations from Pulido *et al* had not been used in a Code compliant manner; they should have been adapted and stated as such, and were therefore in breach of Clause 10.2. GlaxoSmithKline further alleged a breach of Clause 9.1 as high standards had not been maintained.

#### **RESPONSE**

Actelion submitted that the points relating to Clauses 7.5 and 10.2 were linked to points raised under Clauses 7.2 and 7.8, regarding how the morbidity-mortality data from Pulido *et al* had been represented. As discussed above, Actelion submitted that it had been consistent with the SPC. Actelion therefore refuted that it was in breach of any of the clauses. Subsequently, Actelion submitted that it had maintained high standards at all times and it denied a breach of Clause 9.1.

#### **PANEL RULING**

The Panel noted its comments and rulings above. The Panel considered that the impression of reduced mortality given by the claims at issue could not be substantiated and in that regard high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted the alleged breach of Clause 7.5 which required that substantiation for any information, claim or comparison be provided as soon as possible, and certainly within ten working days, at the request of members of the health professions or appropriate administrative staff. The Panel noted that in inter-company dialogue, Actelion had failed to provide substantiation for the implied mortality claim. A breach of Clause 7.5 was ruled.

The Panel noted that although the detail aid had featured the outcome of Pulido *et al* no actual

quotations from the paper had been included. In that regard there could be no breach of Clause 10.2 and the Panel ruled accordingly.

## **B Leavepiece (ref OPS 13/0039)**

### **1 Claim 'In stable patients already receiving PAH-specific therapies, Opsumit offered a 38% reduction in relative risk reduction in morbidity-mortality at 3 years (p=0.009 [ARR 14%])'**

This was a slim leavepiece which opened out to A5. The claim at issue appeared on page one of the material as the second claim beneath the headline 'Opsumit – proven to reduce morbidity-mortality in pulmonary arterial hypertension'. The first claim read, Opsumit is effective as monotherapy and in combination with PDE5i, as shown in the first long-term, event-driven outcome trial in PAH'.

#### **COMPLAINT**

GlaxoSmithKline alleged that the claim was misleading in breach of Clause 7.2 as there was no statistically significant mortality benefit shown in Pulido *et al* or in the Opsumit SPC.

#### **RESPONSE**

Actelion submitted that the claim at issue was consistent with the definition of the primary endpoint of Pulido *et al* and the SPC, which included the same

hyphenated term. There was no requirement to examine the relative contribution of components making up the composite endpoint. Actelion denied a breach of Clause 7.2.

#### **PANEL RULING**

The Panel noted its comments and rulings above with regard to the presentation of the composite endpoint. The Panel noted that the context in which the claim appeared was different to the detail aid as the leavepiece did not refer to 'tomorrow' or the 'future'. The Panel noted, however, that the claim appeared immediately after a claim about 'the first long-term event-driven outcome trial' ie Pulido *et al*. As above, the Panel considered that without the additional information provided in Pulido *et al* or in the SPC, it was not clear that the treatment effect for the primary event-driven outcome (morbidity-mortality) was driven by a decrease in morbidity, not mortality. In the Panel's view, the reader had not been given sufficient information upon which to make a fully informed decision about the therapeutic value of Opsumit. The Panel considered that the claim was misleading in that regard. A breach of Clause 7.2 was ruled as alleged.

<b>Complaint received</b>	<b>1 May 2014</b>
<b>Case completed</b>	<b>2 July 2014</b>

# GENERAL PRACTITIONER v MEDA

## Promotion of Dymista

A general practitioner alleged that an advertisement for Dymista (fluticasone/azelastine nasal spray), issued by Meda Pharmaceuticals and published in GP, 28 April 2014, was misleading.

The complainant noted that the advertisement featured the prominent claim that Dymista 'can be considered the drug of choice for the treatment of AR [allergic rhinitis]'. However, in the complainant's view, as Dymista was indicated for the relief of AR symptoms if monotherapy with either intranasal antihistamine or glucocorticoid was not considered sufficient it was a second- or third-line treatment and not the drug of choice. The complainant alleged that the advertisement was unacceptable.

The detailed response from Meda is given below.

The Panel noted that the dark blue artwork and text of advertisement were prominent against a clear white background. The advertisement was headed with the Dymista product name and non-proprietary names. Below this was a depiction of the nasal spray being activated and this was followed by the claim that Dymista 'can be considered the drug of choice for the treatment of AR'; 'drug of choice' appeared in bolder and bigger font than the rest of the claim. The claim was referenced to Leung *et al* (2012) and was a quotation from that publication. The indication for Dymista was stated to the lower right of the claim in smaller black font. The prescribing information appeared along the lower edge of the advertisement.

The Panel noted Meda's submission that the claim was based on a published paper and that all the claims were based on material pre-vetted by the MHRA.

The Panel noted that Leung *et al* (2012) was in fact 'The Editors' Choice' of papers from a clinical journal. The editors had commented on Carr *et al* (2012) which was the source paper. In their review Leung *et al* stated that [Dymista] could be considered the drug of choice for the treatment of AR.

The Panel noted that although the claim at issue was an accurate quotation from Leung *et al*, (and Carr *et al*) the Code required that any quotation used in promotional material must comply with the Code. Further, the Code stated that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like.

In the Panel's view, the claim that Dymista was 'the drug of choice' implied that no other medicine could, or should, be chosen as first-line therapy. Dymista was, however, a second-line therapy which

should only be used when monotherapy with either intranasal antihistamine or glucocorticoid was not considered sufficient. The Panel noted that although the indication for Dymista appeared in smaller print to the lower right of the claim, it did not negate the impression otherwise given by the claim. The Panel considered that the claim was all-embracing by virtue of the use of 'the'. A breach of the Code was ruled. The Panel considered that the claim gave a misleading impression regarding Dymista's place in the treatment of AR which could not be substantiated. Breaches of the Code were ruled.

A general practitioner, complained about a Dymista (fluticasone propionate/azelastine hydrochloride) advertisement (ref UK/DYM/13/0022(2)a) issued by Meda Pharmaceuticals Ltd and published in GP, 28 April 2014. Dymista was a nasal spray indicated for relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis (AR) if monotherapy with either intranasal antihistamine or glucocorticoid was not considered sufficient.

### COMPLAINT

The complainant noted that the advertisement featured the prominent claim that Dymista 'can be considered the drug of choice for the treatment of AR'. However, Dymista was indicated for the relief of symptoms of moderate to severe seasonal and perennial AR if monotherapy with either intranasal antihistamine or glucocorticoid was not considered sufficient. In the complainant's view, Dymista was, therefore, a second- or third-line treatment and not the drug of choice and although the claim was in quotation marks it appeared to be designed to deliberately mislead. The complainant alleged that this was unacceptable advertising.

When writing to Meda, the Authority asked it to respond in relation to Clauses 7.2, 7.4, and 7.10 of the Code.

### RESPONSE

Meda submitted that all Dymista promotional materials were pre-vetted by the Medicines and Healthcare Products Regulatory Agency (MHRA) at launch and Meda was required to include the full indication wherever the quotation was used in order to qualify its positioning and full indication. Meda disputed that the advertisement and specifically the quotation 'can be considered the drug of choice' was misleading or unsubstantiated in breach of Clauses 7.2, 7.4 and 7.10.

In response to a request from the case preparation manager for further comment, Meda submitted that the advertisement did not contravene Clause 7.2 as it clearly listed the Journal of Allergy and Clinical



Immunology, volume 129, number 5 as a reference and stated the full indication.

Meda submitted that the claims in the advertisement were substantiated; they were based on the results of the research referenced in the advertisement and Meda had prominently stated the full indication.

Meda disagreed that the advertisement was not in line with Clause 7.10; no exaggerated or all-embracing claims had been made. Meda submitted that all claims were based on MHRA pre-vetted material and the above mentioned reference was listed.

## PANEL RULING

The Panel noted that the dark blue artwork and text of advertisement were prominent against a clear white background. The advertisement was headed with the Dymista product name and non-proprietary names. Below this was a depiction of the nasal spray being activated and this was followed by the claim that Dymista 'can be considered the drug of choice for the treatment of AR'; 'drug of choice' appeared in bolder and bigger font than the rest of the claim. The claim was referenced to Leung (2012) and was a quotation from that publication. The indication for Dymista was stated to the lower right of the claim in smaller black font. The prescribing information appeared along the lower edge of the advertisement.

The Panel noted Meda's submission that the claim was based on a published paper and that all the claims were based on material pre-vetted by the MHRA.

The Panel noted that Leung *et al* (2012) was in fact 'The Editors' Choice' of papers from the May 2012 edition of the Journal of Allergy and Clinical Immunology. The editors had commented on Carr *et al* (2012) which was the source paper. In their review Leung *et al* stated that [Dymista] could be considered the drug of choice for the treatment of AR. The source paper ie Carr *et al* compared the

efficacy of Dymista with two first-line therapies ie intranasal fluticasone propionate and intranasal azelastine in 3,398 patients with moderate to severe seasonal AR in three multicentre, randomized, double-blind, placebo- and active-controlled, 14-day, parallel-group trials. Carr *et al* reported that Dymista was significantly more effective than intranasal fluticasone or azelastine and that their results showed that it could be considered the drug of choice for the treatment of AR.

