NUMBER 94 November 2016

# CODE OF PRACTICE REVIEW

PMCPA | Prescription Medicines Code of Practice Authority

**The Prescription Medicines Code of Practice Authority (PMCPA) was established by The Association of the British Pharmaceutical Industry (ABPI) to operate the ABPI Code of Practice for the Pharmaceutical Industry independently of the ABPI. The PMCPA is a division of the ABPI which is a company limited by guarantee registered in England & Wales no 09826787, registered office 7th Floor, Southside, 105 Victoria Street, London SW1E 6QT.**

## UPDATE ON THE CODE

The next version of the ABPI Code of Practice will be in 2018. In the meantime the PMCPA is working on updating its guidance. The PMCPA Compliance Network was asked to help with this and to identify possible short and long term changes to the Code. The Review Group and the ABPI Medical Expert Network and others have also contributed to the discussion. This is part of the ongoing work to ensure that the Code and its operation remain fit for purpose.

The Compliance Network members agreed a priority list of areas for further consideration across four separate workstreams:

**Workstream 1**: **Clause 3 Guidance** to be reviewed including medical science liaison roles, advanced budgetary notification, and to add references to the Early Access to Medicine Scheme and conditional licences.

**Workstream 2: Meetings** a Q and A is to be developed as well as other guidance.

**Workstream 3: Patient Support Programmes and Clause 18**, additional guidance.

**Workstream 4: Services Linked to Products and Clause 18**, additional guidance.

The PMCPA is very grateful to the members of the workstreams for volunteering and for their contributions so far. Further updates will be published on the PMCPA website in due course.

## END OF THE YEAR, A TIME TO LOOK BACK – AND FORWARD

The Code of Practice Review published in February 1995 was the first time case reports were published in something like their current format, with a short summary preceding the main report. The main difference, however, was that the reports did not name the respondent company or the medicines involved where no breach was ruled. As you can imagine a summary which stated *'A general practitioner complained that an advertisement was misleading and that the claims could not be substantiated. The Panel accepted that there was sufficient information to substantiate the claims and no breach was ruled'* was far from illuminating and the main body of the report shed no further light (Case AUTH/172/6/94).

However, changes agreed by ABPI member companies in 1995 meant that reports on complaints received on or after 1 January 1996 would all name the company and the medicine involved regardless of whether or not a breach of the Code had been ruled. This additional transparency was welcomed.

Although many of the matters raised in complaints 20 or so years ago were similar to those raised today some of the case reports published in February 1995 refer to materials or activities which will surprise you. For instance one company was ruled not to be in breach of the Code with regard to a competition it had run in connection with the promotion of a medicine (Case AUTH/184/7/94). Entrants had to answer six questions and complete a tie-breaker. Ten prizes, each of £100, were offered - the maximum acceptable cost to a donor of a prize in a promotional competition at that time. In the event only 20 entries were received and only two of those were completely correct!

Another company was ruled in breach of the Code because an air freshener which it had provided as a promotional aid, and which looked like a tablet bottle, had been labelled with the name of the medicine being promoted; this was likely to cause confusion (Case AUTH/201/8/94).

Of course promotional competitions are no longer permitted (they went out with the 2006 edition of the Code) and nor are air fresheners and other branded promotional aids (the 2011 Code saw their demise) but which of today's accepted practices will seem odd to those who look back in in years to come? Equally, in 1995, would anyone have predicted that case reports (Cases AUTH/2812/12/15 and AUTH/2873/9/16) would discuss the provision of frozen yoghurt from exhibition stands?

Today the review of case reports for educational purposes is an important element of the Compliance Network meetings which the PMCPA has hosted regularly for the last five years – the first meeting was held in November 2011. Members of the network and/or the PMCPA select five or six recently completed cases for review at each quarterly meeting and together we discuss the rulings and the wider learnings that might be appropriate to take forward from each. The PMCPA also reviews relevant cases as part of its seminars and, of course, also takes learnings from the completed cases to inform and shape its guidance on various aspects of the Code. We all need to look backwards sometimes in order to move forwards!

## 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 dates on which places remain available are:

Thursday 26 January 2017
Wednesday 1 March 2017

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).*

## HOW TO CONTACT THE AUTHORITY

Our address is:
Prescription Medicines Code of Practice Authority
7th Floor, Southside, 105 Victoria Street, London SW1E 6QT

www.pmcpa.org.uk

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| Telephone: | 020 7747 8880 |
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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 lmatthews@pmcpa.org.uk).

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

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| Heather Simmonds: | 020 7747 1438 |
| Etta Logan: | 020 7747 1405 |
| Jane Landles: | 020 7747 1415 |
| Tannyth Cox: | 020 7747 8883 |

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.

# ONLINE TRAINING FOR HEALTH PROFESSIONALS, JUST WHAT THE DOCTOR ORDERED…

The PMCPA has monitored feedback from those who have been taking the updated e-learning module for health professionals and has discovered that people with a surprisingly wide range of roles are doing it, and that the vast majority would recommend it to others.

The e-learning module was updated in the summer to reflect the launch of the Disclosure UK website. This was to ensure that those working with the pharmaceutical industry are fully aware of the requirements of the Code.

Not only have doctors, nurses and pharmacists been logging on to the e-learning module, but also company senior managers and representatives, PR consultants and industry specialists who regularly give it the maximum score.

While the e-learning module does not replace formal examinations, it is most valued for its practicality, as it uses specific situations to demonstrate where particular caution is needed. Those taking it say that they welcome the opportunity to test their knowledge.

If you are interested in testing your knowledge, there is a link to the training on the home page of the PMCPA website. Don't forget to give us your feedback.

**CASE AUTH/2823/2/16**

# ANONYMOUS, CONTACTABLE v GRÜNENTHAL

## Conduct of representatives

**A contactable complainant who wished to remain anonymous complained about Grünenthal's practices including the pressure put on representatives to perform in a manner which risked bringing the industry into disrepute.**

**The complainant referred to a previous upheld complaint about Grünenthal's expected call rates and alleged that Grünenthal's defence in that case that representatives were not incentivised on achieving call rates was untrue. The complainant alleged that sales representatives' bonus payments were based on unethical call rate expectations.**

**At the start of each quarter representatives created cycle plans which listed target customers and how many times they would be seen that quarter. The complainant understood that even stating that Grünenthal would see each of those customers once each quarter was a breach of the Code which allowed three calls per year. The complainant stated that Grünenthal was not happy with one call per customer per quarter which led to some representatives stating that they would see particular health professionals more than eleven times in a four month period. This was compounded by the fact that even if a representative achieved in excess of their sales vs target, if they did not achieve a minimum of 90% of the cycle plan they would not receive any bonus payment. This led to both the falsifying of calls and some representatives reporting more than twenty calls on one single doctor in a three month period. All representatives, even new representatives making their first call, were told to record calls as 'requested return visit' on the customer relationship management (CRM) system.**

**The complainant explained that Grünenthal also ran a GP pain education programme (GP-PEP). Representatives were to ask health professionals to act as paid speakers for these meetings. However, unless the health professional had prescribed the relevant product (most often Palexia (tapentadol hydrochloride)) to a minimum number of patients, they were not permitted by the company to speak. The complainant alleged that company compliance was poorly monitored, some consultants had spoken at meetings without a contract in place and others had not been paid for services provided. Representatives were set a target number of meetings to hold per quarter. Again, although their bonus did not rely on this, it was listed as a key performance indicator and failure to achieve the target level of meetings each quarter resulted in a reduction, or in some cases, a complete removal of an annual pay rise.**

**The detailed response from Grünenthal is given below.**

**The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The complainant had not provided any material to support his/her allegations but had provided a detailed account of their concerns. Further the complainant had not given details of the dates regarding his/her allegations. The case preparation manager had informed Grünenthal that the case would be considered under the Code relevant to the time that activities took place and had asked for details and copies of materials etc for representatives in the past two years.**

**1 Activity targets for representatives**

**In the previous case, Case AUTH/2652/11/13, Grünenthal was ruled in breach of the Code on the narrow ground alleged because the email in question was not sufficiently clear about the differences between call rates and contact rates as referred to in the relevant supplementary information in the Code.**

**The Panel noted Grünenthal's submission in the case now before it, Case AUTH/2823/2/16, that activity targets were established as part of overall cycle plans. The Panel further noted Grünenthal's submission that 'activity' could take the form of a face-to-face (1:1) call with a specified individual, or contact established when the individual was a delegate at a meeting. Grünenthal did not set or incentivise expected call or contact rates, instead it was the general collective 'activity' that was monitored.**

**The cycle plans were created by each representative based on local knowledge of what was required to drive business and the total number of interactions planned per individual target customer was also established by the representative based on what they had the potential to achieve. This could be zero, 1, 2, 3 etc … interactions over the cycle period, including calls requested by a customer. Representatives were not driven by Grünenthal to plan a minimum number of interactions with any given health professional. The Panel noted Grünenthal's submission that the default activity against all customers when working on a draft cycle plan was '1'. Representatives were instructed to increase or decrease this number accordingly for individual health professionals in order to create their overall cycle plan. The acceptance of '0' and '1' was described in briefing material sent to representatives.**

**Once the provisional cycle plans were created they were reviewed and/or challenged by line managers based on reasonable potential to attain the plan proposed and adherence to compliance requirements.**

**The Panel noted Grünenthal's submission that achievement of an individual's cycle plan each year was always based on total actual volume of calls vs total target volume so no daily call rate was required or stipulated.**

**The Panel considered that Grünenthal's submission that no daily call rate was required was not wholly accurate. Representatives were given a minimum interaction capacity per day and their provisional cycle plans were reviewed/challenged by line managers then validated. An email from a commercial director to the sales force made it clear that a key performance indicator on the cycle plan data was the daily rate of work that the quarterly volume of contacts delivered. In the Panel's view, the number of expected daily interactions would include, over the cycle plan, calls on target customers and others.**

**The Panel noted that Grünenthal promotional teams were provided with a commercial standards document at the beginning of each year which clarified business expectations including instructions to plan activity in line with the requirements of the Code, in addition to reminders within other communications. The Commercial Directorate Standards 2015 and 2016 defined a call as a one to one event with a customer and a contact as being a call or a meeting event. The documents further stated that the CRM system recorded customer interactions which was an internal term defined as a face-to-face call or meeting with a customer and on the same slide stated 'Our anticipated activity rates take into account the PMCPA code of conduct [respective year] and each customer should not have more than 3 unsolicited calls per year. However it is assumed a significant proportion of this activity will be on customer request'. The slide concluded that other activity could take place outside of the target lists and cycle plan and detailed that Grünenthal was resourced to deliver a certain number of total customer contacts per day. The 2016 slide stated in addition that this activity should not compromise the target activity achievement. The Panel queried how and where this other activity taking place outside of the target lists and cycle plans would be recorded. The Panel also noted that this contradicted Grünenthal's submission that in the last quarter of 2015 and in 2016 there was no expectation with regard to non-target activity.**

**The 2015 Grünenthal Sales Team Incentive Scheme stated that the Palexia SvT and Versatis SvT quarterly targets were set per business unit by the CDMT. Quarterly targets were set per account by the business unit. These were managed to ensure, amongst other things that there was an equal challenge per representative. This enclosure also stated that the daily interaction rate was at least 5/day to include face to face meeting interactions named and unnamed target and not target customers. There was no mention of the Code requirements in this presentation.**

**The Panel noted Grünenthal's submission that it discovered that three out of 56 representatives registered more than three cold calls with the same individual health professional over a calendar year (this affected 15 individual health professionals with 4-6 interactions logged as cold calls). According to Grünenthal each representative insisted that he/she had entered the majority of their calls erroneously as cold calls indicating that there had been an error in call recording within the CRM system as opposed to an error in customer facing activity; each provided confirmation to support these calls as 'requested return visits' where relevant, such that no more than three cold calls were conducted on any individual health professional.**

**The Panel noted that three representatives out of 25 who had started in 2014 and 2015 had not logged any cold calls when they first started seeing customers; they were confused about the definition of a cold call. Two of the three said they thought that if they were invited by a receptionist or a secretary to return at a specified time to see a health professional, this would then be classed as a 'requested return visit'. According to Grünenthal this was not Grünenthal's internal standard, nor what was detailed during internal CRM training. The third individual said she incorrectly thought the 'requested return' option was to record an invitation for a future meeting (ie the health professional requested a return visit). The three representatives had not accurately recorded their interactions in the CRM system so Grünenthal did not have a clear oversight, but each representative maintained that he/she did not conduct more than three cold calls on any given individual.**

**The Panel further noted Grünenthal's definitions of a 'cold call' ie a call where no prior arrangement had been made to visit/re-visit the health professional, and a 'requested return visit', used when the health professional had agreed to, or made arrangements for the representative to return to continue agreed business objectives.**

**The Panel noted its comments above, the training/briefing provided by Grünenthal to its representatives together with the company's definitions of 'cold call' and 'requested return visit' and understood why representatives might be confused with how to record certain activities.**

**The Panel noted that whilst some documents provided by Grünenthal included the relevant Code requirements, others did not. The Panel noted that each of these documents had to standalone.**

**The Panel was concerned about Grünenthal's submission that as the majority of its representatives had worked the same territories with the same health professionals for a number of years, health professionals and representatives often formed relationships whereby the customer provided an invitation to a given representative to visit on a regular basis to maintain contact to ensure they remained up to date with therapy area and product developments to optimise their patient care, so they were aware of meetings and events led by or supported by Grünenthal, or to support broader understanding of clinical experience with Grünenthal products. The Panel noted Grünenthal's submission that these invitations might not be specific with reference to time or topic but were genuine and legitimate.**

**That a representative had a long standing relationship with a health professional when**

**combined with the activities cited by Grünenthal did not, in the Panel's view, mean that all subsequent calls were solicited as implied. Whether such a call was solicited would depend on a consideration of all the circumstances. Certainly in the Panel's view a 1:1 call in response to a broad open invitation without reference to time or topic was unlikely to be viewed as a solicited call.**

**The Panel was also concerned that a number of briefing documents, when referring to the Code and its supplementary information, qualified the requirement that there be no more than three unsolicited calls per year. For instance, the 2014 Commercial Team Standards activity twice when referring to the call limit stated 'However it is assumed a significant proportion of this historic industry activity was based on customer request'. It also stated with reference to the number of unsolicited calls that 'However it is assumed that a proportion of activity will be based on customer request'. Similar qualifications were repeated in the Commercial Directorate Standards' presentations for 2015 and 2016. In the Panel's view, this qualification was misleading and downplayed the importance of the restriction on the number of cold calls and might encourage representatives to proactively seek return calls such that they might not all be *bona fide* solicited calls.**

**The Panel noted all of its comments above. Grünenthal had failed to be sufficiently clear about how representatives could meet the cycle plan and comply with the Code. In addition, the Panel considered that Grünenthal had failed to provide its representatives with information that was sufficiently clear about the differences between call rates and contact rates within the context of the cycle plans and target interactions and the Panel ruled a breach of the Code.**

**The Panel, noting its comments and ruling above, considered that Grünenthal had failed to comply with its undertaking given in in Case AUTH/2652/11/13 and a breach of the Code was ruled.**

**Whilst the Panel had concerns, as noted above, there was, on balance, no evidence that representatives over called on health professionals as alleged and the Panel ruled no breach of the Code which was upheld on appeal by the complainant.**

**The Panel noted its comments above and considered that briefing provided by Grünenthal to its representatives regarding the definitions of call rates and requested return visits and its qualification of the requirement that there be no more than 3 unsolicited visits per year was such that it was likely to lead to a breach of the Code. A breach of the Code was ruled.**

**Noting its rulings above, the Panel considered that Grünenthal had failed to maintain high standards and a breach of the Code was ruled. The Panel noted that some efforts had been made to refer to the relevant requirements of the Code and comply with the undertaking but considered that overall these were insufficient. The Code requirements were not referred to in all relevant documents and where such references did appear they were insufficient as set out above. An undertaking was an important document. The Panel noted that inadequate action leading to a breach of undertaking was an example of an activity likely to be in breach of Clause 2. The Panel was concerned that following Case AUTH/2652/11/13, Grünenthal was still not sufficiently clear about the differences between call rates and contact rates as referred to in the relevant supplementary information within the context of representative's interactions and cycle plans. Bearing that in mind and noting its rulings above the Panel ruled a breach of Clause 2.**

**2 GP-PEP Programme**

**The Panel noted Grünenthal's submission that health professionals did not have to have prescribed Grünenthal medicines for a minimum number of patients before they could be selected as a speaker but Grünenthal expected speakers to have had at least some experience with their use so that they could refer to this when speaking, however no expectation was made in terms of the extent of their use. This was to ensure that speakers would be able to provide advice on how to select the right patient for different medicines, and how to treat to achieve the greatest potential pain relief. In principle, the Panel did not consider that this was unreasonable. The Panel also noted the working instruction which included the criteria upon which speakers were selected and the process for recruiting a speaker. Potential speakers should be medical doctors and/ or selected nurse or pharmacist prescribers who, *inter alia*, had experience prescribing Grünenthal products which was similar to earlier versions; no version of the working instruction required that a health professional prescribe Grünenthal medicines for a minimum number of patients to be selected as a speaker as alleged. On this narrow ground no breaches of the Code were ruled which were upheld on appeal by the complainant.**

**The Appeal Board noted that before a consultant provided a service a written contract or agreement, which specified the nature of the services to be provided and the basis for payment of those services, had to be signed in advance. The Appeal Board noted Grünenthal's submission that neither electronic nor hard copy contracts could be located for four speakers in 2014 and two in 2015. The Appeal Board ruled a breach of the Code.**

**With regard to the allegation that company compliance was poorly monitored as some consultants had spoken at meetings without a contract in place and some had not paid for services provided, the Panel noted Grünenthal's submission that a review of all GP-PEP meetings conducted in 2014, 2015, and 2016 (n = 271) found that 5 speaker agreements were signed after the meeting took place, therefore the Panel ruled a breach of the Code. The Panel considered that Grünenthal had failed to maintain high standards in this regard and a breach of the Code was ruled.**

**The Panel then considered the allegation that representatives were set a target number of**

**meetings to hold per quarter and although their bonus did not rely on this payment, it was listed as a key performance indicator and failure to achieve the target level of meetings each quarter resulted in a reduction, or in some cases, no annual pay rise. The Panel noted Grünenthal's submission that it had never set representatives a target number of meetings since the programme was established in 2012 and the number of meetings bore no impact on bonus or pay rise as alleged. The Panel noted that the onus was on the complainant to prove his/her complaint on the balance of probabilities and the Panel considered that there was no evidence in this regard. The Panel thus ruled no breach of the Code which was upheld on appeal by the complainant.**

**The Panel noted its rulings above and decided that a ruling of Clause 2 which was reserved as a sign of particular censure was not warranted in this instance and no breach of that clause was ruled which was upheld on appeal by the complainant.**

A contactable complainant, who wished to remain anonymous, complained about Grünenthal Ltd's practice and the pressure put on its sales representatives to perform in a manner which risked bringing the industry into disrepute.

**COMPLAINT**

The complainant stated that in the past a complaint was made about Grünenthal and its expected call rates on health professionals which he/she understood was upheld.

The complainant alleged that Grünenthal's defence in that case that sales representatives were not incentivised on achieving call rates could not be further from the truth. The complainant alleged that sales representatives' bonus payments were based on unethical call rate expectations.

At the start of each quarter representatives listed their 'target customers' and how many times they would be seen the following quarter. The complainant understood that even stating that Grünenthal would see each of those customers once in each quarter was a breach of the Code which allowed three calls per year. The complainant stated that Grünenthal was not happy with one call per customer per quarter. The list was checked by the customer relationship management (CRM) champion who discussed issues with a senior employee before passing the cycle plans. It was openly stated that experienced representatives should not just be entering in '1's' down the list. This led to some representatives stating that they would see particular health professionals more than eleven times in a four month period. This was compounded by the fact that even if the said representative achieved in excess of their sales vs target, if they did not achieve a minimum percentage of the cycle plan that was put in place they would not receive any bonus payment. This led to both the falsifying of calls and some representatives reporting more than twenty calls on one single doctor in a three month period.

Representatives were told to record calls as 'requested return visit' on the CRM system. This could never be true for new representatives making their first calls but they were told to record them in this way anyway.

The complainant explained that Grünenthal also ran a GP pain education programme (GP-PEP). The sales representatives were to ask health professionals to act as paid speakers for these meetings. However, unless the health professional had prescribed the product they were required to speak on (most often Palexia (tapentadol hydrochloride)) to a minimum number of patients, they were not permitted by the company to speak. The company compliance was poorly monitored as some consultants had spoken at meetings without a contract in place. Grünenthal had also failed to pay consultants for services provided.

Representatives were then set a target number of meetings to hold per quarter. Again, although their bonus did not rely on this payment, it was listed as a key performance indicator and failure to achieve the target level of meetings each quarter resulted in a reduction, or in some cases, a complete removal of an annual pay rise.

When writing to Grünenthal, the Authority asked it to consider the requirements of Clauses 2, 9.1, 15.4, 15.9 and 29 of the Code with regard to the conduct of representatives. With regard to the GP-PEP Programme the Authority asked it to consider the requirements of Clauses 2, 9.1, 18.1 and 23.1. The case would be considered under the requirements of the Code relevant to the time the activities took place. Clause 23 of the current Code was Clause 20 in the Second 2012 Edition of the Code and the 2014 Code.

**RESPONSE**

Grünenthal addressed each matter in turn.

**1 Activity targets for representatives**

Grünenthal submitted that activity targets were established as part of overall 'cycle plans' as part of overall account planning. An overall summary of the principles were provided. Cycle plans were created by each individual representative (known internally as account representatives (ARs) or account managers (AMs); previously pain sales managers, (PSMs)) based on their own local knowledge of what was required to drive business. The cycle plans were created and finalised in collaboration with any relevant cross-functional colleagues who might be working in the same localities to ensure complementary activities.

In 2014 and 2015, there were four cycle periods per year. In 2016 and moving forward, there were three cycle periods per year. Before each new cycle period, sales representatives were sent a list of all health professionals on their territory from which they were required to create a list of target customers whom they identified to be important to their local business. The principles of targeted activity were described. Representatives were asked to conduct a review to identify the need for any changes to their list of target customers and amend accordingly. Examples of instructions provided to

representatives were provided. On average, each target list comprised over 100 customers dependent on the internal experience of the representative, local market access and geography (Grünenthal referred to an email as an example of communication in this regard). Representatives were asked to complete a prospective activity plan for the upcoming period for each individual target customer based a number of identified factors.

Grünenthal noted that 'activity' could take the form of a face-to-face (1:1) call with a specified individual, or contact established when the individual was a delegate at a meeting. Grünenthal did not set or incentivise expected call or contact rates, instead this general collective 'activity' was monitored.

The total number of interactions planned per individual target customer was established by the representative themselves based on what they had the potential to achieve. This could be zero, 1, 2, 3 … interactions over the cycle period, including calls requested by a customer (Grünenthal referred to its briefing materials which stated 'Replace the 1 in the 'Planned Calls' field with the number you are actually and compliantly planning (call contracts)'. Representatives were asked to plan those interactions themselves based on their own knowledge of their customers and local business. They were not driven by the company to plan a minimum number of interactions with any given individual health professional; decisions were made by the local representative.

The promotional teams were provided with a commercial standards document at the beginning of each year. Examples of 2015 and 2016 were provided. These documents clarified all business expectations including instructions to plan activity in line with the requirements of the Code, in addition to regular reminders within other communications.

In 2013, 2014, and the first three quarters of 2015, the interaction capacity per representative per day was set at a minimum of 2 target customers via face-to-face (1:1) call or contact at a meeting, plus a requirement to add 'non-target activity'. This generated a total of 5-7 expected interactions with health professionals per working day. This gave a volume of interactions to be achieved per period per employee and ensured representatives had a framework for their working day. Achievement of an individual's cycle plan was based on total actual volume of calls vs total target volume so no daily call rate was required nor stipulated.

In quarter 4 2015, the interaction capacity per day was increased to a minimum of 3 target customer interactions per day via face-to-face (1:1) calls or through contact at a meeting. There was no expectation with regards non-target activity in that quarter. Achievement of the cycle plan was based on total actual volume versus total target volume so there was no daily call rate required nor stipulated.

Three cycle plans per annum with a duration of four months per cycle were introduced in 2016, C1, C2 and C3. For 2016 C1, the interaction capacity per day was set at a minimum of 3 target customer interactions per day, via a face-to-face (1:1) call or a meeting. There was no expectation with regards non-target activity. This gave a volume of interactions to be achieved per target customer per period per employee. Achievement of the cycle plan was based on total actual volume vs total target volume so no daily call rate was required.

Once the provisional cycle plans were created by individual representatives, they were reviewed and/or challenged by line managers based on reasonable potential to attain the plan proposed, and adherence to compliance requirements. There was no additional review or approval step outside of this as alleged by the complainant. Once the validation exercise was completed, the cycle plans were uploaded into the CRM system and the team started activity to achieve them. Data was extracted and reviewed regularly so the teams could see their progress towards their cycle plan attainment but it should be noted that activity was only one component of overall cycle plans. (Grünenthal referred to examples of internal communications regarding the performance and attainment of cycle plans.)

Grünenthal therefore refuted any allegation that it had driven activity with health professionals that exceeded the requirements of Clause 15.4 which was supported by its briefing material that did not advocate, either directly or indirectly, any course of action that would be likely to lead to a breach of the Code (Clause 15.9).

**How Grünenthal bonused activity targets for sales representatives since January 2014**

The 2013 incentive scheme was based on several measures and details were provided. There were no activity parameters in the 2013 scheme.

The 2014 incentive scheme was based on several measures in addition to growth and sales. A pre-qualifier was introduced based on activity volume, but not on any daily call rate. It used the representative self-created cycle plans to ensure that activity was taking place within target areas rather than on any accessible customer. To qualify the representative had to achieve a minimum 90% of their quarterly cycle plan activity.

The initial incentive scheme in 2015 included pre-qualifying criteria to attain 90% cycle plan volume. In May 2015, the H1 scheme was retrospectively amended to remove the activity component. The second half of 2015 did not have any activity measures.

Initial 2015 incentive scheme included pre-qualifying criteria: 90% volume attainment of cycle plans, minimum interaction rate 5 per day but this was removed from the updated 2015 incentive scheme.

The 2016 incentive scheme was based on several measures including achieving a minimum 90% of their cycle plan (volume of actual calls/volume of planned calls). This was not based on any daily call rate.

Grünenthal submitted that as was evidenced above, and contrary to the accusation made by the complainant, Grünenthal had never stipulated that 'the primary factor in sales representatives receiving their bonus payments was … based on unethical call rate expectations'.

Grünenthal noted that the complainant alleged that 'even stating you will expect to see each of those customers once in each quarter is already on [sic] breach of the codes guide of 3 calls in a year'. The requirements stipulated in the supplementary information to Clause 15.4 specified that 'the number of calls made on a doctor or other prescriber by a representative each year should not normally exceed three on average'. This did not cover the planning of calls with specific individual customers based on existing relationships, ongoing projects and following customer requests so Grünenthal disagreed with the allegation made in that regard.

Grünenthal noted that the complainant further alleged that 'Grünenthal are not happy with representatives just stating one call per customer per quarter', and alleged a review of submitted cycle plans by the CRM Champion and a senior employee. The default activity against all customers when working on a draft cycle plan was '1'. Representatives were instructed to increase or decrease this number accordingly for individual health professionals in order to create their overall cycle plan. The acceptance of '0' and '1' was described in briefing material sent to representatives (examples were provided in briefing materials and additional notes section of internal communications). A review of submitted cycle plans was not conducted by the CRM Champion and a senior employee as alleged.

Grünenthal submitted that there were no activity parameters in the 2013 scheme at all, daily call rate or other (Grünenthal referred to the Grünenthal Sales Incentive Scheme 2013.

Grünenthal submitted that its response to Case AUTH/2652/11/13 was correct, complete and reflective of the situation in 2013. There was no incentive on any activity (including call rates) in the 2013 scheme, just Palexia growth and Versatis SvT. Grünenthal submitted that it did not provide a false response to Case AUTH/2652/11/13, nor did it fail to comply with its undertaking.

Grünenthal conducted a review of 1:1 call data within the CRM system in response to this complaint. It was identified that three representatives out of 56 registered more than three cold calls with the same individual health professional over a calendar year (this affected 15 individual health professionals with 4-6 interactions logged as cold calls). Each of these representatives were spoken to during an internal investigation and provided notes to support the visits they logged. Each insisted that they had entered the majority of their calls erroneously as cold calls and provided a breakdown accordingly. This was therefore indicative that there had been an error in call recording within the CRM system as opposed to an error in the customer facing activity of these representatives. As each provided confirmation to support these calls as 'requested return visits' where relevant, such that no more than three cold calls were conducted on any individual health professional by a Grünenthal representative, there was no evidence to suggest that there had been a breach of Clause 15.4.

Grünenthal submitted that all new representatives received training on how to use the CRM system when they started. The training presentation delivered to the most recent group of new starters in February 2016 was provided. The logging of calls and use of the drop-down menu to record whether a call was a cold call or a requested return visit was detailed on slide 49. The presentation was delivered by senior managers who provided a concurrent demonstration of functionality in the test system whilst using the slides on a separate screen during training sessions. Whilst the use of the drop-down menu was not detailed on slide 49, it was discussed and demonstrated during training.

A review of activities logged in the CRM system by all new starters to promotional field based roles in 2014 and 2015 was conducted upon receipt of this complaint. Of the 25 field based promotional staff who started with Grünenthal in 2014 or 2015, three had not logged any cold calls when they first started seeing customers.

When these individuals were contacted during the internal investigation, they described being confused in their understanding of what a cold call was. Two of the three said they thought that if they were invited by a receptionist or a secretary to return at a specified time to see a health professional, this would then be classed as a 'requested return visit' rather than a cold call. This was not Grünenthal's internal standard, nor what was detailed during internal CRM system training. The third individual said she incorrectly thought the 'requested return' option was to record an invitation for a future meeting (ie the health professional requested a return visit).