The Panel noted that although the claim at issue was an accurate quotation from Leung *et al*, (and Carr *et al*) Clause 10.2 of Code required that any quotation chosen by a company for use in promotional material must comply with the requirements of the Code itself. Further, the supplementary information to Clause 7 stated that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like.

In the Panel's view, the claim that Dymista was 'the drug of choice' implied that no other medicine could, or should, be chosen as first-line therapy. Dymista was, however, a second-line therapy which should only be used when monotherapy with either intranasal antihistamine or glucocorticoid was not considered sufficient. The Panel noted that although the indication for Dymista appeared in smaller print to the lower right of the claim, it did not negate the impression otherwise given by the claim. The Panel considered that the claim was all-embracing by virtue of the use of 'the'. A breach of Clause 7.10 was ruled. The Panel considered that the claim gave a misleading impression regarding Dymista's place in the treatment of AR which could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

<b>Complaint received</b>	<b>1 May 2014</b>
<b>Case completed</b>	<b>30 June 2014</b>

# NHS TRUST CHIEF PHARMACIST v LILLY

## Nurse consultancy agreement

The chief pharmacist at an NHS trust, complained about Eli Lilly's approach when it contacted one of the trust's ADHD (attention deficit hyperactivity disorder) nurse specialists to request that he/she speak on behalf of Lilly about its product Strattera (atomoxetine hydrochloride) which was indicated in the treatment of ADHD. The nurse in question managed and prescribed for patients.

The complainant noted that, according to an email from Lilly's compliance department the nurse had been contracted for speaking, advisory board, consulting or research collaboration services. The complainant stated that payment for research collaboration of a prescriber was potentially an inducement to prescribe and recommend similar to other health professionals which could lead to disrepute for the complainant's trust with other trusts. The complainant alleged that the arrangement in question was akin to seeding research where a company paid for a product to be prescribed under the auspices of research. The complainant queried whether Lilly had disclosed the payment.

The detailed response from Lilly is given below.

The Panel noted that the complainant had submitted his complaint after seeing the email referred to above. The Panel assumed that the recipient was the person within the trust, nominated by the nurse, to comment on his/her proposed relationship with Lilly before any contracted services were undertaken. The Panel noted Lilly's submission that this increased transparency around any proposed relationship or consultancy agreement. In that regard the Panel considered that it was unfortunate that the document listed the potential interactions with the nurse and not the intended interaction ie one speaking engagement at a clinical meeting. In the Panel's view, this might have led to the complainant's confusion about the nurse's role.

The Panel noted that Lilly had asked the ADHD nurse specialist in question to speak for 40 minutes, with 20 minutes for questions and answers, at a local clinical meeting entitled the Strattera Experience Programme. In that regard the Panel considered that the need for a suitable speaker had been identified and there was no evidence that the choice of the nurse in question to fulfil that role was inappropriate. No breach of the Code was ruled. The Panel noted that because of the confusion within the trust about the nurse's role in relation to his/her relationship with Lilly, the meeting, had been cancelled and thus no consultancy fee had been paid. In that regard there was no fee to disclose and so the Panel ruled no breach of the Code.

The Panel further noted that the nurse had not been contracted to collaborate in research; there was no study proposed which was akin to a seeding study as postulated by the complainant. No breach of the Code was ruled. The Panel noted that a particular clause cited by the complainant defined a non-interventional study of a marketed medicine and in that regard it could not be breached. The Panel further noted that there was no evidence to suggest that the consultancy agreement was offered as an inducement to prescribe Strattera. No breach of the Code was ruled.

A chief pharmacist at an NHS trust, complained about Eli Lilly's approach when it contacted one of the trust's ADHD (attention deficit hyperactivity disorder) nurse specialists to request that he/she speak on behalf of Lilly about its product Strattera (atomoxetine hydrochloride). Strattera was indicated for the treatment of ADHD in children of 6 years and older, in adolescents and in adults as part of a comprehensive treatment programme.

### COMPLAINT

The complainant noted that the ADHD nurse specialist had been contracted for speaking, advisory board, consulting or research collaboration services as stated in an email from Lilly's compliance department. The complainant submitted that the nurse managed and prescribed for patients and that if he/she was paid to undertake research in lieu of a direct contracted payment, there was a potential breach of Clause 13.2 as it could be construed as a promotional payment to put someone in a study and therefore prescribe the study medicine. The complainant was concerned that the two were not clearly separated and the arrangement was potentially in breach of Clause 18.1.

The complainant further submitted that under Clause 20, the use of any consultants was sought after the need for research was identified. The complainant alleged that the arrangement in question was the other way round so was construed as an inducement which was akin to seeding research where a company paid for a product to be prescribed under the auspices of research. The complainant did not distinguish between a medical consultant and a specialist nurse and considered that that argument was academic. The complainant stated that payment for research collaboration of a prescriber was potentially an inducement to prescribe and recommend similar to other health professionals which could lead to disrepute for the complainant's trust with other trusts.

The complainant queried whether Lilly had disclosed the payment. A small payment would be seen differently to a significantly larger payment

especially as any kind of gift or hospitality should be reasonable.

The complainant applauded Lilly for notifying the trust of the arrangements and in an attached email cited a number of clauses of the Code.

When writing to Lilly the Authority asked it to respond in relation to Clauses 12.2, 13.2, 18.1, 20.1 and 20.2 of the Code as cited by the complainant.

## RESPONSE

Lilly denied any breach of the Code and submitted that based on the complainant's letter and attachments a misunderstanding had occurred. In Lilly's view, some of its documentation might have led to the confusion and it intended to address the matter by slightly amending the notification letter.

Lilly submitted that the nurse specialist was asked, as an appropriate speaker, to speak at a Lilly organised, clinical meeting. The request to the nurse was accompanied by Lilly's required documentation; an annual master service agreement (MSA) detailing key terms governing the relationship which applied to each statement of work entered into between Lilly and the health professional during the term of the MSA and a statement of work detailing the specific work that was to be undertaken by the nurse and the honorarium for this work. Examples of these documents were provided. A signed master service agreement was received by Lilly in April 2014.

As of January 2014, Lilly required that before any health professional undertook contracted services with the company, he/she nominated an individual who Lilly would notify of its intention to work with the relevant health professional. This created transparency of the relationship that was being requested by Lilly and the nominated person to comment on the proposed relationship before any contracted services were undertaken. A copy of a letter of notification was provided.

Lilly noted that the complainant had welcomed the information being sent. The document was referred to in the email chain submitted as: 'Notification of Lilly's Business interaction with ...'. (sent 28 April) Lilly submitted that the first paragraph of the letter listed the potential interactions that the employee might have with Lilly, which included speaking, advisory board, consulting or research collaboration. This letter might have led to the confusion as it did not make entirely clear that the nurse had been solely contracted for one speaking engagement as specified in a statement of work. This document was sent to the nominated individuals in the employee's trust to increase the transparency of all working relationships that Lilly might be seeking to conduct with health professionals over the course of the entire term of the MSA. Whilst the nurse with whom Lilly had contracted was provided with a statement of work (copy provided) detailing the exact arrangements for these contracted services, the nominated individual was not provided with this confidential information, since the contracted services were directly between Lilly and the relevant

health professional. Lilly stated that in order to avoid any future misunderstandings, it intended to clarify in the notification that specific engagements would be as stated in a statement of work between Lilly and the relevant health professional.

An email from Lilly (sent 29 April) provided by the complainant made it clear that the nurse would be speaking at a single meeting with none of the other potential business interactions being part of that request. The meeting was cancelled following the concerns raised by the nominated individual. The nurse did not undertake the speaking engagement and consequently no payment had been or would be made to him/her. Lilly did not have any on-going or any planned contracted services with the nurse.

In the case in question the proposed contract fell under Clause 20.1 of the Code and Lilly denied that any breach had taken place. Lilly noted the clauses cited by the complainant and in that regard it denied that any breach of Clause 18.1 had taken place. Payment for a speaking engagement would be appropriate and fell under Clause 20.1 not 18.1. Lilly denied any breach of Clauses 12.2 and 13.2 which it submitted were not relevant to this case. Since there was no request for any research collaboration Lilly denied any breach of Clauses 13.2, 18.1 and 20. Clause 20.2 was cited and the complainant queried whether Lilly had disclosed payments referred to under this Clause. In this case no payment was made as the speaking engagement was declined. Lilly submitted that it was committed to transparency with regard to financial arrangements with health professionals and disclosed all such payments in accordance with the Code. Payments made to health professionals in relation to contracted services in 2012 and 2013 could be found on its website, [www.lilly.co.uk](http://www.lilly.co.uk).

In summary, Lilly denied a breach of the Code but it understood how the confusion might have arisen.

## PANEL RULING

The Panel noted that the complainant had submitted his complaint after seeing an email from Lilly to inform the recipient (the recipient's name was redacted by the complainant) that the company had contracted the named nurse for 'speaking, advisory board, consulting or research collaboration services'. The Panel assumed that this document had been sent to the recipient as he/she was the person within the trust, nominated by the nurse, to comment on his/her proposed relationship with Lilly before any contracted services were undertaken. The Panel noted Lilly's submission that this increased transparency within a trust around any proposed relationship or consultancy agreement. In that regard the Panel considered that it was unfortunate that the document listed the potential interactions with the nurse but did not state the intended interaction ie one speaking engagement at a clinical meeting. In the Panel's view, this might have led to the complainant's confusion about the nurse's role.

The Panel noted that the nurse in question was an ADHD nurse specialist who had been asked by

Lilly, to speak for 40 minutes, with 20 minutes for questions and answers, at a local clinical meeting entitled the Strattera Experience Programme. In that regard the Panel considered that the need for a suitable speaker had been identified and there was no evidence that the choice of the nurse in question to fulfil that role was inappropriate. No breach of Clause 20.1 was ruled. The Panel noted that because of the confusion within the trust about the nurse's role in relation to his/her relationship with Lilly, the meeting, originally scheduled for June 2014, had been cancelled and thus no consultancy fee had been paid. In that regard there was no fee to disclose and in any event the fee would not have to be disclosed until 2015 and so the Panel ruled no breach of Clause 20.2.

The Panel further noted that the nurse had not been contracted to collaborate in research; there was no study proposed which was akin to a seeding study as postulated by the complainant. No breach of Clause 12.2 was ruled. The Panel noted that Clause 13.2 defined a non-interventional study of a marketed medicine and in that regard it could not be breached. No breach of that clause was ruled. The Panel further noted that there was no evidence to suggest that the consultancy agreement was offered to the nurse as an inducement to prescribe Strattera. No breach of Clause 18.1 was ruled.

**Complaint received**            **2 May 2014**

**Case completed**                **1 July 2014**

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# VOLUNTARY ADMISSION BY NAPP

## Conduct of representative

Napp Pharmaceuticals voluntarily admitted that one of its representatives had potentially gained an interview with a health professional under the false pretence of wanting to discuss a new medicine when he/she only wanted to discuss an existing one. Further, the representative had also appeared to link the health professional's opinion of Napp's medicines to the company's sponsorship of a conference.

In accordance with Paragraph 5.6 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority, the Director treated the matter as a complaint.

The detailed response from Napp is given below.

The Panel noted that according to Napp the consultant and representative each gave differing accounts of the basis upon which the representative had gained the interview. The consultant understood that the meeting was arranged to discuss a new product and had felt tricked into the appointment when the representative had explained that he could not discuss it. The consultant subsequently stated that he could not recall how the meeting had been arranged and acknowledged that his secretary might have misunderstood about the new product. The representative, however, consistently denied gaining an appointment under false pretence and maintained that he/she had always intended to, and had discussed, Targinact during the appointment. No new products were referred to. The representative's position in this regard was supported by an email from the representative apparently to the consultant's secretary and from the logging and record of the appointment in the company's internal systems. The Panel noted that the health professional had been sufficiently concerned to complain about the matter to his local health management which had subsequently contacted Napp. Nonetheless, in the Panel's view and on the available evidence, it was impossible to determine whether the interview with the consultant was gained under the false pretence of wanting to discuss a new medicine and the Panel therefore ruled no breach of the Code. Neither was there any evidence to suggest that the word 'new' had been used to describe a product. No breach of the Code was ruled. Consequently, the Panel did not consider that Napp had failed to maintain high standards and ruled no breach of the Code including Clause 2.

The Panel noted that the second admission concerned an apparent link between the consultant's and local health professionals' opinions of Napp's medicines and the company's sponsorship of a conference. The first aspect of this admission concerned what was said during

the meeting between the representative and the consultant and the second aspect concerned what was stated in emails to the conference organiser. In relation to the meeting, again the consultant and the representative gave differing accounts although both agreed that the conference had been discussed - the representative denied discussing cancellation or levels of sponsorship whilst the consultant stated that they had discussed the event in great detail. The consultant believed that the representative wished to cancel Napp's sponsorship because he did not have positive opinions about Targinact and because of what he had said about 'wider opinions' about the product; the consultant later recognised that he did not check his understanding with the representative at the time.

The Panel noted that in an email to the conference organiser, the representative stated that he/she had initially looked at becoming a gold sponsor and continued 'However, after a discussion with a senior palliative care clinician he informs me that our product does not have much relevance within palliative care in [named region]'. The representative indicated that he/she would still sponsor the meeting but at a lower level. This position was reiterated in a further email which concluded 'The meeting will be useful in getting the views of other clinicians around ... and hopefully if positive we can step up to gold sponsor next year'. The representative had subsequently advised Napp that he/she had reduced the level of sponsorship on receipt of an internal business email detailing new business needs and budgetary requirements. The Panel noted that there was no evidence that the consultant was copied in on the email to the conference organiser or otherwise provided with a copy of it. Nor was there any evidence to indicate that the complainant was the senior palliative care clinician referred to in the email. Nonetheless, the Panel noted that the email to the conference organiser was consistent with that consultant's view that conference sponsorship was linked to positive views on Targinact and its use. Similarly, the Panel noted that the email was consistent with the representative's position that the level of sponsorship was to be reduced rather than cancelled.

The Panel considered there was insufficient evidence to determine precisely what was said about sponsorship at the meeting between the consultant and the representative. Nor was there any evidence before the Panel that any personal benefit would accrue to the consultant as a result of such sponsorship. The Panel thus ruled no breaches of the Code including Clause 2.

In relation to the emails to the conference organiser, in the Panel's view these clearly implied that the

**company's provision of gold level sponsorship was dependent upon Napp's product (not named) being seen by a senior palliative care clinician to be relevant within the region. This was contrary to the Code and a breach was ruled. The representative had not maintained a high standard of ethical conduct in this regard and a breach of the Code was ruled. The Panel was very concerned about the unacceptable impression created by the emails; high standards had not been maintained and a breach of the Code was ruled. Nonetheless, it did not consider that the circumstances warranted a ruling of a breach of Clause 2 and no breach of that clause was ruled.**

Napp Pharmaceuticals Limited voluntarily admitted that one of its representatives had potentially gained an interview with a health professional under the false pretence of wanting to discuss a new medicine when he/she only wanted to discuss an existing medicine. Further, the representative had also appeared to link the health professional's opinion of Napp's medicines to the company's sponsorship of a meeting.

In accordance with Paragraph 5.5 of the Constitution and Procedure the admission was treated as a complaint and the matter was taken up with Napp.

## COMPLAINT

Napp explained that the representative in question had many years' experience and had latterly joined the company as an account manager for the specialist pain team which promoted Targinact (oxycodone/naloxone combination) tablets which received a marketing authorization in December 2008. The representative had passed the ABPI examination before joining Napp and as part of his/her induction to the company, received mandatory internal training on Targinact, Code of Business Ethics, systems training, and compliance in the field. In March 2014 someone telephoned on behalf of a hospital pharmacist and asked to speak to the representative's manager but gave no detail as to why. Upon notification of this request, the representative's manager returned the call but was informed that the person no longer wanted to discuss the matter on the telephone but instead would write an official letter directly to Napp. However, no letter was received and since the circumstances of the matter were not disclosed to Napp, following discussion between the representative's manager and personnel, no further action was taken at that time.

In April 2014, a clinical effectiveness pharmacist (from the same locality as the pharmacist referred to above) telephoned the representative's manager to discuss a complaint he had received from a palliative care consultant about the behaviour of the representative during a medical sales appointment between the consultant and the representative in March. During this telephone conversation the nature of the complaint, which was subsequently confirmed in an email, could be divided into two distinct elements.

Firstly, gaining an appointment with a health professional under false pretence. The allegation was that the appointment with the consultant was believed to have been made to discuss a 'new drug', but instead Targinact was discussed, viz. 'The consultant felt "tricked" into an appointment'. The second allegation concerned the withdrawal and possible cancellation of monetary sponsorship of a regional palliative care conference because of the consultant's negative view of Targinact – interpreted by the consultant and the local health managers to be the basis of an inducement to prescribe.

Given the serious nature of these allegations and potential breaches of the Code, as a result of this telephone conversation, the representative's manager immediately arranged an investigatory meeting with the representative.

The representative denied the first allegation and showed an email trail which detailed how the initial appointment with the consultant was arranged and booked and in which the representative verified and made it clear that there was no mention of 'discussion of a new product' or any similar words in arranging for and booking the meeting. The representative also made it clear that in the logging and record of the completed appointment on internal company systems there was no mention of 'new product' or the word 'new' and also that this was the case in the telephone call to the consultant's secretary.