The territories for each of the identified individuals did not lend themselves to easy speculative calls so each had said that only approximately 10% of their contact time with health professionals was based on cold calls. Unfortunately, they had not accurately recorded their interactions in the CRM system for the company to have a clear oversight, but each maintained that they did not conduct more than three cold calls on any given individual. Grünenthal therefore identified an error in record keeping by three individuals as opposed to the conduct of activity that was in breach of the requirements of Clause 15.4. Grünenthal submitted that this was not indicative of a failure to maintain high standards by the individual representatives, nor the company, as the error rested in record keeping, not inappropriate over calling on individual health professionals. Grünenthal did not have any evidence to indicate that any of those representatives over called on any individual health professional as each confirmed that they had not. Each of the individuals received one-to-one re-training from their line manager on the definitions to apply when recording calls within

the CRM system so the records accurately reflected activities in the field.

In summary Grünenthal submitted that it was asked to respond in relation to Clauses 2, 9.1, 15.4, 15.9 and 29. Grünenthal refuted the allegations made against each of these clause requirements as outlined above.

In response to a request for further information Grünenthal submitted that it required all interactions between Grünenthal staff and health professionals or other relevant decision makers to be logged within 24 hours of the interaction in the CRM system. When a face-to-face contact was recorded, the nature of the interaction must be recorded using options from a drop-down menu in order for the activity to be logged and was a mandatory field in the system. There were two options that might be selected:

- 'cold call' ie a call where no prior arrangement had been made to visit/re-visit the health professional, or
- 'requested return visit', used when the health professional had agreed to, or made arrangements for the representative to return to continue agreed business objectives.

An image of the CRM system was provided. Grünenthal submitted that functionality of the system allowed a plethora of reports to be run on any information entered across the UK business as a whole, at an individual representative level, or against an individual health professional, including the number of cold calls logged. Reports could be run by users or centrally (certain roles had access to enhanced reports, eg CRM Manager, Head of Sales, Head of Compliance, amongst others).

Grünenthal submitted that it proactively provided all new starters with training on the requirements of the Code on commencement of employment and continued to do so at regular intervals. Specific training on interactions with health professionals and the recording of calls in the CRM system (including the annual limit of unsolicited calls per individual health professional) was provided during training on the CRM system. Regular briefing documents reinforced this training on an ongoing basis as previously described and evidenced.

Grünenthal submitted that for the benefit of better and long-lasting business opportunities, it preferred its customer facing staff to form solid relationships with customers, rather than assume a 'scatter-gun' coverage approach to appointments. Grünenthal wished to hold relationships with health professionals who had a clinical interest or responsibility in the management of pain. As such, there were various reasons why a significant proportion of customer-facing activity should be focussed on ongoing projects and plans at customer request: reviewing emerging data within the therapy area or data specific to Grünenthal products, developing and supporting formulary submissions, making arrangements to present data to broader teams, making arrangements for customers to share their experience with other clinicians as a speaker at meetings, discussing medical educational goods and services etc.

Grünenthal submitted that there was a greater value for both health professional and Grünenthal in interactions such as these rather than old style 'cold calls', therefore Grünenthal wished its representatives to focus on those quality relationships and interactions instead of simply knocking on doors. Activity associated with projects was not seen to be unsolicited when there was an existing arrangement with the health professional for follow-up discussions/calls.

Grünenthal submitted that there were many plans and projects designed with the input of health professionals for the benefit of the NHS and patients at a local, regional or national level. Those individual health professionals would have a close ongoing relationship with their primary Grünenthal contact in order to execute or support those plans and projects.

Grünenthal noted that the supplementary information to Clause 15.4 described attendance at meetings, a visit requested by a doctor or other prescribers, calls made in order to respond to a specific enquiry, and a visit to follow up a report of an adverse event, as exceptions to the limit of three cold calls per annum. Calls associated with ongoing projects, discussion of speaker engagements, development of formulary submissions and the like were not unsolicited as there was an existing arrangement with given health professionals, and were examples of calls that were requested by the health professional, sometimes in order to respond to a specific enquiry.

Grünenthal submitted that the majority of its representatives had worked the same territories with the same health professionals for a number of years. Over such a period of time, health professionals and representatives often formed relationships whereby the customer provided an invitation to a given representative to visit on a regular basis to maintain contact. This might be to ensure they remained up to date with therapy area and product developments to optimise their patient care, they were aware of meetings and events led by or supported by Grünenthal, or to support broader understanding of clinical experience with Grünenthal products. Grünenthal submitted that whilst these invitations might not be specific with reference to time or topic, they were genuine and legitimate.

Grünenthal submitted that its reference to 'existing relationships' covered all such engagements related to project work and when a non-specific invitation was offered by a health professional to a representative to maintain contact.

**2 GP-PEP**

Grünenthal submitted that the criteria upon which speakers were selected were described in the working instruction (WIN) for the conduct of PEP meetings. Grünenthal noted that there was an internal change in name of these meetings from 'GP-PEP meetings' when the programme started in 2012 to 'PEP meetings' in 2015.

The current version of WIN was provided as were the 'recruiting a GP-PEP speaker' sections of previous versions:

**'Recruiting a PEP speaker**

AR/AMs overseen by the RAMs or RAMs on their own are responsible for the recruitment of PEP speakers. There must be a strong rational for the recruitment of speakers (see criteria below).

**Criteria for potential speakers:**

- Speakers should be medical doctors and/or selected nurse or pharmacist prescribers who are
  - o experts in pain management,
  - o be locally regarded as experts in their area of practice,
  - o have current experience prescribing GRT products,
  - o be willing to speak about their experience with GRT products as part of each PEP meeting,
  - o have good presentation skills,
  - o be able to commit to presenting at 2-3 meetings a year (minimum).
- Speakers must be local. A national speaker may be used if no speaker is currently available within the local geography.
- Product data training will be provided by the local MSL close to the date of the speaker's first meeting and updates provided as and when required.
- Training must not be provided unless a meeting is planned for them to speak at.
- Potential speakers must be made aware that PEP meetings are promotional meetings and therefore subject to the requirements of the ABPI Code.'

Version 1 of the WIN effective April 2012 did not specify criteria for selecting a speaker. Two examples of the speaker justification forms were provided.

Grünenthal submitted that whilst interacting with health professionals, its representatives might identify that a certain individual had the potential to be suitable to speak on behalf of the company at promotional meetings. Representatives must have agreement from their line manager in order to progress before any discussions were had with the health professional.

A selection of different versions of speaker agreement forms and speaker briefing documents were provided. The 'New PEP Speaker Standard Introduction email' was also provided (dated February 2015).

Grünenthal submitted that as demonstrated within all versions of its WIN, health professionals did not have to have prescribed Grünenthal medicines for a described minimum number of patients before they could be selected as a speaker. As these meetings were promotional meetings for Grünenthal products, Grünenthal expected them to have had at least some experience with their use so they could refer to this when speaking, however no expectation was made in terms of the extent of their use. This ensured they would be able to provide advice on how to select the right patient for different medicines, and how to treat a patient to achieve the greatest potential pain relief. With no experience of using Grünenthal products, speakers would not have the necessary insight and expertise expected by delegates attending such meetings, and the validity of such meetings would be drawn into question.

As described above, and demonstrated within all versions of the WINs, Grünenthal submitted that there was no minimum number of patients for whom health professionals had to have prescribed Grünenthal products to in order to be recruited as a speaker. Speakers must be experts in pain management and have adequate experience to discuss case studies.

Grünenthal submitted details of the average payments made to speakers and chairpersons providing services to support the GP-PEP/PEP programme in 2014 and 2015. These figures were inclusive of any preparatory work that had been undertaken in addition to speaking services at the GP-PEP/PEP meeting.

A review was conducted of all GP-PEP and PEP meetings conducted in 2014, 2015, and 2016 to date in response to this complaint. The total number of meetings conducted over this period was 271. During the review, it was found that 5 speaker agreements were signed after the meeting took place. One was signed in advance of the meeting date on an app that was being trialled but the signature did not properly load therefore a hard copy contract was signed after the event in order to allow payment to be processed. Two were signed after the event due to miscommunication between two members of staff, each of whom believed the other to be responsible for obtaining the signature. One was signed the day after the event due to a lack of oversight by the meeting organiser. One was signed after the event when numerous attempts to ask the speaker to sign the contract in advance of the meeting were not responded to by the speaker.

Grünenthal submitted that whilst it was disappointed to report that it found any contracts that were not signed in advance of the meeting date, it did not believe this low overall figure (<2% of total) to indicate a systematic failure of the company to adhere to high standards (Clause 9.1).

Contrary to what had been alleged by the complainant, Grünenthal submitted that it had never set representatives a target number of meetings to hold per quarter since the GP-PEP/PEP programme was established. Grünenthal preferred the investment of time and effort be afforded in areas where the meetings would be genuinely useful rather than working solely to the achievement of metrics. This also meant that the number of meetings completed by a representative bore no impact on their bonus or annual pay rise as alleged. Within the priorities identified for all representatives, Grünenthal included the statement 'PEP, KnEx and speaker meeting goals are achieved as agreed with the line manager', but this referred to the conduct of such meetings rather than an arbitrary number of meetings that must be delivered.

Unfortunately there were five instances whereby speaker contracts were not signed with speakers in advance of their speaking services, however in the context of the number of speaker meetings held over this period (271), Grünenthal did not believe that this indicated a failure to maintain high standards (<2% of total). Grünenthal submitted that its selection process for recruiting speakers to present at promotional meetings on its behalf was not in breach of the requirements of Clause 18.1. Thereby it refuted that any of its activities in this regard were in breach of Clause 2.

**General summary**

Grünenthal submitted that since it was notified of this complaint, some of its employees had been contacted and told that this complaint was made by one of those ex-employees. Grünenthal's employees were deeply upset that the company was being targeted by these ex-employees.

Grünenthal reiterated its commitment to adhering to the Code in both the letter and spirit and was disappointed to have received this complaint however it was confident that its activities were in line with the requirements of the Code.

**PANEL RULING**

The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The complainant had not provided any material to support his/her allegations but had provided a detailed account of their concerns. Further the complainant had not given details of the dates regarding his/her allegations. The case preparation manager had informed Grünenthal that the case would be considered under the Code relevant to the time that activities took place and had asked for details and copies of materials etc for representatives in the past two years.

**1 Activity targets for representatives**

The Panel noted that Clause 15.4 of the 2016 and 2015 Codes required representatives to ensure that the frequency, timing and duration of calls on, *inter alia*, health professionals, together with the manner in which they were made, did not cause inconvenience. (The 2014 Code had similar requirements but the clause referred to appropriate administrative staff rather than other relevant decision makers). The supplementary information to that clause stated, *inter alia*, that companies should arrange that intervals between visits did not cause inconvenience. The number of calls made on a doctor or other prescriber by a representative each year should normally not exceed three on average excluding attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up a report of an adverse reaction. Thus although a representative might speculatively call upon or proactively make an appointment to see a doctor or other prescriber three times on average in a year, the annual number of contacts with that health professional might be more than that. The supplementary information to Clause 15.4 also advised that when briefing representatives companies should distinguish clearly between expected call rates and expected contact rates. Targets must be realistic and not such that representatives breached the Code in order to meet them. Clause 15.9 stated that briefing material must not advocate directly or indirectly any course of action which would be likely to lead to a breach of the Code.

The Panel disagreed with Grünenthal's submission that Clause 15.4 did not cover the planning of calls with specific individual customers based on existing relationships.

Case AUTH/2652/11/13 concerned an email sent by a senior employee to remind the sales force to enter data into a customer relationship management (CRM) system [Advance] daily and to instruct representatives on expected call rates. The complainant noted that the email only referred to interactions and thus failed to reflect the Code which stated 'When briefing representatives, companies should distinguish clearly between expected call rates and expected contact rates'. Grünenthal was ruled in breach of Clause 15.4 on the narrow ground alleged because the email in question was not sufficiently clear about the differences between call rates and contact rates as referred to in the relevant supplementary information.

Turning to the case now before it, Case AUTH/2823/2/16, the Panel noted Grünenthal's submission that activity targets were established as part of overall cycle plans which were part of overall account planning. The Panel further noted Grünenthal's submission that 'activity' could take the form of a face-to-face (1:1) call with a specified individual, or contact established when the individual was a delegate at a meeting. The Panel noted Grünenthal's submission that it did not set or incentivise expected call or contact rates, instead it was the general collective 'activity' that was monitored.

The Panel noted that although a representative might call on a doctor or other prescriber three times in a year the number of contacts with that health professional in the year might be more than that provided it was made clear that only three of those contacts could be cold calls. Without this explanation, instructions to representatives regarding interactions might advocate a course of action which was likely to breach the Code. The Panel noted that Grünenthal could organise its sales force as it saw fit but, nonetheless, had to ensure that interactions with health professionals and instructions to representatives complied with the Code. In the Panel's view companies needed to be especially cautious and therefore clear and unambiguous about Code requirements when they used terms such as 'interaction' and 'activity' which differed from the language used in the Code.

The Panel noted Grünenthal's submission that cycle plans were created by each individual representative based on their own local knowledge of what was required to drive business and the total number of interactions planned per individual target customer

was also established by the representative based on what they had the potential to achieve, and could be zero, 1, 2, 3 etc… interactions over the cycle period, including calls requested by a customer; they were not driven by the company to plan a minimum number of interactions with any given individual health professional. The Panel noted Grünenthal's submission that the default activity against all customers when working on a draft cycle plan was '1'. Representatives were instructed to increase or decrease this number accordingly for individual health professionals in order to create their overall cycle plan. The acceptance of '0' and '1' was described in briefing material sent to representatives.

Once the provisional cycle plans were created they were reviewed and/or challenged by line managers based on reasonable potential to attain the plan proposed, and adherence to compliance requirements. The Panel noted Grünenthal's submission that there was no additional review or approval step outside of this.

The Panel noted Grünenthal's submission regarding cycle plans, and how they had changed over the years. In 2013, 2014 and the first three quarters of 2015, the interaction capacity per day was set at a minimum of 2 target customers, via face to face (1:1) call or contact at a meeting, plus a requirement to add 'non-target activity' which generated a minimum of 5-7 expected interactions with health professionals per working day. In quarter 4 of 2015 and in 2016, this increased to a minimum of 3 target customer interactions per day and there was no expectation with regard to non-target activity. The Panel noted Grünenthal's submission that achievement of an individual's cycle plan each year was always based on total actual volume of calls vs total target volume so no daily call rate was required or stipulated. The complainant had not mentioned a daily call rate as implied by Grünenthal. Three cycle plans per annum with a duration of four months per cycle were introduced in 2016 as opposed to four cycles of three months previously.

The Panel considered that Grünenthal's submission that no daily call rate was required was not wholly accurate. Representatives were given a minimum interaction capacity per day and representatives' provisional cycle plans were reviewed and challenged by line managers then validated. An email dated 2 May 2014 from the commercial director to the sales force made it clear that a key performance indicator on the cycle plan data was the daily rate of work that the quarterly volume of contacts delivered. In the Panel's view, the number of expected daily interactions would include, over the cycle plan, calls on target customers and others.