The representative confirmed that he/she discussed the palliative care conference with the consultant but denied discussing the cancellation or reduction in monetary sponsorship for the conference. This was contrary to the consultant's and the health manager's view. The representative also understood that both the consultant and the health manager were of the view that sponsorship of the conference had been completely withdrawn. The representative noted that monetary sponsorship had only been reduced, not cancelled. The representative explained that he/she had decided to reduce the level of sponsorship in response to recent information sent to him/her about business needs and budgetary requirements.

Napp telephoned the consultant, who stated that he could not remember how the meeting had been arranged and his secretary could have possibly misunderstood about the new product. The consultant noted that the representative stated that he/she could not talk about the new product even though the consultant had asked about it and he/she wanted to speak about Targinact.

However, the consultant was clear that, viz. '... [we] spoke about the sponsored event. [The representative] stated that he/she had intended to sponsor the event but given what [the consultant] had said about 'wider opinion' [the representative] now probably wouldn't'. The consultant stated that he believed the representative wanted to cancel sponsorship for the conference because the consultant did not have positive opinions about Targinact, although the consultant also

recognised and stated that ‘... [I] did not check [my] understanding with [the representative] at the time.’ Napp informed the consultant that the representative had acknowledged discussing the conference with him, but he/she denied discussing sponsorship or levels of sponsorship. The consultant refuted this position and replied that ‘[the representative] brought [the discussion of the event] up and they had discussed the event in great detail’.

Following this telephone call with the consultant, Napp considered that it needed to speak to the representative again and at a second meeting the representative verified and confirmed the statements he/she had made in the first meeting. The representative also confirmed that during the appointment he/she only talked about Targinact and nothing ‘new’.

The representative again confirmed that he/she discussed the palliative care conference with the consultant but did not discuss cancelling or reducing, sponsorship; he/she had reduced the level of sponsorship for the conference based on the new information provided to him/her about business needs and budgetary requirements, not on the opinions of the consultant. The representative stated in an email to a conference organiser, ‘However, after a discussion with a senior palliative care clinician he informs me our product does not have much relevance within palliative care in [named region]’; the representative acknowledged that this might be interpreted incorrectly as an inducement to prescribe, but the representative detailed that no specific health professional (ie the consultant), nor any specific product (ie Targinact), was mentioned. The email trail also later contained the sentence ‘This meeting will be useful in getting the views of other clinicians ... and hopefully if positive we can step up to gold sponsor next year’.

As detailed in the email conversation between the clinical effectiveness pharmacist and the representative’s manager, a medicines management group (MMG) meeting was convened in May 2014. In consideration of this case with the available evidence to it, the MMG barred the representative with immediate effect, and also notified Napp that it would complain to the Authority with specific regard to the two allegations above. On notification of this decision, Napp subsequently informed the Authority accordingly.

Napp noted that the representative had recently left the company and so it had not been able to ask him/her further investigatory and confirmatory questions. Consequently, the true meaning and explanation of the ‘if positive’ wording in his/her email was unclear, and whether this was, or was not, intended as a true inducement to prescribe. Napp was unclear whether the ‘if positive’ statement referred specifically to the prescribing and use of Targinact, or whether it referred more broadly to the general view of clinicians on the palliative care conference itself.

As a consequence of this incomplete evidence, Napp reviewed and interpreted this case on the balance of probability and available evidence.

Napp provided a summary of the allegations as follows:

**Allegation 1:**

Gaining an appointment with a health professional under false pretence, *viz.* the meeting with the consultant alleged to have been gained and arranged to discuss a ‘new product’, but an old medicine (ie Targinact) was discussed instead.

**Clause 7.11**

Targinact is not a ‘new’ medicine. In the meeting between the consultant and the representative, Targinact was discussed. The representative’s account of the intention, arrangement and booking of the appointment with the consultant was not to discuss any ‘new’ medicine – it was always to discuss Targinact.

The evidence from email trails detailing the booking of the appointment and the representative’s and the consultant’s witness statements, did not indicate that it was ever the representative’s intention to discuss any ‘new product’ or anything ‘new’. Moreover, the consultant had stated and confirmed that the representative actually refused to talk about any new product or anything new at all, even despite direct questioning by the consultant. The consultant acknowledged that he could not fully remember how the meeting had been arranged and further affirmed that his secretary could have misunderstood that the meeting was arranged with the intention to talk about a ‘new product’. There was no record of any telephone calls which might have taken place between the secretary and the representative.

On the balance of the available evidence, Napp concluded that the representative did not use the word ‘new’ in arranging the appointment and thus Napp denied a breach of Clause 7.11.

**Clause 15.3**

Although the consultant had stated and believed that the appointment was gained under false pretence or subterfuge, as detailed above concerning Clause 7.11, there was no strong or confirmatory evidence to demonstrate that the appointment was gained with an intention to discuss a ‘new product’ or anything ‘new’. The consultant had stated that he could not himself be sure of the arrangements on how the appointment was made.

Napp thus denied a breach of Clause 15.3.

**Allegation 2:**

The monetary sponsorship of a conference made on the basis, and due to a health professional’s view, on a medicine interpreted as an inducement to prescribe, *viz.* the level of monetary sponsorship for the palliative care conference was reduced based on the consultant’s negative view on Targinact.

**Clause 15.2**

The representative’s emails were ambiguous and did not appear to uphold the high standards required by the Code.

Napp thus considered that there might have been a breach of Clause 15.2.

### **Clause 18.6**

There were conflicting views in the statements made by the representative, the consultant and the local health managers about the reasons for reducing monetary sponsorship of the conference or whether this was even discussed during the meeting, although it was certainly discussed by email, albeit with a conference organiser.

It was also clear that there were different possible interpretations relating to the temporality of the representative's decision to reduce sponsorship as detailed in his/her email to the conference organiser. The representative requested to reduce sponsorship after his/her appointment with the consultant, but did so also after an internal business email detailing the new business needs and budgetary requirements.

Finally, it was also clear that the precision and meaning of the representative's email sentences were unknown,

'... However, after a discussion with a senior palliative care clinician he informs me our product does not have much relevance within palliative care in [named region] ...' and,

'... This meeting will be useful in getting the views of other clinicians ... and hopefully if positive we can step up to gold sponsor next year ...'.

Napp stated that it was important to note that in these sentences, no health professional, ie the consultant, was specifically mentioned, that no product, ie Targinact, was specifically mentioned (indeed Napp marketed a wide range of varied products in different therapy areas that were used in palliative care), and to carefully consider whether the 'if positive' wording related specifically to a medicine (medicines), or more broadly on the health professional's views in general on the meeting itself.

Napp was thus unsure whether Clause 18.6 had been breached.

The Authority asked Napp to consider this matter in relation to Clauses 2, 7.11, 9.1, 15.2, 15.3, 18.1 and 18.6 of the Code.

### **RESPONSE**

In relation to Clause 9.1, Napp submitted, on the balance of its internal investigation, that the appointment with the consultant was not gained under a false pretence as alleged. The representative confirmed that he/she had reduced his/her contribution due to budgetary changes and a need to prioritise his/her spend. However, in relation to the second allegation, the wording in the emails might be considered ambiguous. Therefore, the Authority's opinion was sought on whether the representative had failed to uphold high standards.

In relation to Clause 18.1, Napp noted that the second allegation related to the provision of

sponsorship for the organisation of a health professional educational conference and not to a specific member (or members) of the health profession(s) including administrative staff. Napp submitted that this monetary sponsorship constituted a provision of medical educational goods and services to an institution and should therefore be considered under Clause 18.6 alone. Allegation 2 did not involve any specific gift, pecuniary advantage or benefit directly to the health professional(s) (ie the consultant or the local health managers) or to the organiser of the palliative care conference and therefore Napp did not believe that Clause 18.1 was applicable. However, if the Panel considered that Clause 18.1 was relevant, then Napp referred to its comments above regarding Clause 18.6 as the same rationale would apply to Clause 18.1. Napp denied a breach of Clause 18.1.

In relation to Clause 2, Napp did not believe from the evidence presented that the representative's conduct had brought discredit upon, or reduced confidence in, the pharmaceutical industry. Napp considered that there was sufficient uncertainty from the available hard evidence and investigation as to whether there had been clear breaches of Clauses 7.11, 9.1, 15.2, 15.3, 18.1 and 18.6 of the Code. Napp also considered it improbable that an ABPI qualified representative with many years' experience, who had been specifically trained on the Code and compliance when he/she joined Napp, would intentionally offer an inducement to prescribe. Napp believed it more likely that the unfortunate wording and turn of phrase in his/her emails was unintentional.

### **PANEL RULING**

The Panel noted that Napp's admission concerned the basis upon which one of its representatives had gained an interview with a consultant and an apparent link made by the representative at the interview and subsequently in an email to a meeting organiser, between Napp's sponsorship of a meeting and the consultant's opinion of its medicines. Neither the consultant nor the meeting organiser were party to the complaint.