The Panel noted Grünenthal's submission regarding how activity targets were bonused. A pre-qualifier based on activity volume, but not on any daily call rate, was introduced in 2014 to be eligible for the bonus scheme. It used the representatives' self-created cycle plans to ensure that activity was taking place within target areas rather than on any accessible customer. To qualify the representative had to achieve a minimum 90% of their quarterly cycle plan activity.

An additional Palexia growth element was added for the second half of 2014 but did not stipulate any activity inputs or pre qualifiers. The initial incentive scheme in 2015 included pre-qualifying criteria to attain 90% cycle plan volume but in May 2015, the scheme was retrospectively amended to remove the activity component which was re-introduced in 2016.

The Panel noted that the Grünenthal promotional teams were provided with a commercial standards document at the beginning of each year which clarified business expectations including instructions to plan activity in line with the requirements of the Code, in addition to reminders within other communications. The Commercial Directorate Standards 2015 and 2016 presentations defined a call as a one to one event with a customer and a contact as being a call or a meeting event. The documents further stated that CRM recorded customer interactions which was an internal term defined as a face-to-face call or meeting with a customer and on the same slide stated 'Our anticipated activity rates take into account the PMCPA code of conduct [respective year] and each customer should not have more than 3 unsolicited calls per year. However it is assumed a significant proportion of this activity will be on customer request'. The slide concluded that other activity could take place outside of the target lists and cycle plan and detailed that Grünenthal was resourced to deliver 5-7 total customer contacts per customer facing day. The 2016 slide stated in addition and that this activity should not compromise the target activity achievement. The Panel queried how and where this other activity taking place outside of the target lists and cycle plans would be recorded. The Panel also noted that this contradicted Grünenthal's submission that in the last quarter of 2015 and in 2016 there was no expectation with regard to non-target activity.

The 2015 Grünenthal Sales Team Incentive Scheme stated that the Palexia SvT and Versatis SvT quarterly targets were set per business unit by the CDMT. Quarterly targets were set per AR account by the business unit. These were managed by the RAM to ensure, amongst other things that there was an equal challenge per AR. This enclosure also stated that the daily interaction rate was at least 5/day to include face to face meeting interactions named and unnamed target and not target customers. There was no mention of the Code requirements in this presentation.

The Panel noted Grünenthal's submission that it discovered that three out of 56 representatives registered more than three cold calls with the same individual health professional over a calendar year (this affected 15 individual health professionals with 4-6 interactions logged as cold calls). According to Grünenthal each representative insisted that he/she had entered the majority of their calls erroneously as cold calls indicating that there had been an error in call recording within the CRM system as opposed to an error in customer facing activity; each provided confirmation to support these calls as 'requested return visits' where relevant, such that no more than three cold calls were conducted on any individual health professional.

The Panel noted that three representatives out of 25 who had started in 2014 and 2015 had not logged any cold calls when they first started seeing customers; they were confused about the definition of a cold call. Two of the three said they thought that if they were invited by a receptionist or a secretary to return at a specified time to see a health professional, this would then be classed as a 'requested return visit' rather than a cold call. According to Grünenthal this was not Grünenthal's internal standard, nor what was detailed during internal CRM training. The third individual said she incorrectly thought the 'requested return' option was to record an invitation for a future meeting (ie the health professional requested a return visit). The three representatives had not accurately recorded their interactions in the CRM system so Grünenthal did not have a clear oversight, but each representative maintained that he/she did not conduct more than three cold calls on any given individual.

The Panel noted Grünenthal's submission that the logging of calls and use of the drop-down menu to record whether a call was a cold call or a requested return visit was detailed on slide 49 of a training presentation delivered by the sales force effectiveness manager and CRM manager to the most recent group of new starters. The Panel noted Grünenthal's contradictory submission that whilst the use of the drop-down menu was not detailed on slide 49, it was discussed and demonstrated during training.

The Panel further noted Grünenthal's definitions of a 'cold call' ie a call where no prior arrangement had been made to visit/re-visit the health professional, and a 'requested return visit', used when the health professional had agreed to, or made arrangements for the representative to return to continue agreed business objectives.

The Panel noted its comments above, the training/briefing provided by Grünenthal to its representatives together with the company's definitions of 'cold call' and 'requested return visit' and understood why representatives might be confused with how to record certain activities. The Panel queried how many other representatives might be recording calls incorrectly due to confusion that was not identified during the review.

The Panel noted that whilst some documents provided by Grünenthal included the relevant Code requirements, others did not. The Panel noted that each of these documents had to standalone.

The Panel was concerned about Grünenthal's submission that as the majority of its representatives had worked the same territories with the same health professionals for a number of years, health professionals and representatives often formed relationships whereby the customer provided an invitation to a given representative to visit on a regular basis to maintain contact to ensure they remained up to date with therapy area and product developments to optimise their patient care, or they were aware of meetings and events led by or supported by Grünenthal, or to support broader understanding of clinical experience with Grünenthal products. The Panel noted Grünenthal's submission that these invitations might not be specific with reference to time or topic but were genuine and legitimate.

That a representative had a long standing relationship with a health professional when combined with the activities cited by Grünenthal did not, in the Panel's view, mean that all subsequent calls were solicited as implied. Whether such a call was solicited would depend on a consideration of all the circumstances of the case. Certainly in the Panel's view a 1:1 call in response to a broad open invitation without reference to time or topic was unlikely to be viewed as a solicited call under Clause 15.4 and its supplementary information.

The Panel was also concerned that a number of briefing documents, when referring to Clause 15.4 and its supplementary information, qualified the requirement that there be no more than three unsolicited calls per year. For instance, the 2014 Commercial Team Standards activity twice when referring to the call limit stated 'However it is assumed a significant proportion of this historic industry activity was based on customer request'. It also stated with reference to the number of unsolicited calls that 'However it is assumed that a proportion of activity will be based on customer request'. Similar qualifications were repeated in the Commercial Directorate Standards' presentations for 2015 and 2016. In the Panel's view, this qualification was misleading and downplayed the importance of the restriction on the number of cold calls and might encourage representatives to proactively seek return calls such that they might not all be *bona fide* solicited calls.

The Panel noted all of its comments above. Grünenthal had failed to be sufficiently clear about how representatives could meet the cycle plan and comply with the supplementary information to Clause 15.4. In addition, the Panel considered that Grünenthal had failed to provide its representatives with information that was sufficiently clear about the differences between call rates and contact rates within the context of the cycle plans and target interactions as referred to in the supplementary information to Clause 15.4 of the Code. The Panel ruled a breach of Clause 15.4.

The Panel noted the narrow ground of its ruling in Case AUTH/2652/11/13 wherein the complainant had alleged that an email only referred to interactions and thus failed to reflect the Code in relation to distinguishing between expected call and contact rates. A breach was ruled on the narrow ground alleged. Turning to the present case, the Panel noting its comments and ruling above considered that Grünenthal had failed to comply with its undertaking given in in Case AUTH/2652/11/13 and a breach of Clause 29 was ruled.

Whilst the Panel had concerns, as noted above, about Grünenthal's briefing of its representatives with regard to the requirements of Clause 15.4 and how calls were being logged and it noted that certain years required representatives to achieve 90% of their quarterly cycle plan to qualify for the bonus scheme, they were created based on an expected number of interactions per day as set by Grünenthal,

the Panel noted that there was no evidence before it that representatives had falsified calls and whilst the Panel was concerned about the effect of the material on representatives' behaviour, there was, on balance, no evidence that representatives over called on health professionals contrary to the requirements of Clause 15.4 as alleged and the Panel ruled no breach of that clause.

The Panel noted that Clause 15.9 required, *inter alia*, companies to prepare detailed briefing material for medical representatives on the technical aspects of each medicine which they will promote. Briefing material must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. The Panel noted its comments above and considered that briefing provided by Grünenthal to its representatives regarding the definitions of call rates and requested return visits and its qualification of the requirement that there be no more than 3 unsolicited visits per year was such that it was likely to lead to a breach of the Code. A breach of Clause 15.9 was ruled.

Noting its rulings above, the Panel considered that Grünenthal had failed to maintain high standards and a ruling of Clause 9.1 was ruled. The Panel noted that some efforts had been made to refer to the relevant requirements of the Code and comply with the undertaking but considered that overall these were insufficient. There were some references to the supplementary information to Clause 15.4 in some of the newsletters. Such newsletters largely dealt with administrative matters and the technical requirements of setting up and organising a cycle plan online rather than representatives' field activity. The Code requirements were not referred to in all relevant documents and where such references did appear they were insufficient as set out above. An undertaking was an important document. The Panel noted that inadequate action leading to a breach of undertaking was an example of an activity likely to be in breach of Clause 2. The Panel was concerned that following Case AUTH/2652/11/13, Grünenthal was still not sufficiently clear about the differences between call rates and contact rates as referred to in the relevant supplementary information within the context of representative's interactions and cycle plans. Bearing that in mind and noting its rulings above the Panel ruled a breach of Clause 2.

**2 GP-PEP**

The Panel noted that Clause 18.1 required that no gift, pecuniary advantage or benefit may be supplied, offered or promised to members of the health professions or to other relevant decision makers in connection with the promotion of medicines or as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine, subject to the provisions of Clauses 18.2 and 18.3. Clause 23.1 stated, *inter alia*, that the hiring of consultants to provide the relevant service must not be an inducement to prescribe, supply, administer, recommend, buy or sell any medicine.

The Panel noted Grünenthal' submission that health professionals did not have to have prescribed Grünenthal medicines for a described minimum number of patients before they could be selected as a speaker but Grünenthal expected speakers to have had at least some experience with their use so that they could refer to this when speaking, however no expectation was made in terms of the extent of their use. This was to ensure that speakers would be able to provide advice on how to select the right patient for different medicines, and how to treat to achieve the greatest potential pain relief. In principle, the Panel did not consider that this was unreasonable. The Panel also noted the working instruction for the conduct of PEP meetings submitted by Grünenthal included in the list of criteria for potential speakers that they should be medical doctors and/or selected nurse or pharmacist prescribers who, *inter alia*, had experience prescribing Grünenthal products which was similar to earlier versions; no version of the working instruction required that a health professional prescribe Grünenthal medicines for a minimum number of patients to be selected as a speaker as alleged. On this narrow ground no breach of Clauses 18.1 and 23.1 was ruled.

With regard to the allegation that company compliance was poorly monitored as some consultants had spoken at meetings without a contract in place and Grünenthal had failed to pay consultants for services provided, the Panel noted Grünenthal's submission that a review of all GP-PEP meetings conducted in 2014, 2015, and 2016 (over 250) found that 5 speaker agreements were signed after the meeting took place. One was signed in advance of the meeting date on an app that was being trialled but the signature did not properly load therefore a hard copy contract was signed after the event in order to allow payment to be processed. Two were signed after the event due to miscommunication between two members of staff, each of whom believed the other to be responsible for obtaining the signature. One was signed the day after the event due to a lack of oversight by the meeting organiser. One was signed after the event when numerous attempts to ask the speaker to sign the contract in advance of the meeting were not responded to by the speaker. The Panel noted that Clause 23.1 of the current Code which was Clause 20 in the Second 2012 Edition of the Code and the 2014 Code required that, *inter alia*, a written contract or agreement must be agreed in advance of the commencement of the services which specified the nature of the services to be provided and the basis for payment of those services. The Panel did not know in which year the meetings were held where the speaker agreements were signed after the meeting took place but as the complaint was received before 1 May 2016, the Panel ruled a breach of Clause 20.1 of the Code as this was the same in the Second Edition of the 2012 Code, the 2014 Code and the 2015 Code. The Panel considered that Grünenthal had failed to maintain high standards in this regard and a breach of Clause 9.1 was ruled.

The Panel then considered the allegation that representatives were set a target number of meetings to hold per quarter and although their bonus did not rely on this payment, it was listed as a key performance indicator and failure to achieve

the target level of meetings each quarter resulted in a reduction, or in some cases, a complete removal of an annual pay rise. The Panel noted Grünenthal's submission that it had never set representatives a target number of meetings to hold per quarter since the GP-PEP/PEP programme was established in 2012 and the number of meetings completed by a representative bore no impact on their bonus or annual pay rise as alleged. The Panel noted that the onus was on the complainant to prove his/her complaint on the balance of probabilities and the Panel considered that there was no evidence in this regard. The Panel thus ruled no breach of Clause 9.1.

The Panel noted its rulings above and decided that a ruling of Clause 2 which was reserved as a sign of particular censure was not warranted in this instance and no breach of that clause was ruled.

**APPEAL FROM THE COMPLAINANT**

The complainant appealed all the Panel's rulings of no breach of the Code and provided additional evidence to support each of the original allegations as follows:

**1 Activity targets for representatives**

The complainant noted that the Panel had ruled no breach of Clause 15.4 as it had no evidence that representatives had over called on health professionals contrary to the requirements of that clause.

The complainant requested that the PMCPA interrogated Grünenthal's CRM system and cycle plans submitted in 2015 by a named representative, who during this time planned to call on a named doctor 11 times in one quarter. This was originally entered as a planned activity of 13 times in one quarter but was subsequently reduced to 11 by his line manager.

**2 GP-PEP**

With regard to the Panel's rulings of no breaches of Clause 18.1 and 23.1, the complainant alleged that emails were sent regarding the minimum requirements of prescribing to be met by consultants used for GP-PEP. The requirement clearly stated that consultants should have prescribed the given medicine to a minimum of 10 patients. Grünenthal had provided the working instruction only and not any copies of email correspondence regarding sign up of consultants. The complainant unfortunately did not have copies of those emails, however, he/she alleged that if such correspondence was requested Grünenthal would have had to make those available.

The complainant alleged that a named doctor from a named hospital spoke on behalf of Grünenthal at a meeting at a named hotel in July 2015, there was no contract in place and as far as the complainant was aware there was still no contract in place.

With regard to the Panel's ruling of no breach of Clause 9.1, it stated that there was no evidence to support the complaint that representatives were targeted on the number of GP-PEP meetings and this was linked to a reduction or removal of a pay increase. In that regard, the complainant attached an appraisal documents from two years, clearly showing that GP-PEP was used as a measurable parameter of performance and was in fact given a 15% weighting in one year. The complainant noted that the Panel had noted its ruling of no breach in the above and decided that a ruling of a breach of Clause 2, which was reserved as a sign of a particular censure, was not warranted in this instance and no breach was ruled. The complainant asked that in light of the additional information and the fact that Grünenthal had responded to the PMCPA's request for information in what could only be described as a dishonest manner by withholding information and falsely representing facts, that the Appeal Board reconsider a breach of Clause 2 in this instance.

The complainant stated that in light of the seriousness of the breaches he/she wanted to be kept informed of the actions which the PMCPA would take against Grünenthal and if any individual company representatives within Grünenthal would be held accountable. It was apparent that Grünenthal had not learnt any lessons from the ruling against it in 2013 and the complainant considered that this was something that should obviously be taken extremely seriously and trusted this would be done when deciding on appropriate sanctions.