According to Napp the consultant and representative each gave differing accounts of the basis upon which the representative had gained the interview. It was difficult in such circumstances to determine where the truth lay. A judgement had to be made on the available evidence. The consultant understood that the meeting was arranged to discuss a new product and advised Napp that he had felt tricked into the appointment when the representative had explained that he could not discuss it. According to Napp, the consultant had subsequently stated that he could not recall how the meeting had been arranged and acknowledged that his secretary could have possibly misunderstood about the new product. The representative, however, had consistently denied gaining an appointment under false pretence and maintained that he/she had always intended to, and had discussed, Targinact during the appointment. No new products were referred to. The Panel noted that a redacted email from the representative



apparently to the consultant's secretary referred to 'a pain product that I would like to discuss with you'. The product was not identified nor was it described as new. According to Napp, the representative's account was supported by the logging and record of the appointment in the company's internal systems. The Panel noted that the health professional had been sufficiently concerned to complain about the matter to his local health management which had subsequently contacted Napp. Nonetheless, in the Panel's view and on the available evidence, it was impossible to determine where the truth lay. There was insufficient evidence to establish whether the interview with the consultant was gained under the false pretence of wanting to discuss a new medicine and the Panel therefore ruled no breach of Clause 15.3. Neither was there any evidence to suggest that the word 'new' had been used to describe a product. No breach of Clause 7.11 was ruled. Consequently, the Panel ruled no breach of Clauses 9.1 and 2.

The Panel noted that the second admission concerned an apparent link between the consultant's and local health professionals' opinions of Napp's medicines and the company's sponsorship of a conference. The first aspect of this admission concerned what was said during the meeting between the representative and the consultant and the second aspect concerned what was stated in emails to the conference organiser. In relation to the meeting, again the consultant and the representative gave differing accounts although both agreed that the conference had been discussed. According to Napp, although the representative denied discussing cancellation or levels of sponsorship, the consultant refuted this and stated that they had discussed the event in great detail. The consultant believed that the representative wished to cancel Napp's sponsorship because he did not have positive opinions about Targinact and because of what he had said about 'wider opinions' about the product. According to Napp the consultant recognised that he did not check his understanding with the representative at the time. The Panel noted that the account of the consultant and the representative differed and noted its comments above about the difficulty of determining where the truth lay in such circumstances.

The Panel noted that in an email to the conference organiser, the representative stated that he/she had initially looked at becoming a gold sponsor and continued 'However, after a discussion with a senior palliative care clinician he informs me that our product does not have much relevance within palliative care in [named region]'. The representative explained that he/she was still willing to sponsor

the meeting and enquired about lower levels of sponsorship. This position was reiterated in another email which concluded 'The meeting will be useful in getting the views of other clinicians ... and hopefully if positive we can step up to gold sponsor next year'. The representative had subsequently advised Napp that he/she had reduced the level of sponsorship on receipt of an internal business email detailing new business needs and budgetary requirements. The Panel noted that there was no evidence that the consultant with whom the representative had held the initial meeting described above was copied in on the email to the conference organiser or otherwise provided with a copy of it. Nor was there any evidence to indicate that he was the senior palliative care clinician referred to in the email. Nonetheless, the Panel noted that the email to the conference organiser was consistent with that consultant's view that during the aforementioned meeting, sponsorship was linked to positive views on Targinact and its use. Similarly, the Panel noted that the email was consistent with the representative's position that the level of sponsorship was to be reduced rather than cancelled.

The Panel considered there was insufficient evidence to determine precisely what was said about sponsorship at the meeting between the consultant and the representative. Nor was there any evidence before the Panel that any personal benefit would accrue to the consultant as a result of such sponsorship. The Panel thus ruled no breach of Clause 18.1 and consequently Clauses 9.1 and 2.

In relation to the emails to the conference organiser, in the Panel's view these clearly implied that the company's provision of gold level sponsorship was dependent upon Napp's product (not named) being seen by a senior palliative care clinician to have relevance within the region. This was contrary to Clause 18.6 and a breach of that clause was ruled. The representative had not maintained a high standard of ethical conduct in this regard and a breach of Clause 15.2 was ruled. The Panel was very concerned about the unacceptable impression created by the emails; a breach of Clause 9.1 was ruled. Nonetheless, it did not consider that the circumstances warranted a ruling of a breach of Clause 2 which indicated particular censure and was reserved for such use. No breach of Clause 2 was ruled.

**Complaint received**                      **2 May 2014**

**Case completed**                            **8 July 2014**

# VOLUNTARY ADMISSION BY ROCHE

## Number of pages of advertising

Roche voluntarily admitted that that an edition of the British Journal of Haematology (BJH) bore advertising for MabThera (rituximab) on four pages. As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Roche.

Roche explained that it was informed by its media buying agency that due to the inadvertent inclusion of a two page MabThera bound-in card by the printing house, two separate double page advertisements for MabThera appeared in the May-II edition of BJH.

The detailed response from Roche is given below.

The Panel noted that Roche's printing agency had in error included two double page advertisements for MabThera in the May-II edition of the BJH; one appeared on the inside and outside back cover and the other appeared in the form of a double sided bound-in card. The Panel noted that the double sided bound-in card was originally supplied for publication in the June-I edition of BJH. Correct details about the publication dates had been provided to both the media buying agency and the printers. The Panel noted that the printers had accepted responsibility for the error. Nonetheless, it was an accepted principle under the Code that pharmaceutical companies were responsible for the acts or omissions of those who worked on their behalf. In the Panel's view, Roche had been let down by the printers. That four pages of the journal bore advertising for MabThera was a clear breach of the Code as acknowledged by Roche; the Panel ruled accordingly.

Roche Products Ltd voluntarily admitted that an edition of the British Journal of Haematology (BJH) bore advertising for MabThera (rituximab) on four pages.

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Roche.

## VOLUNTARY ADMISSION

Roche explained that it was informed by its media buying agency that due to the inadvertent inclusion of a two page MabThera bound-in card by the printing house, two separate double page advertisements for MabThera appeared in the 19 May edition of BJH.

Roche noted that inclusion of four pages of advertising for a product in a journal was in breach of the requirement that no issue of a journal may bear advertising for a particular product on more than two pages. Roche stated that the advertisements were certified separately as required

by Clause 14.1 and were never intended to appear together in the same publication.

A letter from the printing house explained that it was the result of human error by one of its client service representatives. The representative in question had been counselled and understood the severity of the issue and a secondary detailed checklist had since been implemented to make certain that no errors of that description would occur again. All information would be double checked against the checklist going forward and all client representatives had been coached on the extra procedure.

Roche accepted overall responsibility for the actions of any third party acting on its behalf and therefore acknowledged a breach of Clause 6.3. Roche noted that it was committed to the appropriate use of medicines, protecting the safety of patients and strove to maintain high standards in the ethical promotion of its medicines. As such the company and its employees understood the strict requirements of UK medicines regulations and the Code.

On discovering the issue, the matter was appropriately escalated to senior management and a thorough investigation carried out to understand the root cause of the issue. Roche worked with the agency and publisher to understand the full facts so that it could identify any necessary preventative actions to prevent future reoccurrence.

When writing to confirm that the matter would be taken up under the Code, the Authority asked Roche to provide any further comments it might have in relation to Clause 6.3.

## RESPONSE

Roche submitted that an advertisement for MabThera subcutaneous (sc) was planned to be included in the May-II edition of the BJH. The advertisement position was the outside back cover with the prescribing information on the inside back cover. A separate two page advertisement, taking the form of a bound card, was planned to be included in the next edition, June-I. Due to human error, the bound card was included in the May-II edition meaning that there were four pages of MabThera sc advertising in one edition. Both advertisements (ref RXUKMABO00662e and RXUKMABO00662f) had been separately certified and were never intended to appear in the same edition.

Roche submitted that the parties involved were the media buying agency, the publishing company for BJH, printers of the bound card and the printing agency.

Roche submitted that its standard operating procedure (SOP) on approval and certification stated 'A contract and a project confirmation form (where applicable) must be in place with any third party used in the production of materials or involved in activities that come within the scope of the ABPI Code of Practice. All parties involved in the production of such materials/activities, working on Roche's behalf or under Roche's instruction, must be fully aware of any procedural requirements in those contracts/project confirmation forms (PCF) as well as the requirements of this SOP'. As stated within the SOP, it was standard practice within Roche to have both a contract and project confirmation form in place with each third party supplier. All contracts included provisions for both the third party supplier with whom Roche was directly contracting and any subcontractors with whom the third party supplier engaged to carry out activities on its behalf. A copy of the master service agreement (msa) with the media buying agency provided by Roche stated that the agency would perform the services under the agreement and under any project confirmation, in compliance with all applicable national and international laws, rules, regulations, the Code and industry guidelines as amended from time to time. Roche provided a detailed chronology of events. As a result of its investigation, Roche noted that the inclusion of the MabThera bound-in card intended for the June-I issue in the May-II issue was due to human error at the printers.

Roche submitted that the root causes of the breach were as follows:

- 1 The bound-in card intended to be included in the May-II edition was late arriving at the printers. The Roche bound-in card had already arrived at the printers ready for use in the June-I issue. The client services representative at the printer wrongly assumed that the Roche bound-in cards were to be included in the May-II edition. The 'make up' was not checked by the client services representatives in order to confirm which bound-in card should be included.
- 2 There was no second check performed by the printers prior to mass-printing and collation of the journal, nor prior to journal distribution.
- 3 There was a second check performed by the publishers but this was an online check only of the regular journal pages and hence only included review of non-bound-in pages. Therefore the publishers would not identify the presence of an incorrect bound card.