**COMMENTS FROM GRÜNENTHAL**

**1 Activity targets for representatives, Clause 15.4**

Grünenthal submitted that at the outset of investigating this complaint, all calls recorded against individual health professionals in its CRM system were assessed to identify whether more than three calls had been logged against any individual health professional in a calendar year. As detailed above three representatives were identified to have registered more than three cold calls with the same health professional over a calendar year. This affected 15 health professionals (4-6 interactions were logged as cold calls). Grünenthal interviewed each representative (including one who had retired from the organisation), and as per its submission, each insisted that they had not conducted more than three cold calls with any health professional. As previously presented, the figures identified were therefore indicative of an error in call recording in the CRM system rather than inappropriate over calling on health professionals.

Grünenthal submitted that in response to the complainant's appeal, an additional review was conducted specific to the calls that the quoted representative logged against the named doctor in 2014, 2015 and 2016. The number of interactions (planned and completed) were four face-to-face calls in 2015, and there had been four face-to-face calls to date in 2016 (there were no recorded interactions against this health professional by the quoted representative in 2014). None of these calls were 'cold calls'.

**2 GP-PEP, Clauses 18.1 and 23.1**

Grünenthal submitted that a senior manager who was in place during the time periods referred to in

the complaint had confirmed that there had never been targets associated with a minimum number of prescriptions required by health professionals in order to be considered as a speaker. Formal working instructions had been in place since the programme was initiated as stated above, and no version had ever referred to a minimum number of patients or prescriptions required in order to commission a health professional as a speaker. Grünenthal continued to refute the allegation that the GP-PEP was an inducement to prescribe, contrary to the requirements of Clause 18.1, and in addition continued to maintain that engaging health professionals as speakers in relation to this programme was appropriate and consistent with the requirements of Clause 23.1. Without copies of the emails referred to by the complainant, any further information on who might have sent such emails, or any other further or better particulars in relation to this allegation, Grünenthal regretted that it was unable to investigate this any further.

Grünenthal submitted that with regard to the review of all speaker services in 2014, 2015 and 2016 as referred to above, it was exceedingly disappointed and embarrassed that its original response was not wholly complete. In response to the complainant's comments, Grünenthal reviewed all the speaker services provided by the named doctor speaker in the stated time period and found that he/she had spoken at a meeting in July 2015 but no contract could be found, either as an electronic version attached to the record in the CRM system, or as a hard copy. The status of the meeting in the CRM system was 'Cancelled' which indicated it had not gone ahead, therefore it was not included in its initial review. Attendees were however listed as having attended the meeting, and there were associated costs which indicated the meeting did take place (although no payment had been made to the named doctor).

Grünenthal submitted that it was feasible that a contract was signed but not received by head office for payment to be processed, however, the representative who commissioned this health professional to speak had now left the company and it was unable to verify whether or not he/she created an agreement and obtained a signature covering the services provided in advance of the commencement of services or not.

Grünenthal submitted that in light of the above, it further reviewed of all the contracts assessed as part of its original submission. Grünenthal provided the raw data and summaries as an enclosure. In summary, five speaker agreements were signed after the meeting took place in 2014, and four in 2015 (none for 2016). This differed to Grünenthal's original submission where it stated five agreements had been signed after meetings had taken place. The initial manual review of all contracts in preparation for Grünenthal's original submission was conducted by sales managers and the results sent to the internal investigating manager. Unfortunately, rather than using the drop-down options that had been installed in an Excel tracker to indicate where contracts had not been signed in advance of a meeting, there were four instances of 'colour coding' the line entries instead. No explanation had been provided to the investigating manager about the use of the colour coding and as such, the numbers for Grünenthal's submission were calculated using a filter based on the selection of the assigned drop-down options. The investigating manager regretted not identifying these anomalies and querying this when the data was collated.

Grünenthal submitted that neither electronic nor hard copy contracts could be located for four speakers in 2014 and two in 2015 (including the named doctor). It was not a requirement for colleagues to upload scanned copies of signed contracts in the CRM system until mid-2015, therefore if paperwork was lost in the post before this point, Grünenthal unfortunately did not have any back-up copies. Grünenthal identified this gap in its process in mid-2015 and copies of all signed agreements must now be attached to applicable records in the CRM system for reference in such an eventuality.

Grünenthal confirmed that the seven speakers for whom it could not locate signed contracts had not been paid for the services they provided as it processed payments against agreements submitted to finance. Grünenthal did not however have any evidence that it could share with the Appeal Board to confirm that there was a signed agreement in place to cover the services provided, or that they signed contracts before the services were provided. These contracts were not identified as being missing in the original review as the instructions provided to the sales managers asked that they identify using drop-down options in an Excel tracker whether agreements with speakers had been signed in advance of the meeting, on the day of the meeting, or after the meeting. A fourth option should have been offered to indicate where no contract could be located (hard copy or electronic), but this wasn't anticipated to be seen at the outset of the investigation.

Grünenthal apologised unreservedly for the error in its original submission in which it stated that only five speaker agreements were signed after meetings took place during 2014-2016, whereas in fact the figure was nine (five in 2014 and four in 2015).

**Clause 9.1**

Grünenthal provided the full performance review document provided by the complainant for 2013 which was easier to read than the scanned images provided (Grünenthal noted that this referred only to 2013 – Grünenthal had not received any images for two years as referred to by the complainant, only those that matched the 2013 appraisal).

Grünenthal submitted that the Non-short term incentive (STI) goal 'Annual A plan objectives and activities delivery e.g. GP PEP, KnEx etc. (C= 90% of objectives met) 15%' referred to the cycle plan created by the individual themselves. As per its response above, Grünenthal had a 'bottom-up' approach to planning activities as local representatives should know how best to grow their local business. They therefore devised their own local business plan which they were assessed

against. This might include planning and delivering speaker meetings in key areas, or might not – this was determined by the representative. There was not a company standard required for each representative with regards completing a company determined number of GP-PEP meetings, as local environments differed on the potential success of being able to run meetings of this nature; each representative decided whether this was a suitable and relevant objective based on their assessment of their local environment. The performance assessment provided described a weighting of 15% given to achieving at least 90% of what the representative said they would deliver, but this was in reference to all objectives and activities that comprised the cycle plan, not just delivering speaker meetings. The representative's salary increase was not purely dependent on his/her achievement of the Non-STI Goals and core activities as documented in the 2013 appraisal form. In addition, the completion of all duties as specified in his/her job description and the individual's behaviours and approach were also considered when deciding on a salary increase. The calculation of an overall rating for representatives was determined by the line manager, comprising of their performance against core activities, non-STI goals, job requirements and behaviours. The examples of the assessment of three different representatives in 2013 were provided.

**Clause 2**

Grünenthal submitted that it had provided a complete and factually accurate submission in response to the allegation that representatives were targeted on the number of GP-PEP meetings, therefore the complainant's accusation of false representation was incorrect. Grünenthal disputed the alleged breach of Clause 2.

**FINAL COMMENTS FROM THE COMPLAINANT**

**1 Activity targets for representatives, Clause 15.4**

The complainant stated that his/her appeal was not about the number of times a representative 'cold called/spec called' a health professional and he/she had not suggested that this was the case. The appeal, actually questioned the fact that Grünenthal used cycle plans as a targeted measure for representatives on which sales bonus was or was not payable and that within those plans representatives were expected to plan more than one call per customer per quarter. The complainant submitted that he/she had stated that Grünenthal's CRM system which held the cycle plans showing calls planned on a given [health] professional over the period of a quarter would show that representatives were planning prior to a quarter to visit a health professional more times than was allowable within the Code. The complainant noted that he/she had suggested that the CRM system should have been interrogated and provided details of a cycle plan which would show a named customer whom a representative was planning to see 13 times, later reduced to 11 times in a quarter. Representatives were instructed to always change the default option to requested a return visit.

The complainant alleged that no representative could state before the beginning of a three month period that a health professional would 'request a return visit' 11 times within the next three months. To plan that level of activity and then to achieve it would suggest some inaccuracies either in the way in which these calls were recorded and a definitive plan to act in breach of the Code.

The complainant alleged that the part of the system that required interrogation was the cycle plans and not the calls logged. The complainant also suggested that as Grünenthal archived all of its CRM system data at the end of each quarter, that the archived data was checked rather than the current live data set.

**2 GP-PEP, Clauses 18.1 and 23.1**

The complainant alleged that as Grünenthal had chosen to ignore the details in his/her complaint it had failed to respond to the complaint accurately. Grünenthal had stated that 'working instructions' had been in place and that these had never stated a minimum requirement for prescribing by health professionals used as speakers. The complainant noted that Grünenthal had only provided the working instructions as its evidence in appeal but that although figures were not stated in these documents, Grünenthal had been very careful in only stating these figures in presentations at company meetings and emails. The original PEP presentation was made by several people at a company meeting. The complainant stated that with regards to the meeting at the named hotel in July 2015 where the named doctor was the speaker, he/she could categorically state, as he/she was the representative who carried out that meeting, that the meeting did take place and that the hotel was paid £400 by Grünenthal for catering costs. With this in mind the complainant failed to understand how Grünenthal could suggest that it thought that the meeting had been cancelled. The complainant stated that when he/she left Grünenthal the meeting was not marked in the system as cancelled. Again the complainant suggested that the status had been amended within the system since he/she had left the company and would again suggest that archive files be accessed in order to prove that this was the case.

Grünenthal stated that the representative responsible (the complainant) had left the company and it had been unable to verify whether a contract was signed for the services of the named doctor speaker. The complainant was extremely shocked and disappointed to read this comment as Grünenthal had his/her contact details and despite still being in contact with him/her until early 2016, Grünenthal had made absolutely no attempt to contact him/her to verify this information.

**Clause 9.1**

Firstly the complainant stated that he/she was shocked that Grünenthal, rather than accept the copy of the appraisal document which had been amended to not reveal his/her identity found the time to trawl through its system in order to identify the owner.

The complainant considered that Grünenthal's subsequent inclusion of the document was in some way made in order to intimidate.

The complainant noted the comments made by Grünenthal in its defence were at best ill-informed and at worst a poor attempt at deception. Grünenthal stated that, 'that the Non-STI goal 'Annual A Plan objectives and activities delivery eg GP PEP, KnEx etc 15%' referred to the cycle plan created by the individuals.

The complainant referred the Appeal Board to the actual document sent by Grünenthal. There were 6 Non STI goals listed as measures, each with a percentage weighting against them. The first of these referred to 'A Plan activity Cycle plan delivery x 4 (100% = call volume)' and this had a weighting of 15%. The second Non-STI goal however, specifically stated 'eg GP PEP, KnEx etc' and this too had a weighting of 15%. The complainant was disappointed that Grünenthal suggested that it had set two separate Non-STI goals on a performance review document that were identical in an attempt to defend its actions.

**Clause 2**

Despite Grünenthal's assurances that it had provided complete and factual information the complainant alleged that this was not the case. Grünenthal had either deliberately or through incompetence failed to respond to the actual points made in the appeal, instead supplying irrelevant information and failing to provide the suggested information.

From the information that Grünenthal had supplied the complainant suggested that it had taken reports from the post archived CRM data which was not representative of information which was originally submitted. Grünenthal had not tried to contact representatives about speaker contracts and instead chose to state that the representatives were not contactable. The complainant alleged this was a blatant lie. Grünenthal had deliberately misrepresented data from the PDP, again either through incompetence or as a deliberate attempt to avoid the truth.

The complainant alleged that Grünenthal had for some time a culture ensuring that call reporting within the CRM system was made in such a way as to fit in with requirements of the Code. With all of this in mind the complainant alleged that Grünenthal's actions had brought the industry in disrepute.

**APPEAL BOARD RULING**

The Appeal Board was concerned about this case noting the Panel's rulings of breaches of Clauses 15.4, 29, 9.1 and 2 (Point 1) and Clause 9.1 (Point 2) had been accepted by Grünenthal. The company referred to changes in its systems instigated as a result of this case.

**1 Activity targets for representatives**

The Appeal Board noted from the supplementary information to Clause 15.4 that the number of cold calls made on a doctor or other prescriber by a representative each year should not normally exceed three on average; the representatives from Grünenthal submitted that the company set 3 cold calls per year as an absolute which must not be exceeded. The Appeal Board noted that Grünenthal had some data to show that three of its representatives had called upon individual health professionals more than three times in a year. Upon investigation Grünenthal submitted that each representative insisted that they had recorded the calls incorrectly in the CRM system and had not cold called more than 3 times on an individual health professional.

The Appeal Board noted that in his/her appeal the complainant had alleged that during 2015 a named representative originally planned to call on a named doctor 13 times in one quarter which was subsequently reduced to 11 by the line manager. The Appeal Board noted that Grünenthal had conducted an additional review specific to the calls logged by the representative against the doctor in 2014, 2015 and 2016 and none of these were cold calls. Grünenthal submitted that the health professional in question was one of its speakers and so some of the visits to him/her would be by the local representative to get speaker agreements signed.

The Appeal Board considered it was unusual for three representatives to make the same error in call recording such that calls which were not cold calls were nonetheless recorded as such. Although the Appeal Board was concerned about these errors it noted that the burden was on the complainant to prove his/her complaint on the balance of probabilities. The Appeal Board considered that, on balance, there was insufficient robust evidence to show that representatives had over called on health professionals as alleged and it upheld the Panel's ruling of no breach of Clause 15.4. The appeal on that point was unsuccessful.

**2 GP-PEP**

The Appeal Board noted that in its response to the complaint, Grünenthal had submitted that five speaker contracts had been signed after the relevant event took place. Following the appeal Grünenthal subsequently found this to be incorrect, and its review identified nine in total (five in 2014, and four in 2015). In addition to this, Grünenthal submitted that no contracts (electronic or hard copy) could be found for four speakers in 2014, and two in 2015 (including that of a doctor named by the complainant). The Appeal Board was concerned about this omission. The Appeal Board noted from the representatives from Grünenthal that as there were no contracts for the six speakers, none had been paid.

The Appeal Board noted from the company representatives at the appeal that the meeting involving the named doctor, as referred to by the complainant in his/her appeal, had in all likelihood gone ahead as its investigation had revealed that there were expenses attached to it. Grünenthal's investigation had also revealed that that the CRM status of the meeting had been marked as cancelled

by the line manager of the representative who organised the event.

The Appeal Board noted that Clause 23.1 stated that before a consultant provided a service a written contract or agreement, which specified the nature of the services to be provided and the basis for payment of those services, had to be signed in advance. The Appeal Board noted Grünenthal's submission that neither electronic nor hard copy contracts could be located for four speakers in 2014 and two in 2015. Given the lack of evidence of an agreement in advance for these six speakers the Appeal Board ruled a breach of Clause 23.1. The appeal on that point was successful.

The Appeal Board noted that the GP-PEP Speaker Justification form (GB-MK-908-0003-T13-AA) stated that in order to decide if a health professional could be a GP-PEP speaker one of the questions to be asked was 'Does the healthcare professional have sufficient experience prescribing Palexia SR and/or Versatis for them to be considered a credible product speaker at a Grünenthal GP-PEP meeting?'. The Appeal Board queried how representatives would interpret 'sufficient' but nonetheless considered that it was reasonable for a company to establish if a speaker on a particular medicine was familiar with it. The complainant referred to emails which indicated that consultants should have prescribed the medicine to 10 patients, but did not have copies of them. In response to questioning Grünenthal had been unable to find the emails in question. The Appeal Board considered that it had no evidence to show that Grünenthal required health professionals to prescribe its medicines for a minimum number of patients before being selected as speakers as alleged and thus it upheld the Panel's ruling of no breach of Clause 18.1. The appeal on that point was unsuccessful.

The Appeal Board noted Grünenthal's submission that it had never set representatives a target number of meetings to hold per quarter since GP-PEP was established in 2012; the number of meetings completed by a representative did not affect his/her bonus or annual pay rise as alleged. The Appeal Board noted that the onus was on the complainant to prove his/her complaint on the balance of probabilities, and as it considered that there was no evidence in this regard it upheld the Panel's ruling of no breach of Clause 9.1. The appeal on that point was unsuccessful.

The Appeal Board noted its rulings above and decided that a ruling of Clause 2, which was reserved as a sign of particular censure, was not warranted in this instance and it upheld the Panel's ruling of no breach in that regard. The appeal on that point was unsuccessful.

**Complaint received** **23 February 2016**

**Case completed** **16 August 2016**

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**CASE AUTH/2836/4/16**

# ASTRAZENECA v JANSSEN

## Promotion of Invokana

**AstraZeneca UK complained about two leavepieces and a journal advertisement for Invokana (canagliflozin) issued by Janssen-Cilag.**

**Invokana was a sodium glucose co-transporter 2 inhibitor (SGLT2i) indicated to improve glycaemic control in adult type 2 diabetics: as monotherapy when diet and exercise did not provide adequate glycaemic control in those for whom using metformin was inappropriate and as add-on therapy with other glucose lowering medicines, including insulin, when these together with diet and exercise did not provide adequate glycaemic control.**

**The front page of the October 2015 leavepiece stated 'Invokana 100mg and 300mg efficacy and flexibility* at a single price'. This claim was referenced to Lavalle-González *et al* (2013), Schernthaner *et al* (2013) and the Invokana prescribing information. A footnote at the bottom of the page stated '*The recommended starting dose of Invokana is 100mg once daily. In patients tolerating Invokana 100mg once daily, who have an eGFR [estimated glomerular filtration rate] ≥60mL/min/1.73m$^2$ and need tighter glycaemic control, the dose can be increased to 300mg'.**

**Page 2 included comparisons between Invokana 100mg and 300mg and baseline and Invokana 100mg and 300mg and sitagliptin (Merck Sharp & Dohme's product Janumet). The comparison with sitagliptin was referenced to Lavalle-González *et al*. The claim on page 2 'The only SGLT2i to offer reductions in HbA1c greater than 1% across four clinical trials' was referenced to Schernthaner *et al*, Stenlöf *et al* (2013), Forst *et al* (2014) and Wilding *et al* (2013). Page 3 included claims 'Invokana can be used in combination with other anti-diabetic agents' referenced to the Invokana summary of product characteristics (SPC) and the patient information leaflet.**

**The claim on page 3 'Invokana is generally well-tolerated with a low risk of hypoglycaemia †' was referenced to Lavalle-González *et al*, and the Invokana SPC. The explanation for † appeared in very small print, amongst over 6 lines of equally small text, at the bottom of the page; the incidence of hypoglycaemia was stated (approximately 4% among treatment groups including placebo) when used as monotherapy or as add-on to metformin. Hypoglycaemia was the most commonly reported adverse reaction when Invokana was used as add-on therapy with insulin or a sulphonylurea. When Invokana was used with insulin or an insulin secretagogue (eg sulphonylurea) a lower dose of insulin secretagogue might be considered to reduce the risk of hypoglycaemia.**

**The claim 'Invokana 100mg can continue to be prescribed in patients who develop an eGFR 45-60mL/min/1.73m2‡4' was referenced to the SPC. Reference 2 was Schernthaner *et al* but it was not clear whether 2 referred to reference 2 or to m$^2$. The explanation for ‡, again in very small print at the bottom of the page, stated that the Invokana dose should be adjusted to or maintained at 100mg for patients developing moderate renal impairment (eGFR 45-60mL/min/1.73m$^2$). If renal function fell persistently below eGFR 45mL/min/1.73m$^2$ or CrCl <45mL/min [creatinine clearance] Invokana treatment should be discontinued.**

**The front page of the January 2016 leavepiece stated 'The only SGLT2 inhibitor with a proven efficacy profile vs sitagliptin in dual therapy was also referenced to Lavalle-González'.**

**AstraZeneca noted that Section 4.2 of the Invokana SPC stated that 'The recommended starting dose of canagliflozin is 100mg once daily. In patients tolerating canagliflozin 100mg once daily who have an eGFR ≥60 mL/min/1.73m$^2$ or CrCl ≥60 mL/min and need tighter glycaemic control, the dose can be increased to 300mg once daily orally'.**

**AstraZeneca alleged that promotional claims regarding the 300mg dose of Invokana that were based upon Lavalle-González *et al*, Schernthaner *et al*, Stenlöf *et al*, Forst *et al* and Wilding *et al* were misleading in breach of the Code. For example, in the October 2015 leavepiece claims were made about the efficacy of the 300mg dose, as well as its comparative efficacy vs sitagliptin. The studies used to support these claims, however, used 300mg as a starting does in SGLT2 inhibitor-naïve patients, ie in a manner inconsistent with the posology in the SPC. AstraZeneca alleged that use of these studies to substantiate claims for the 300mg dose was thus misleading. Further, comparisons to sitagliptin which referenced the above studies were misleading.**

**AstraZeneca stated that Janssen acknowledged during inter-company dialogue that no evidence existed to substantiate claims for the 300mg dose where Invokana was given in a manner consistent with the SPC. AstraZeneca alleged this breached the Code and demonstrated a failure to maintain high standards.**

**The detailed response from Janssen is given below.**

**The Panel noted that some of the studies cited in the October 2015 leavepiece used Invokana 300mg as the starting dose. This was inconsistent with the indication in the SPC that the recommended starting dose was 100mg. In certain patients the dose could be increased to 300mg.**

**The Panel noted Janssen's submission that differences in the dosing regimen during clinical development and the dosing set out in the SPC were common in conditions when patients might require different doses to manage their condition. The Panel also noted that there was no recommended**

**time period in the SPC for the 100mg dose before a patient could have a dose increase to 300mg.**

**The Panel noted Janssen's submission that some of SPC data were from studies in which treatment was started at 300mg rather than 100mg and increasing to 300mg as required. Section 4.8, Undesirable effects stated that the safety evaluation included patients treated with 100mg and 300mg Invokana who took part in nine phase 3 clinical studies. Section 5.1, Pharmacodynamic properties, stated beneath the heading 'Clinical efficacy and safety' that 10,285 type 2 diabetics participated in nine double-blind controlled clinical efficacy and safety studies conducted to evaluate the effects of Invokana on glycaemic control. It appeared to the Panel that the studies in Sections 4.8 and 5.1 were the same.**

**The Panel considered that data in the SPC could be used in promotional material provided it was presented in context. The Panel noted that Table 2 in Section 5.1 compared efficacy results from placebo-controlled clinical studies at 26 weeks (18 weeks when added to insulin therapy). It included a comparison of Invokana 100mg and 300mg as an add-on to metformin at 26 weeks and included data on reductions in HbA1c (-0.94 from baseline (7.95)) for 300mg dose and in weight (85.4kg at baseline reduced by 4.2% for 300mg dose). This section of the SPC also stated that in placebo-controlled studies Invokana 100mg and 300mg resulted in mean reductions in systolic blood pressure of -3.9mmHg and 5.3mmHg respectively compared to placebo. This section of the SPC did not give any details about the starting dose of Invokana ie whether it was 100mg or 300mg or whether there were any differences resulting from starting with 300mg compared to 100mg Invokana. Neither was this detail included in the leavepiece. The leavepiece gave results at 52 weeks. The SPC only included data at 26 weeks.**

**The Panel also noted AstraZeneca's submission that Janssen acknowledged there was no published evidence regarding whether there was a clinically meaningful difference in the observed efficacy of Invokana 300mg whether it was initiated at the start of therapy or following the 100mg dose.**

**The efficacy results from active-controlled clinical studies were given in Table 3 of the SPC and included a comparison with sitagliptin as triple therapy (with metformin and sulphonylurea) at 52 weeks. There was no data in the SPC setting out the comparison in the leavepiece ie comparing sitagliptin and Invokana 100mg and 300mg as add-on therapy to metformin alone. The SPC did not include comparisons of Invokana and sitagliptin in relation to their effects on systolic blood pressure.**

**The Panel noted that the claims in the leavepiece comparing sitagliptin and Invokana 300mg as add-on to metformin were based on the registration studies not all of which were included in detail in the SPC including in Table 3.**

**The Panel considered it was very difficult to understand the basis of the comparison on page 2 of the leavepiece as the claims were followed by * and the explanation was provided within over 6 lines of small type at the foot of page 3. It was not clear on page 2 that the recommended starting dose was 100mg Invokana.**

**The Panel noted AstraZeneca's allegation that it was a breach of the Code to use references from studies starting at 300mg Invokana to support claims in the leavepiece. The Panel noted Janssen's submission that the data in the leavepiece were from the pivotal registration studies, reviewed by the Committee for Medicinal Products for Human Use (CHMP) as part of the marketing authorization and the SPC was based on these data. The Panel noted Janssen's submission that the SPC included data where treatment started with 300mg Invokana rather than being increased from 100mg. The Panel therefore considered on the very narrow grounds of the complaint that it was not necessarily inconsistent with the SPC to cite studies with a starting dose of Invokana of 300mg in the leavepiece as alleged. Similarly, the use of these references to substantiate claims for 300mg Invokana was not necessarily misleading as alleged. There was no complaint that the detailed data in the leavepiece was inconsistent with the detailed data in the SPC. No breach of the Code was ruled which was upheld on appeal by AstraZeneca.**

**With regard to the comparison with sitagliptin the Panel noted its ruling above and decided that was also relevant here. The Panel ruled no breach of the Code which was upheld on appeal by AstraZeneca.**

**The Panel noted that none of the five studies cited on page 3 for the Invokana 300mg dose claims started patients on 100mg and increased up to 300mg Invokana as stated in the indication section of the SPC. AstraZeneca alleged that there was no data to substantiate claims for the 300mg dose when given in a manner consistent with the SPC. The Panel noted its comments above regarding the SPC which included Invokana 300mg data as a starting dose. It decided that, on balance, in general the claims could be substantiated by the studies cited. However, the Panel noted page 3 included a claim that Invokana reduced HbA1c greater than 1% across four clinical trials. This was not so as at week 52 in Wilding *et al* (one of the four cited studies) 300mg Invokana reduced HbA1c by 0.96%. Thus the Panel ruled a breach of the Code.**

**In the circumstances, the Panel did not consider that there had been a failure to maintain high standards. No breach of the Code was ruled which was upheld on appeal by AstraZeneca.**

**The journal advertisement, dated September 2015, was headed 'Invokana 100mg and 300mg efficacy and flexibility* at a single price'. A footnote in very small print at the bottom of the page stated '*The recommended starting dose of Invokana is 100mg once daily. In patients tolerating Invokana 100mg once daily, who have a eGFR ≥60mL/min/1.73m$^2$ and need tighter glycaemic control, the dose can be increased to 300mg'.**

**The heading was followed by hanging signs representing cost, reductions in HbA1c, kg and mmHg. There were then sections headed 'Invokana 100mg' and 'Invokana 300mg'. The Invokana 100mg section included favourable comparison in HbA1c, weight and blood pressure reductions vs sitagliptin in dual therapy as add-on therapy to metformin referenced to Lavalle-González *et al*. The Invokana 300mg section included favourable comparison with HbA1c, weight and blood pressure reductions with sitagliptin in dual and triple therapy as add-on to metformin and as add-on to metformin and sulphonylurea. Each section contained comparisons between the Invokana dose and sitagliptin.**

**The same claim appeared on the front page of the October 2015 leavepiece which was also followed by the hanging signs.**

**AstraZeneca alleged that 'flexibility' breached the Code and was inconsistent with the SPC. The journal advertisement used 'flexibility' in its title and gave equal prominence to the 100mg and 300mg doses implying that 300mg dose could be initiated and/or administered interchangeably with 100mg. This impression was not negated by the small footnote near the bottom of the page that 'The recommended starting dose of INVOKANA is 100mg once-daily. In patients tolerating INVOKANA 100mg once-daily, who have an eGFR ≥60ml/min/1.73m$^2$ and need tighter glycaemic control, the dose can be increased to 300mg once-daily'.**

**AstraZeneca stated that the same was true for the October 2015 leavepiece.**

**AstraZeneca alleged that 'flexibility' constituted promotion outside the scope of the marketing authorization; the claim was misleading and as it was not possible to substantiate claims around 'flexibility' this was a failure to maintain high standards.**

**The Panel considered that the claim in the advertisement ('Invokana 100mg and 300mg efficacy and flexibility at a single price)' did not make it sufficiently clear where each dose fitted in to the treatment pathway. The Panel did not accept Janssen's submission that the claim was qualified by the use of the asterisk and its explanation regarding the recommended starting dose. It was a principle under the Code that claims should not be qualified by footnotes, they should be capable of standing alone as regards accuracy etc.**

**The Invokana SPC was clear that the recommended starting dose was 100mg once daily. There was no indication in the posology section as to how long the 100mg starting dose should be used before increasing it to 300mg in appropriate patients.**

**The Panel considered that the claim 'flexibility' could be read as relating to the starting dose and not as submitted by Janssen that some patients started out on 100mg could increase their dose to 300mg and this would not mean an increase in cost. The Panel considered that the claim was misleading and inconsistent with the SPC. The Panel ruled breaches of the Code. With regard to substantiation the Panel accepted that there was data relating to both doses and in relation to starting with the 300mg dose as referred to above. The Panel thus ruled no breach of the Code which was upheld on appeal by AstraZeneca.**

**On balance, the Panel did not consider that the claim meant that high standards had not been maintained and no breach of the Code was ruled which was upheld on appeal by AstraZeneca.**

**AstraZeneca alleged that overall the claims at issue represented a deliberate attempt to misrepresent the facts and noted that the European Public Assessment Report for Invokana twice stated that patients should always be initiated on the 100mg dose for safety reasons.**

**AstraZeneca therefore alleged that use of the word 'flexibility' had the potential to compromise patient safety and to bring discredit to, and reduce confidence in, the pharmaceutical industry in breach of Clause 2.**

**The Panel noted its rulings above. It did not consider that the use of the word 'flexibility' compromised patient safety such that Janssen had brought discredit upon or reduced confidence in the pharmaceutical industry. The Panel therefore ruled no breach of Clause 2 of the Code which was upheld on appeal by AstraZeneca.**

AstraZeneca UK Limited complained about the promotion of Invokana (canagliflozin) by Janssen-Cilag Ltd. The materials at issue were two leavepieces (refs October 2015 PHGB/VOK/0815/0020 and January 2016 PHGB/VOK/0815/0020(1)) and a journal advertisement (ref September 2015 PHGB/VOC/0815/0018).