Roche explained that preventative actions included the following:

- 1 The printers had implemented a revised workflow and secondary detailed checklist, a copy of which was provided, in an attempt to ensure no similar errors would occur again. Roche provided copies of the previous process and highlighted the points at which extra line management checks would be

implemented to avoid any future issues. Further information provided by Roche showed the previous paperwork and the two extra pieces of paperwork which were now required as a final safeguard. All information would be double checked against the aforementioned paperwork going forward. Additionally, all client services representatives had been trained on the new procedure.

- 2 Roche would communicate the breach internally to all relevant employees and request that all franchise teams informed all agencies involved with journal advertisements of the breach and ask them to review their own processes to ensure that a similar breach could not occur.

In response to a query from the case preparation manager, Roche explained that its standard agency contract contained provisions requiring the agency to comply with the Code and required each agency to be trained in Code aspects relevant to their work. All contracts contained provisions regarding subcontractors in that they must also conform to the same requirements. The media buying agency's contract contained all those provisions.

Roche submitted that as stated in its previous correspondence, it was committed to the appropriate use of medicines and protecting the safety of patients and strove to maintain high standards in the ethical promotion of its medicines and as such the company and its employees understood the strict requirements of UK medicines regulations and the Code.

#### PANEL RULING

The Panel noted that Roche's printing agency had in error included two double page advertisements for MabThera in the May-II edition of the BJH; one appeared on the inside and outside back cover and the other appeared in the form of a double sided bound-in card. The Panel noted that the double sided bound-in card was originally supplied for publication in the June-I edition of BJH. Correct details about the publication dates had been provided to both the media buying agency and the printers. The Panel noted from an email provided by Roche, that the printers had accepted responsibility for the error. Nonetheless, it was an accepted principle under the Code that pharmaceutical companies were responsible for the acts or omissions of those who worked on their behalf. In the Panel's view, Roche had been let down by the printers. That four pages of the journal bore advertising for MabThera was a clear breach of Clause 6.3 as acknowledged by Roche; the Panel ruled accordingly.

<b>Complaint received</b>	<b>23 May 2014</b>
<b>Case completed</b>	<b>1 July 2014</b>

# ANONYMOUS v ALLERGAN

## Meeting arrangements

An anonymous, non-contactable complainant alleged that Allergan had inappropriately approved materials for, and selected delegates to attend, a neuroscience meeting.

The complainant explained that the meeting was put through as a stand meeting at which other companies would be present in order to circumvent the approval requirements. The complainant alleged that the meeting was advertised as a funded training course rather than a meeting solely sponsored by Allergan which had selected the attendees and had possibly paid their travel costs. The complainant named three senior employees who he/she alleged were all complicit in the wrong doing.

The complainant further explained that the slides used were approved by the medical department on the basis that exhibiting costs were shared with other companies, however no other companies were present and slides, which did not go through Allergan's Zinc approval system, were used for an Allergan engineered meeting.

The detailed response from Allergan is given below.

The Panel noted that the complainant was anonymous and non-contactable. A complainant had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and like all complaints were judged on the evidence provided by the parties. The weight to be attached to any evidence might be adversely affected if the source was anonymous.

The Panel noted that the parties' accounts of the meeting differed. The complainant had referred to a meeting held at a named hospital with a named consultant in October 2013. The only meeting which Allergan could identify which involved the same hospital and consultant, was held in May 2013. The complainant had alleged that the meeting was solely sponsored by Allergan whereas Allergan submitted that this was not so, there were two other sponsors. The complainant had referred to an Allergan engineered meeting and alleged that the company had selected the attendees. Allergan submitted that the meeting was organised by a third party; its only involvement was to provide part sponsorship, it did not select attendees or pay their travel costs as surmised by the complainant. The complainant had referred to training slides being submitted to Allergan for approval. Allergan submitted that it did not receive any slides or materials associated with the meeting as it was an independent, third party course. The company stated that as it had had no involvement or influence on the content of the meeting and it had not

provided any speakers, there was no requirement to review slides and materials used at the meeting.

The Panel noted that the complainant had named three senior employees who he/she alleged were complicit in the alleged wrong doing. However, according to Allergan only one of those named had been involved with the meeting and the role of one of the employees within the company had been incorrectly cited by the complainant.

The Panel noted the substantial differences in the parties' accounts and that no evidence had been provided by the complainant to support his/her allegations. The Panel considered that the nature of these differences and the evidence provided by Allergan was such that there were grounds to doubt the veracity of the complaint. The Panel noted its statement above about the burden of proof.

The Panel considered that there was no evidence before it to indicate that the slides required certification as alleged. Allergan's sponsorship of the meeting was approved in Zinc using the company's meeting approval process. No breach of the Code was ruled.

The Panel noted that the meeting was a one day training course on the pharmacology of botulinum toxins and their use around the eye. In that regard the Panel considered that it was not an unreasonable educational meeting for Allergan to sponsor. The Panel noted Allergan's submission that it had not provided any support to any delegates attending the meeting with regard to registration or travel as alleged and had not provided any subsistence. It paid for the exhibition stand fee alone. In the Panel's view Allergan's involvement with the meeting was not unacceptable. No breach of the Code was ruled.

The Panel did not know what the complainant meant when he/she alleged that the meeting was advertised as a funded training course rather than a meeting sponsored by Allergan. The complainant had not provided a copy of the advertisement to support his/her allegation. The Panel thus ruled no breach of the Code.

The Panel noted its rulings above and considered that there was no evidence to show that either the company or its representatives had failed to maintain high standards. No breach of the Code were ruled. The Panel consequently ruled no breach of Clause 2.

An anonymous, non-contactable complainant alleged that Allergan Ltd had inappropriately approved materials for, and selected delegates to attend, a neuroscience meeting.

## COMPLAINT

The complainant explained that the meeting was initially entered as a training meeting, however due to poor planning and a delay in getting speaker/trainer slides approved the meeting was put through as a stand meeting at which other companies would be present in order to circumvent the approval requirements. The meeting was advertised as a funded training course rather than a meeting solely sponsored by Allergan. The complainant alleged that no other companies were present or ever invited and attendees were selected by Allergan. This information was only shared by management; those involved were three named senior employees; the complainant provided details of each employee's role within the company.

The complainant stated that the meeting was held in October 2013 at a named hospital and the trainer, a consultant ophthalmologist, was unaware of the inappropriate approval. The complainant alleged that details of the course, agenda items, venue and content were emailed to the sales team who forwarded the details to prospective delegates. The course had around ten UK attendees and although unsure, the complainant alleged that it was more than conceivable that Allergan had covered their travel costs. The complainant was unsure of how the sales team was told to record the meeting but it would be in the call report history.

The complainant further explained that there had been issues with the course as the slides used were not deemed suitable for medical approval. The trainer was asked to resubmit his slides but he declined and in the end the course was approved on the basis that exhibiting costs were shared with other companies and slides, which did not go through Allergan's Zinc approval system, were used for an Allergan engineered meeting.

The complainant alleged that the three named senior employees were all complicit in the wrong doing and the meeting was held with the particular support of one of those named. The complainant stated that this was perhaps one example of other similar activities and needed highlighting as it was a clear breach. Given it occurred during Allergan's audit phase, the complainant questioned how seriously some took the audit and adherence to the Code.

The complainant stated that he/she did not write in malice but in exasperation that some flexed the rules to suit themselves; their false claims of being compliant made it unacceptable. The complainant was concerned that if this matter was reported directly, the individuals involved would brush it under the carpet, place blame elsewhere and claim no knowledge. The complainant alleged that for the meeting to be signed off and go ahead, all of the named senior employees were fully involved and aware.

When writing to Allergan, the Authority asked it to respond in relation to Clauses 2, 9.1, 14.1, 15.2 and 19 of the Code.

## RESPONSE

Allergan submitted that although the complaint referred to a meeting held in October 2013, it could not identify any meeting that corresponded to that date; it had, however, found an event sponsored in May 2013 which formed the basis of the response below.

Allergan explained that the trainer named by the complainant was a consultant ophthalmologist with a special interest in neuro ophthalmology; he/she was the clinical lead of the botulinum toxin service at the named NHS foundation trust. Along with another named consultant who was an oculoplastic surgeon, he/she ran a number of independent courses and training events.

In response to a request that Allergan sponsor one of his/her independent courses, the consultant ophthalmologist was asked to send a request in writing which was duly received. Allergan agreed to co-sponsor the event and to have a promotional stand at the meeting held in May 2013, paying a sponsorship fee of £1,200. As there was no local Allergan representative, no stand was placed at the meeting and no Allergan employees attended.