Invokana was a sodium glucose co-transporter 2 inhibitor (SGLT2i) indicated for the treatment of type 2 diabetes mellitus in adults to improve glycaemic control: as monotherapy when diet and exercise did not provide adequate glycaemic control in patients for whom using metformin was inappropriate due to intolerance or contraindications and as add-on therapy with other glucose lowering medicinal products, including insulin, when these together with diet and exercise did not provide adequate glycaemic control.

**1 Starting dose**

The front page of the October 2015 leavepiece stated 'Invokana 100mg and 300mg efficacy and flexibility* at a single price'. This claim was referenced to Lavalle-González *et al* (2013), Schernthaner *et al* (2013) and the Invokana prescribing information. A footnote at the bottom of the page stated '*The recommended starting dose of Invokana is 100mg once daily. In patients tolerating Invokana 100mg once daily, who have an eGFR [estimated glomerular filtration rate] ≥60mL/min/1.73m$^2$ and need tighter glycaemic control, the dose can be increased to 300mg'.

Page 2 included comparisons between Invokana 100mg and 300mg and baseline and Invokana 100mg and 300mg and sitagliptin (Merck Sharp & Dohme's

product Janumet). The comparison with sitagliptin was referenced to Lavalle-González *et al*. The claim on page 2 'The only SGLT2i to offer reductions in HbA1c greater than 1% across four clinical trials' was referenced to Schernthaner *et al*, Stenlöf *et al* (2013), Forst *et al* (2014) and Wilding *et al* (2013). Page 3 included claims 'Invokana can be used in combination with other anti-diabetic agents' referenced to the Invokana summary of product characteristics (SPC) and the patient information leaflet.

The claim on page 3 'Invokana is generally well-tolerated with a low risk of hypoglycaemia †' was referenced to Lavalle-González *et al*, and the Invokana SPC. The explanation for † appeared in very small print, amongst over 6 lines of equally small text, at the bottom of the page; the incidence of hypoglycaemia was stated (approximately 4% among treatment groups including placebo) when used as monotherapy or as add-on to metformin. Hypoglycaemia was the most commonly reported adverse reaction when Invokana was used as add-on therapy with insulin or a sulphonylurea. When Invokana was used with insulin or an insulin secretagogue (eg sulphonylurea) a lower dose of insulin secretagogue might be considered to reduce the risk of hypoglycaemia.

The claim 'Invokana 100mg can continue to be prescribed in patients who develop an eGFR 45-60mL/min/1.73m$^2$‡4' was referenced to the SPC. Reference 2 was Schernthaner *et al* but it was not clear whether 2 referred to reference 2 or to m$^2$. The explanation for ‡, again in very small print at the bottom of the page, stated that the Invokana dose should be adjusted to or maintained at 100mg for patients developing moderate renal impairment (eGFR 45-60mL/min/1.73m$^2$). If renal function fell persistently below eGFR 45mL/min/1.73m$^2$ or CrCl <45mL/min [creatinine clearance] Invokana treatment should be discontinued.

The front page of the January 2016 leavepiece stated 'The only SGLT2 inhibitor with a proven efficacy profile vs sitagliptin in dual therapy was also referenced to Lavalle-González'.

**COMPLAINT**

AstraZeneca noted that Section 4.2 of the Invokana SPC stated:

> 'The recommended starting dose of canagliflozin is 100mg once daily. In patients tolerating canagliflozin 100mg once daily who have an eGFR ≥60mL/min/1.73m$^2$ or CrCl ≥60mL/min and need tighter glycaemic control, the dose can be increased to 300mg once daily orally.'

AstraZeneca alleged that promotional claims regarding the 300mg dose of Invokana that were based upon the studies referenced, Lavalle-González *et al*, Schernthaner *et al*, Stenlöf *et al*, Forst *et al* and Wilding *et al* were misleading in breach of the Code. For example, in the October 2015 leavepiece claims about the efficacy of the 300mg dose and its comparative efficacy vs sitagliptin were studies in which the 300mg dose was indicated in SGLT2 inhibitor-naïve patients, ie in a manner inconsistent with the posology in the SPC. AstraZeneca alleged that use of these studies to substantiate claims for the 300mg dose was thus misleading in breach of Clause 7.2. Further, comparisons with sitagliptin which referenced the above studies breached Clause 7.3. While the October 2015 leavepiece had been withdrawn, similar claims were made in more recent promotional items such as the January 2016 leavepiece.

AstraZeneca referred to Janssen's notes on the inter-company telephone call on 16 March 2016, which stated:

> '[T]here was no published evidence to suggest that there either is or is not a clinical meaningful difference in the observed efficacy of canagliflozin 300mg whether it was initiated at the start or following the titration posology stated in the SPC.'

AstraZeneca alleged that Janssen therefore acknowledged that no evidence existed to substantiate claims for the 300mg dose where Invokana was given in a manner consistent with the SPC. AstraZeneca alleged this breached Clause 7.4 and demonstrated a failure to maintain high standards in breach of Clause 9.1.

**RESPONSE**

Janssen stated that there were two approved doses 100mg and 300mg, and the posology section of the SPC stated:

> 'The recommended starting dose of canagliflozin is 100mg once daily. In patients tolerating canagliflozin 100mg once daily who have an eGRR ≥ 60mL/min/1.73m$^2$ or CrCl ≥ 60mL/min and need tighter glycaemic control, the dose can be increased to 300mg once daily orally.'

Invokana 100mg and 300mg had been the same list price since August 2015. Efficacy and tolerability data were presented in promotional materials for the 100mg and 300mg doses and it was always made clear within materials that patients should be started on Invokana 100mg.

Janssen refuted AstraZeneca's allegations that claims around 300mg Invokana could not be substantiated and it was misleading to promote results from the pivotal registration studies using Invokana 300mg because of the difference between the Invokana dosing schedule in the clinical development programme and the SPC posology (ie initiate Invokana on 100mg and increase to 300mg if tighter glycaemic control was needed). Janssen submitted that the claims were based on the marketing authorization for Invokana on the approved patient population (adults with type 2 diabetes). The claims could be substantiated by both the provision of the SPC and published papers. Janssen did not agree that it had not maintained high standards (Clause 9.1).

Janssen submitted that claims in relation to 300mg Invokana were referenced to published data from the studies in the extensive clinical development

programme. These studies formed part of the submission to the regulatory authorities and were in the marketing authorizations for both doses. The SPC included data from nine phase 3 clinical studies, eight of which had the doses of 100mg and 300mg Invokana. Results from these studies demonstrated the safety and efficacy profiles of the maintenance doses of 100mg, 300mg Invokana and comparator(s) during the clinical studies and at the study endpoints. The details in Section 4, Clinical particulars, of the SPC were based on the data from these clinical studies.

Janssen stated that in nine phase 3 studies Invokana was studied as an initiation dose and maintenance dose of 100mg or 300mg compared with placebo or active control: as monotherapy and add-on therapy with glucose-lowering medicines including insulin, when diet and exercise alone did not provide adequate glycaemic control. Efficacy results of these studies were described in Section 5.1, Pharmacodynamic properties, and summarised in Tables 2 (Efficacy results from placebo-controlled clinical studies) and 3 (Efficacy results from active-controlled clinical studies) in the SPC. Adverse event information from these studies were assessed and formed part of the overall safety assessment of both doses of Invokana described in Section 4.8, Undesirable effects, of the SPC, which was summarised in Table 1 (Tabulated list of adverse reactions (MedDRA) [ Medical Dictionary of Regulatory Activities] from placebo-controlled studies and from postmarketing experience). All of these studies, except the ongoing cardiovascular safety study, had been published.

Janssen submitted that in line with accepted clinical practice, the posology in the SPC recommended that patients started at the lowest effective dose and then increased if the patient tolerated the 100mg dose and additional efficacy was required. This posology had been determined from the submitted package outlined above.

Janssen submitted that it took patient safety extremely seriously and recognised that in promotional material it needed clarity that the licence recommended initiation on Invokana 100mg with patients increased to 300mg where appropriate. Thus, Janssen had always made clear the licensed posology in promotional materials.

Janssen noted that differences in dosing regimen during clinical development and recommended posology after marketing approvals were common in conditions where patients might require different doses to manage their condition and in order to reach individual treatment goals, eg anti-hyperglycaemic agents, antihypertensive and lipid lowering agents. AstraZeneca, as well as others carried licences for their medicines where similar decisions had been made by the regulatory authorities on data packages where no 'step up' data was submitted.

The clinical study designs, the results in conjunction with the SPC were reviewed by the Committee for Human Medicinal Products (CHMP) and authorized by the European Commission. The CHMP had access to full data from the clinical programme and approved the posology in the SPC based on the information provided. Janssen submitted that the experience and access to data by this committee was more relevant than the experience and access to data available to AstraZeneca. Indeed, AstraZeneca's assertion that Janssen could not use the pivotal registration studies that formed the basis of the marketing authorization to substantiate claims for the 300mg dose was tantamount to saying it could not promote 300mg Invokana.

In summary, Janssen submitted that it had clearly presented information on 100mg Invokana, 300mg Invokana, placebo and/or active control (if included in the study referenced) and the posology for use. The claims for the efficacy of Invokana 300mg were in line with the SPC and could be substantiated. Based on the evidence above, Janssen refuted the allegations that claims for Invokana 300mg were inaccurate, unbalanced, unfair, not objective, ambiguous, outdated, misleading, not capable for substantiation and that Janssen had not maintained high standards. Thus, Janssen denied breaches of Clauses 7.2, 7.3, 7.4 and 9.1.

**PANEL RULING**

The Panel noted that some of the studies cited in the October 2015 leavepiece used Invokana 300mg as the starting dose. This was inconsistent with the indication in the SPC that the recommended starting dose was 100mg. In certain patients the dose could be increased to 300mg.

The Panel noted Janssen's submission that differences in the dosing regimen during clinical development and the dosing set out in the SPC were common in conditions when patients might require different doses to manage their condition. The Panel also noted that there was no recommended time period in the SPC for the 100mg dose before a patient could have a dose increase to 300mg.

The Panel noted Janssen's submission that some of the data included in the SPC were from studies in which treatment was started at 300mg rather than 100mg and increasing the dose as required. Section 4.8, Undesirable effects, stated that the safety evaluation included patients treated with 100mg and 300mg Invokana who took part in nine phase 3 clinical studies. Section 5.1, Pharmacodynamic properties, stated beneath the heading 'Clinical efficacy and safety' that 10,285 type 2 diabetics participated in nine double-blind, controlled clinical efficacy and safety studies conducted to evaluate the effects of Invokana on glycaemic control. It appeared to the Panel that the studies in Sections 4.8 and 5.1 were the same.

The Panel considered that if the data was in the SPC it could, of course, be used in promotional material provided such data was presented in context. The Panel noted that Table 2 in Section 5.1 compared efficacy results from placebo-controlled clinical studies at 26 weeks (18 weeks when added to insulin therapy). It included a comparison of Invokana 100mg and 300mg as an add-on to metformin at

26 weeks and included data on reductions in HbA1c (-0.94 from baseline (7.95)) for 300mg dose and in weight (85.4kg at baseline reduced by 4.2% for 300mg dose). This section of the SPC also stated that in placebo-controlled studies Invokana 100mg and 300mg resulted in mean reductions in systolic blood pressure of -3.9mmHg and 5.3mmHg respectively compared to placebo. This section of the SPC did not give any details about the starting dose of Invokana ie whether it was 100mg or 300mg or whether there were any differences resulting from starting with 300mg compared to 100mg Invokana. Neither was this detail included in the leavepiece. The leavepiece gave results at 52 weeks. The SPC only included data at 26 weeks.

The Panel also noted AstraZeneca's submission that Janssen acknowledged there was no published evidence regarding whether there was a clinically meaningful difference in the observed efficacy of Invokana 300mg whether it was initiated at the start of therapy or following the 100mg dose.

The efficacy results from active-controlled clinical studies were given in Table 3 of the SPC and included a comparison with sitagliptin as triple therapy (with metformin and sulphonylurea) at 52 weeks. There was no data in the SPC setting out the comparison in the leavepiece ie comparing sitagliptin and Invokana 100mg and 300mg as add-on therapy to metformin alone. The SPC did not include comparisons of Invokana and sitagliptin in relation to their effects on systolic blood pressure.

The Panel noted that the claims in the leavepiece comparing sitagliptin and Invokana 300mg as add-on to metformin were based on the registration studies not all of which were included in detail in the SPC including in Table 3.

The Panel considered it was very difficult to understand the basis of the comparison on page 2 of the leavepiece as the claims were followed by * and the explanation was provided within over 6 lines of small type at the foot of page 3. It was not clear on page 2 that the recommended starting dose was 100mg Invokana.

The Panel noted AstraZeneca's allegation that it was a breach of the Code to use references from studies starting at 300mg Invokana to support claims in the leavepiece. The Panel noted Janssen's submission that the data in the leavepiece were from the pivotal registration studies, reviewed by the CHMP as part of the marketing authorization and the SPC was based on these data. The Panel noted Janssen's submission that the SPC included data where treatment started with 300mg Invokana rather than being increased from 100mg. The Panel therefore considered on the very narrow grounds of the complaint that it was not necessarily inconsistent with the SPC to use studies with a starting dose of Invokana of 300mg as references to claims in the leavepiece as alleged. Similarly, the use of these references to substantiate claims for 300mg Invokana was not necessarily misleading as alleged. There was no complaint that the detailed data in the leavepiece was inconsistent with the detailed data in the SPC. No breach of Clause 7.2 was ruled. This ruling was appealed.

With regard to the comparison with sitagliptin the Panel noted its ruling above and decided that was also relevant here. The Panel ruled no breach of Clause 7.3. This ruling was appealed.

The Panel noted that none of the five studies cited on page 3 for the Invokana 300mg dose claims started patients on 100mg and increased the dose to 300mg Invokana as stated in the indication section of the SPC. AstraZeneca alleged that there was no data to substantiate claims for the 300mg dose when given in a manner consistent with the SPC. The Panel noted its comments above regarding the SPC which included Invokana 300mg data as a starting dose. It decided that, on balance, in general the claims were capable of substantiation by the studies cited. However, the Panel noted page 3 included a claim that Invokana reduced HbA1c greater than 1% across four clinical trials. This was not so as at week 52 in Wilding *et al* (one of the four cited studies) 300mg Invokana reduced HbA1c by 0.96%. Thus the Panel ruled a breach of Clause 7.4 of the Code.

In the circumstances, the Panel did not consider that there had been a failure to maintain high standards. No breach of Clause 9.1 was ruled. This ruling was appealed.

**APPEAL BY ASTRAZENECA**

AstraZeneca noted that Section 4.2 of the Invokana SPC stated:

> 'The recommended starting dose of canagliflozin is 100mg once daily. In patients tolerating canagliflozin 100mg once daily who have an eGFR≥60mL/min/1.73m$^2$ or CrCl≥60mL/min and need tighter glycaemic control, the dose can be increased to 300mg once daily orally.'