Allergan considered the following points which in its view confirmed the appropriateness of the meeting arrangements:

- The meeting, held in May 2013 and not October 2013 as alleged, took place in appropriate healthcare premises, the postgraduate education centre of the named hospital, and ran from 10am to 4pm with registration at 9:30am. The postgraduate centre catering service provided a sandwich lunch and there were morning and afternoon coffee breaks. Allergan did not provide any subsistence beyond the agreed sponsorship fee and did not cover any travel costs for the delegates.
- It was a third party meeting, a verbal request for stand sponsorship was made to the representative followed by an email from the course organizers. Allergan was also informed that the course had received CPD accreditation. The course organizers engaged two other sponsors for the meeting one of which was a competitor to Allergan in ophthalmology. According to the information provided to Allergan by course organizers, all companies sponsored the event for the same amount. In preparing this response Allergan contacted both of these companies directly to confirm that they had indeed sponsored the event. One confirmed that it had sponsored the meeting with £300 and a representative attended with a small table stand.
- There was a clear educational objective to the meeting as evidenced by the agenda (copy provided) and provided by the course organizers.
- The meeting participants were neither selected nor invited by Allergan, this was the responsibility of the course organizers. The number of attendees was restricted to ten health professionals and there was no registration cost to the delegates according to the information provided to Allergan by course organizers at the time of the

sponsorship request. Physicians working in ophthalmology and managing blepharospasm were expected to attend.

- Allergan had no involvement or influence on the content of the meeting other than to review the agenda provided by the organizers as part of the stand meeting approval process and noted that it had sufficient educational content to justify a full day meeting. The agenda was titled 'Management of Blepharospasm Training Meeting'. It included sessions on 'Pharmacology of Botulinum Toxin, Anatomy around the Eyes, Common conditions of the eyelids and orbits, Practical aspects of Botulinum toxin use, Common Injection techniques and How to set up an audit of toxin service'. It was not specific to a brand or product.
- The meeting went through the Allergan approval process, a meeting request form was raised, reviewed in Zinc and signed off. The copy approval certificate was provided. The payment was made following the receipt of appropriate documentation from the course organizers.

Allergan submitted that according to the supplementary information to Clause 19.1, 'Pharmaceutical companies may appropriately hold or sponsor a wide range of meetings'. The Code described a range of meetings and principles which applied to sponsorship or holding those meetings.

Allergan noted that the complainant named three of its employees who were alleged to have been involved in the activity. Allergan submitted that one employee (and the only one available for interview as the other two had since left the company) was neither involved in the setting up nor review/approval of the meeting. Allergan was satisfied that he/she had no knowledge of the meeting in question. The second employee received the request from the organizers and initiated the job bag and provided the information to reviewers. The third employee was neither involved in the review nor the sign off of the meeting. He/she never worked in medical as cited in the complaint.

According to Allergan's customer relations management (CRM) system, the Allergan representative covering the territory met the consultant ophthalmologist who organized the meeting in mid January 2013 along with one of the named senior employees to introduce the representative who had returned from extended leave. The representative saw the consultant again in February and March 2013 to discuss the training course and finalize the details of Allergan's support. There were no further notes in the call system. No exhibition stand was set up at the meeting and no Allergan employee attended the meeting due to absence of a territory sales representative. The representative had left the company, therefore it had not been possible to interview him/her with regard to this complaint.

Allergan submitted that it did not receive any slides or materials associated with the meeting as it was an independent course and Allergan's involvement was limited solely to sponsorship. There was no requirement to review any materials that were to be presented at the meeting. As part of Allergan's

investigation, it noted that the meeting as advertised on the Royal College of Ophthalmologists' website confirmed the CPD accreditation and third party nature of the meeting. Allergan submitted that the meeting was neither engineered nor solely sponsored by Allergan as alleged by the complainant.

Allergan was not involved in the planning, organization and conduct of the meeting, therefore it did not produce any invitations. The agenda provided by the organizers, along with their request for sponsorship, was used for the approval of the stand meeting via Allergan's meeting approval process in Zinc. As sponsorship of a local stand meeting, it required examination under Allergan's meeting approval process. The job bag in Zinc was created nine days before the meeting was scheduled to take place and was reviewed two to three days later by two different reviewers who requested further information before receiving final approval in Zinc the day before the meeting. This would not be an unusual situation as for third party organized meetings, company representatives would pursue provision of information and details from organizers before creating a job bag. The certificate was signed by two named Allergan employees on the day the meeting was scheduled to take place.

Allergan submitted that it did not promote the meeting. Allergan did not have information on who attended the meeting. As there was no sales representative on the territory at the time, Allergan did not attend the meeting or put up a stand. Therefore no records existed of the meeting attendees in the CRM system.

Allergan submitted that its payment for sponsorship was made to a company of which the consultant ophthalmologist was an executive, on receipt of appropriate documentation.

Allergan submitted that it maintained high standards while sponsoring this meeting and acted appropriately in the review, approval and overall support of this meeting. Allergan submitted that there was no deviation from company procedures or any breach of Clause 9.1.

The meeting was appropriately reviewed and approved according to company procedures. On receipt of a written request, a meeting request form was created and the review of the job bag occurred within the Zinc system. The approval was granted considering the different requirements of the Code as noted above. Allergan co-sponsored a third party organized meeting and was not involved in organizing or promoting the meeting, selecting or inviting the attendees, or determining the agenda or content. There were no promotional materials linked to the meeting and as a third party organized stand meeting Allergan was not required to review and approve slide decks. Therefore no requirement for certification of any materials and thus no breach of Clause 14.1.

Allergan submitted that it had already clarified the role and involvement of the three senior employees named in the complaint. In addition,

the involvement of two representatives, the Zinc reviewers and two signatories in the meeting had also been addressed. Allergan submitted that there were no concerns with regard to the behaviour of the named employees or any indication that they failed to maintain a high standard of ethical conduct with regards to the sponsorship of the meeting at issue. Allergan further submitted that all of the employees complied fully with the company's procedures and relevant Code requirements in this instance. Therefore Allergan denied a breach of Clause 15.2.

With regard to the requirements of Clause 19, several points had been addressed above under overall conduct of the meeting. The third party organized meeting was held in May 2013 and not in October 2013 as alleged. Allergan co-sponsored the meeting to the value of £1,200 and it planned to have a promotional stand. No hospitality was provided by Allergan. There was a clear educational objective as evidenced by the agenda. The venue, the postgraduate education centre, was an entirely appropriate healthcare premises for this type of meeting. Participants were neither selected nor invited by Allergan, this was the responsibility of the course organizers. Allergan understood that the number of attendees was restricted to ten health professionals and there was no registration cost to the delegates according to the information provided by the organizers at the time of the sponsorship request. The meeting was for physicians who worked in ophthalmology and managed blepharospasm. It was a full day meeting from 10am to 4pm with registration at 9:30am. Allergan denied a breach of Clause 19.1.

Allergan submitted that the subsistence as detailed above was linked to an educational meeting in an appropriate venue with appropriate duration to justify the arrangements. Allergan did not provide any subsistence beyond the stand fee which was paid to the meeting organizers and it thus denied a breach of Clauses 19.2 or 19.3.

As this was a third party organized meeting, Allergan had no involvement or influence on the content of the meeting. As part of company policy, Allergan reiterated the need for organizers to declare sponsorship received from pharmaceutical companies. This was approved as a stand meeting therefore the presence of the stand would be obvious to the attendees with regard to the sponsors of the meeting. Allergan had tried to get a final agenda and materials from the course organizers which unfortunately they had not been able to provide to date. Allergan submitted that to the best of its knowledge, there were no papers or published proceedings from this meeting. Allergan stated that it did not invite or select prospective delegates and did not provide any support with regard to registration or travel. Allergan denied a breach of Clause 19.4.

Considering all of the above Allergan denied a breach of Clause 2.

In conclusion, Allergan was both surprised and concerned to receive this anonymous complaint which appeared to have manipulated some limited

facts and concocted others to malign the company and three named employees. Allergan noted that the complainant had not provided any clear evidence of the incidents that he/she alleged, and that fundamental details such as the date and nature of the meeting were incorrectly cited.

#### **PANEL RULING**

The Panel noted that the complainant was anonymous and non-contactable. A complainant had the burden of proving their complaint on the balance of probabilities. Anonymous complaints were accepted and like all complaints were judged on the evidence provided by the parties. The weight to be attached to any evidence might be adversely affected if the source was anonymous.

The Panel noted that the parties' accounts of the meeting differed. The complainant had referred to a meeting held at a named hospital with a named consultant in October 2013. The only meeting which Allergan could identify which involved the same hospital and consultant, was held in May 2013. The complainant had alleged that the meeting was solely sponsored by Allergan whereas Allergan submitted that this was not so, there were two other sponsors. The complainant had referred to an Allergan engineered meeting and alleged that the company had selected the attendees. Allergan submitted that the meeting was organised by a third party; its only involvement was to provide part sponsorship and it did not select attendees nor pay their travel costs as surmised by the complainant. The complainant had referred to training slides being submitted to Allergan for approval. Allergan submitted that it did not receive any slides or materials associated with the meeting as it was an independent, third party course. The company stated that as it had had no involvement or influence on the content of the meeting and it had not provided any speakers, there was no requirement to review slides and materials used at the meeting.

The Panel noted that the complainant had named three senior employees who he/she alleged were complicit in the alleged wrong doing. However, according to Allergan only one of those named had been involved with the meeting and the role of one of those employees within the company had been incorrectly cited by the complainant.

The Panel noted that there were substantial differences in the parties' accounts and no evidence had been provided by the complainant to support his/her allegations. The Panel considered that the nature of these differences and the evidence provided by Allergan was such that there were grounds to doubt the veracity of the complaint. The Panel noted its statement above about the burden of proof.

The Panel considered that there was no evidence before it to indicate that the slides required certification as alleged. Allergan's sponsorship of the meeting was approved using the company's meeting approval process in Zinc. No breach of Clause 14.1 was ruled.

The Panel noted that the meeting held in May 2013 was a one day training course on the pharmacology of botulinum toxins, anatomy around the eyes, common conditions of the eyelids and orbits and the use of botulinum toxin around the eyelids, eyebrows and orbit. In that regard the Panel considered that the educational content was appropriate and did not consider that it was an unreasonable meeting for Allergan to sponsor. The Panel noted Allergan's submission that it had not provided any support to any delegates attending the meeting with regard to registration or travel as alleged and had not provided any subsistence. It paid for the exhibition stand fee alone. In the Panel's view Allergan's involvement with the meeting was not unacceptable. No breach of Clause 19.1 was ruled.

The Panel did not know what the complainant meant when he/she alleged that the meeting was advertised

as a funded training course rather than a meeting sponsored by Allergan. The complainant had not provided a copy of the advertisement to support his/her allegation. The Panel thus ruled no breach of Clause 19.4.

The Panel noted its rulings above and considered that there was no evidence to show that either the company or its representatives had failed to maintain high standards. No breach of Clauses 15.2 and 9.1 were ruled. The Panel consequently ruled no breach of Clause 2.

**Complaint received**            **29 May 2014**

**Case completed**                **26 June 2014**





# CODE OF PRACTICE REVIEW – August 2014

Cases in which a breach of the Code was ruled are indexed in **bold type**.

<b>2654/11/13 and 2656/11/13</b>	<b>Anonymous contactable member of the public v Bristol-Myers Squibb</b>	<b>Clinical trial disclosure (Onglyza, Nulojix and Yervoy)</b>	<b>Breach Clauses 9.1 and 21.3</b>	<b>No appeal</b>	<b>Page 3</b>
2657/11/13	Anonymous contactable member of the public v AstraZeneca	Clinical trial disclosure (Iressa)	No breach	No appeal	Page 13
2659/11/13	Anonymous contactable member of the public v Pfizer	Clinical trial disclosure (Conbriza and Xiapex)	No breach	Appeal by respondent	Page 23
<b>2661/11/13</b>	<b>Anonymous contactable member of the public v Ferring</b>	<b>Clinical trial disclosure (Firmagon)</b>	<b>Breach Clauses 9.1 and 21.3</b>	<b>No appeal</b>	<b>Page 32</b>
<b>2662/11/13</b>	<b>Anonymous contactable member of the public v Novartis</b>	<b>Clinical trial disclosure (Ilaris and Gilenya)</b>	<b>Breach Clauses 9.1 and 21.3</b>	<b>No appeal</b>	<b>Page 40</b>
2663/11/13	Anonymous contactable member of the public v Pierre Fabre	Clinical trial disclosure (Javlor)	No breach	Appeal by respondent	Page 49
<b>2664/11/13</b>	<b>Anonymous contactable member of the public v Takeda</b>	<b>Clinical trial disclosure (Mepact, Edarbi and Daxas)</b>	<b>Breach Clauses 9.1 and 21.3</b>	<b>No appeal</b>	<b>Page 57</b>
<b>2665/11/13</b>	<b>Anonymous contactable member of the public v Genzyme (Sanofi)</b>	<b>Clinical trial disclosure (Mozobil and Renvela)</b>	<b>Breach Clauses 9.1 and 21.3</b>	<b>No appeal</b>	<b>Page 67</b>
2666/11/13	Anonymous contactable member of the public v Sanofi	Clinical trial disclosure (Multaq and Jevtana)	No breach	No appeal	Page 77
<b>2667/11/13</b>	<b>Anonymous contactable member of the public v Amgen</b>	<b>Clinical trial disclosure (Nplate and Prolia)</b>	<b>Breach Clauses 9.1 and 21.3</b>	<b>No appeal</b>	<b>Page 88</b>
2669/11/13	Anonymous contactable member of the public v Shire	Clinical trial disclosure (Resolor)	No breach	No appeal	Page 97
2670/11/13	Anonymous contactable member of the public v Otsuka	Clinical trial disclosure (Samsca)	No breach	No appeal	Page 105
<b>2671/11/13</b>	<b>Anonymous contactable member of the public v Servier</b>	<b>Clinical trial disclosure (Valdoxan)</b>	<b>Breach Clause 2 Two breaches Clause 9.1 Three breaches Clause 21.3</b>	<b>No appeal</b>	<b>Page 113</b>
2672/11/13	Anonymous contactable member of the public v Merck Sharp & Dohme	Clinical trial disclosure (Brinavess, Victrelis and Sycrest)	No breach	No appeal	Page 124
2673/11/13	Anonymous contactable member of the public v Recordati	Clinical trial disclosure (Silodyx)	No breach	No appeal	Page 136

2674/11/13	Anonymous contactable member of the public v GlaxoSmithKline	Clinical trial disclosure (Benlysta)	No breach	No appeal	Page 146
2676/11/13	Anonymous contactable member of the public v Janssen	Clinical trial disclosure (Incivo)	No breach	No appeal	Page 154
<b>2699/1/14</b>	<b>Anonymous non contactable health professional v Merck Sharp &amp; Dohme</b>	<b>Promotion of ezetimibe and sitagliptin</b>	<b>Breaches Clauses 9.1 and 15.9</b>	<b>Appeal by respondent</b>	<b>Page 162</b>
2702/3/14	General practitioner v Pfizer	Gaining access for remote detailing	No breach	No appeal	Page 176
<b>2706/3/14</b>	<b>Warner Chilcott/ Director v Tillotts</b>	<b>Alleged breach of undertaking</b>	<b>Breach Clause 7.2</b>	<b>No appeal</b>	<b>Page 180</b>
2708/4/14	NHS Employee v ProStrakan	Osteoporosis review	No breach	No appeal	Page 186
<b>2709/4/14</b>	<b>GlaxoSmithKline v Actelion</b>	<b>Presentation of composite endpoints</b>	<b>Three breaches Clause 7.2 Two breaches Clause 7.5 Breaches Clauses 7.8, 7.10 and 9.1</b>	<b>No appeal</b>	<b>Page 193</b>
<b>2710/5/14</b>	<b>General Practitioner v Meda</b>	<b>Promotion of Dymista</b>	<b>Breaches Clauses 7.2, 7.4, and 7.10</b>	<b>No appeal</b>	<b>Page 200</b>
2713/5/14	NHS Trust Chief Pharmacist v Lilly	Nurse consultancy agreement	No breach	No appeal	Page 202
<b>2716/5/14</b>	<b>Voluntary admission by Napp</b>	<b>Conduct of representative</b>	<b>Breaches Clauses 9.1, 15.2 and 18.6</b>	<b>No appeal</b>	<b>Page 205</b>
<b>2717/5/14</b>	<b>Voluntary admission by Roche</b>	<b>Number of pages of advertising</b>	<b>Breach Clause 6.3</b>	<b>No appeal</b>	<b>Page 210</b>
2718/5/14	Anonymous v Allergan	Meeting arrangements	No Breach	No appeal	Page 212



The Prescription Medicines Code of Practice Authority was established by the Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself. Compliance with the Code is obligatory for ABPI member companies and, in addition, over sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about prescription only medicines made available to the public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed or electronic material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend, buy or sell medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the sponsorship of attendance at meetings organised by third parties
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio or video-recordings in any format, broadcast media, non-print media, the Internet, interactive data systems and the like.

It also covers:

- the provision of information on prescription only medicines to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations
- the use of consultants
- non-interventional studies of marketed medicines

- the provision of items for patients
- the provision of medical and educational goods and services
- grants and donations to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of three of the four members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. One member of the Panel acts as case preparation manager for a particular case and that member does not participate and is not present when the Panel considers it.

Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry. Independent members, including the Chairman, must be in a majority when matters are considered by the Appeal Board.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Further information about the Authority and the Code can be found at [www.pmcpa.org.uk](http://www.pmcpa.org.uk)

Complaints under the Code should be sent to the Director of the Prescription Medicines Code of Practice Authority, 7th Floor, Southside, 105 Victoria St, London SW1E 6QT

telephone 020 7747 8880  
facsimile 020 7747 8881  
by email to: [complaints@pmcpa.org.uk](mailto:complaints@pmcpa.org.uk).