AstraZeneca stated that as noted by the Panel, it was possible to use data from all sections of the SPC provided that it was presented in context. For example in Cases AUTH/2506/5/12 and AUTH/2507/5/12, the Panel considered that data in sections other than 4.2 of the SPC might be used in promotional material but such references should be secondary to the statement in Section 4.2 in relation to the recommended posology.

AstraZeneca alleged that efficacy claims for the 300mg dose implied that such results could be expected when the medicine was initiated as per the SPC. This was not the case given that the substantiation provided for the comparisons, Lavalle-Gonzalez *et al*, Schernthaner *et al*, Stenlöf *et al*, Forst *et al* and Wilding *et al*, were studies in which Invokana was started at a dose of 300mg. This was misleading, in breach of Clause 7.2, as it was not possible to state on the basis of these studies, what results could be expected when Invokana was used in line with the licensed posology.

AstraZeneca alleged that in the study used to substantiate comparative efficacy for Invokana 300mg vs sitagliptin (Schernthaner *et al*), sitagliptin was given as recommended in Section 4.2 of its SPC, while Invokana was not. This comparison created

a misleading impression, in breach of Clause 7.3, as it was not possible to draw conclusions on the comparative efficacy of these agents where Invokana was used in line with the licensed posology.

AstraZeneca noted that it had originally also alleged a breach of Clause 7.4 on this point given that, by Janssen's admission during inter-company dialogue, no data existed to substantiate these claims where Invokana was given in line with the licensed posology. AstraZeneca submitted that as the Panel ruled a breach of Clause 7.4 on a separate point from that alleged, it was unable to pursue this matter.

AstraZeneca alleged that the efficacy claims at issue for Invokana 300mg were presented prominently and constituted a core component of Janssen's promotional campaign. Given the totality of the above, it amounted to a failure to maintain high standards in breach of Clause 9.1.

AstraZeneca alleged that if the studies cited were used to support claims for the 300mg dose, it should be made clear that these results were obtained when the medicine was initiated in a manner different to that described in Section 4.2 of the SPC. Such data should be presented alongside data for Invokana 100mg.

**RESPONSE FROM JANSSEN**

Janssen submitted that AstraZeneca originally alleged that promotional claims for Invokana 300mg that were based upon the studies were misleading and in breach the Code. Given that the studies administered Invokana in a manner inconsistent with the SPC, AstraZeneca alleged that use of these studies to substantiate claims for the 300mg dose was misleading.

Janssen addressed the complaint on the grounds that it was acceptable to make efficacy claims based on the pivotal study results of a regulatory approved medicine when the study designs were not identical to the posology but still consistent with the SPC. Inter-company dialogue and the response to the Panel were based on AstraZeneca's original complaint that Janssen could not use pivotal registration trials to substantiate efficacy claims for Invokana 300mg, as patients had not been initiated on 100mg and then increased to 300mg, as per the posology of the Invokana SPC. Janssen submitted this was a direct challenge to a regulatory decision and tantamount to stating that Janssen could not promote Invokana 300mg. Furthermore, Janssen highlighted that such an approach would set a precedent that would affect the promotion of multiple regulatory approved medicines across the industry.

In its appeal, AstraZeneca had modified the complaint and introduced an altered position ie that pivotal studies using Invokana 300mg could be used to substantiate 300mg efficacy claims if a qualifying statement was added, which was secondary to the statement in Section 4.2 of SPC and was presented alongside data for 100mg.

Janssen was deeply concerned that AstraZeneca had broadened the grounds of its complaint and introduced past cases during the appeal process. Janssen did not have the opportunity to discuss these cases nor the AstraZeneca altered view during inter-company dialogue or at the initial PMCPA complaint.

Janssen noted that in the previous cases cited by AstraZeneca, the respondents were found in breach of the Code by promoting off-licence due to misleading presentation of 15-month efficacy data, which was outside the licensed treatment period of 12 months and did not fairly reflect the safety data. Janssen submitted that these cases were not comparable to this case.

Although Janssen accepted the rulings of breaches of Clauses 3.2 and 7.2 with regard to the claim 'Invokana 100mg and 300mg efficacy and flexibility at a single price', and accepted the Panel ruling that 'the claim 'flexibility' could be read as relating to the starting dose', it never claimed that patients could be initiated on 300mg. All materials included a statement confirming:

> 'The recommended starting dose of Invokana is 100mg once-daily. In patients tolerating Invokana 100mg once-daily, who have an eGFR ≥60/mL/min/1.73m$^2$ and need tighter glycaemic control, the dose can be increased to 300mg once-daily.'

Janssen corrected the statement from AstraZeneca that Janssen had admitted during inter-company dialogue, that no data existed to substantiate the claims where Invokana was given in line with the licensed posology. Janssen submitted that this did not accurately reflect the inter-company dialogue on 16 March 2016 as stated in the complaint above that there was '**no published**' evidence to suggest that there either was or was not a clinical meaningful difference in the observed efficacy of Invokana 300mg whether it was initiated at start or following dose regimen stated in the SPC (emphasis added).

Janssen submitted that it had unpublished data from a 26-week simulation study to assess the pharmacokinetic and pharmacodynamic HbA1c profiles of Invokana, using FDA approved modelling strategy. It demonstrated '… there are no differences in HbA1c reduction at 26 weeks between the groups started on 100mg and increased to 300mg and the group initiated and maintained at 300mg dose'. Janssen had not presented this data during inter-company dialogue because originally AstraZeneca complained that Janssen could not use the pivotal registration studies to substantiate Invokana 300mg efficacy claims due to differences in clinical trial design and SPC posology. The simulation study was not relevant to address AstraZeneca's original position.

Due to the altered position of the AstraZeneca complaint during the appeal process, and the misrepresentation by AstraZeneca that no data existed to substantiate the claims where Invokana was given in line with the licensed posology, Janssen submitted that it was now necessary to include new information for consideration: modelling data mentioned above; the pharmacodynamics and pharmacokinetics data in the SPC and a published phase 4 study (Rodbard *et al*, 2016) which showed

that clinical efficacy using a dose escalation schedule from Invokana 100mg to 300mg was consistent with previous pivotal studies where patients started on Invokana 300mg. These data were fundamental to Janssen's response to AstraZeneca's new and broadened challenge.

Janssen submitted that all Invokana promotional materials included data on 100mg and 300mg and always included information that patients should be started on 100mg Invokana in line with the licensed posology. Invokana 300mg was always represented together with 100mg and in the context of the licensed indication.

Janssen submitted that the two four page leavepieces at issue contained information about the efficacy of Invokana 100mg and 300mg with prominent information on the back page about the posology.

Janssen submitted that the one page advertisement contained information about the efficacy of Invokana 100mg and 300mg and had a statement:

> 'The recommended starting dose of Invokana is 100mg once-daily. In patients tolerating Invokana 100mg once-daily, who have an eGFR ≥60ml/min/1.73m$^2$ and need tighter glycaemic control, the dose can be increased to 300mg once-daily.'

Janssen acknowledged the flexibility claim in the advertisement could be misread and accepted the Panel's ruling and submitted that all other materials and claims were clear, not misleading and in line with the SPC.

Janssen emphasised that all 300mg efficacy claims made in the materials in question were presented within context of the licensed indication of Invokana and referenced to respective published clinical reports. Janssen did not promote the initiation of treatment on Invokana 300mg.

Efficacy claims of Invokana 300mg from pivotal studies were consistent with the marketing authorization, referenced to published data from the studies in the extensive clinical development programme, contained within SPC and were in line with the Code.

There were 9 pivotal phase 3 studies in the Invokana clinical development programme; patients were started and continued on a dose of either Invokana 100mg or 300mg, compared to the control group which started on either placebo or active comparators, for example sitagliptin (Schernthaner *et al*). The purpose of these studies was to examine efficacy and tolerability of Invokana.

Comprehensive efficacy and safety data collected in these pivotal studies formed part of the regulatory submission and data from these studies were included in the SPC as part of the marketing authorizations for Invokana. The clinical study designs and the results in conjunction with the SPC were reviewed by CHMP and authorized by the European Commission. The assessment was detailed in Section 2.5.4 Conclusions on the clinical efficacy of the European Public Assessment Report (EPAR) and stated:

> 'In the clinical program, both the 100mg and 300mg dose were shown to be efficient.'

Posology was detailed in Janssen promotional material, including its leavepieces, to ensure dosing information was available. Janssen had never claimed the patients could be initiated on 300mg.

Janssen submitted that it was clear from the pharmacodynamic and pharmacokinetic data detailed in the SPC that the glucose lowering effects of Invokana were maximal after day one of treatment and sustained over the treatment period. In addition, plasma concentration (Cmax) and area under curve (AUC) of Invokana increased in a dose proportional manner and patients reached a steady Cmax and AUC within 4-5 days after dose escalation from 100mg to 300mg.

Section 5.1 Pharmacodynamic properties stated:

> 'Fasting plasma glucose. In four placebo-controlled studies, treatment with canagliflozin as monotherapy or add-on therapy with one or two oral glucose-lowering medicinal products resulted in mean changes from baseline relative to placebo in FPG of -1.2mmol/L to -1.9mmol/L for canagliflozin 100mg and -1 9mmol/L to -2.4mmol/L for canagliflozin 300mg, respectively. These reductions were sustained over the treatment period and near maximal after the first day of treatment.'

Section 5.2 Pharmacokinetic properties stated:

> 'Plasma Cmax and AUC of canagliflozin increased in a dose-proportional manner from 50mg to 300mg. The apparent terminal half-life (t1/2) (expressed as mean ± standard deviation) was 10.6 ± 2.13 hours and 13.1 ± 3.28 hours for the 100mg and 300mg doses, respectively. Steady-state was reached after 4 days to 5 days of once-daily dosing with canagliflozin 100mg to 300mg.'

Janssen submitted that since the glucose lowering effect of Invokana was maximal after day one and a steady state plasma concentration was reached within 4-5 days following dose escalation, there was no scientific reason to expect a difference in clinical efficacy after 26 and 52 weeks if patients were started on 300mg vs if they were started at 100mg and the dose increased to 300mg.

Janssen reiterated that all efficacy claims in its promotional materials were made at endpoints (26 or 52 weeks), within the licensed indication of Invokana, referenced to respective published clinical reports.

Janssen submitted that as indicated above, there was no published data when inter-company dialogue took place to suggest a clinical meaningful difference when patients were initiated on Invokana 300mg or 100mg and increased to 300mg. However Janssen had unpublished modelling data which had established there were no expected differences

in HbA1c reduction at week 26 between initiating Invokana 300mg vs initiating Invokana 100mg and increasing to 300mg.

Janssen submitted that based on the pharmacokinetics, pharmacodynamics, the modelling data and now the published phase 4 study, it was possible to state what results would be expected if Invokana was used in line with SPC posology. Janssen never stated that efficacy claims were based on dosing similar to the posology in the SPC. Janssen thus did not agree that it was necessary to indicate that results from the pivotal studies were initiated in a manner different to Section 4.2 of the SPC. Janssen refuted breaches of Clauses 7.2, 7.3 and 9.1.

Janssen submitted that the inter-company dialogue was based on AstraZeneca's original complaint that the pivotal clinical trials could not be used to substantiate the efficacy claims of Invokana 300mg, due to differences between dosing schedule during study phase and the subsequent SPC posology. This was tantamount to stating that Janssen could not promote Invokana 300mg and therefore a direct challenge to a regulatory decision.

Janssen was concerned that AstraZeneca had now broadened its complaint, introduced new data and misrepresented inter-company dialogue; the focus of its appeal had deviated from its original complaint.

Janssen submitted that it had demonstrated that the promotional claims using the regulatory approved pivotal studies of Invokana 100mg or 300mg highlighted efficacy outcomes reported in the clinical studies, clearly referenced to corresponding published articles. These pivotal studies were the fundamental elements captured in the SPC and therefore promotion with these studies was aligned with the SPC. Janssen had never claimed that patients could start Invokana at 300mg.

Janssen submitted that it had demonstrated that there was no scientific reason to expect a difference in clinical efficacy at study endpoint if patients were started on Invokana 300mg vs if they were started at 100mg and the dose increased to 300mg based on the pharmacodynamic and pharmacokinetic data captured in the SPC and further supported by unpublished modelling data and a recently published phase 4 study (Rodbard *et al*).

Janssen submitted that it took patient safety extremely seriously. The 100mg dose was recommended as a precautionary measure and as such 300mg should only be considered in patients who tolerated 100mg and required additional glycaemic control. This was included in all Janssen's promotional materials.

Janssen submitted that claims related to the efficacy of Invokana 300mg were capable of substantiation, not misleading and consistent with the SPC, maintaining high standards and Janssen had not brought the industry into disrepute. Janssen refuted the breaches of Clauses 7.2, 7.3, 7.4, 9.1 and 2 of the Code.

**FINAL COMMENTS FROM ASTRAZENECA**

AstraZeneca provided further clarity as to why the use of supporting references in regard to efficacy claims for Invokana 300mg was misleading by describing circumstances in which their use might have been appropriate. AstraZeneca submitted that it had not broadened the scope of the complaint but had provided further and better particulars for consideration within the terms of the original complaint.

AstraZeneca stated that its allegation was, and remained, that the materials at issue were misleading because they could lead the audience to believe that the efficacy claims for Invokana 300mg could be expected when the medicine was used in accordance with its licence and the SPC. It was not acceptable to confuse and mislead the audience in such a way.

The very point of an appeal was to introduce further and better particulars that allowed the Appeal Board to consider whether the Panel ruling was correct and in that regard the introduction of past case rulings into the discussion was appropriate. AstraZeneca was surprised that Janssen had suggested otherwise and concerned that such an approach could undermine the logical and regulatory consistency of the Authority.

AstraZeneca submitted that Cases AUTH/2506/5/12 and AUTH/2507/5/12 were relevant to these proceedings as they indicated that references that contained off-licence data to substantiate claims must not be used in a misleading way or to imply the medicine could be used outside of its licence. In the present case, the references in the materials implied that efficacy could be achieved by using Invokana as per the SPC ie with a starting dose of 100mg.

AstraZeneca noted that Janssen had not appealed the Panel's ruling of a breach of Clause 3.2, ie it had accepted the Panel's view that the flexibility claim could be read as relating to the starting dose. AstraZeneca therefore questioned why Janssen denied having promoted that Invokana 300mg as a starting dose.

AstraZeneca had not been previously made aware of any results comparing the efficacy of Invokana given at 300mg from the point of treatment initiation with Invokana given at 100mg and subsequently stepped up to 300mg, ie in line with posology described in the SPC. Therefore, AstraZeneca refuted Janssen's assertion that its wording betrayed an attempt to misrepresent inter-company dialogue.

AstraZeneca noted the following with regard to the unpublished modelling results newly presented by Janssen:

- The data was dated 8 April 2016, ie it was apparently not available when the promotional items at issue were certified (September 2015, October 2015 and January 2016): it was not referenced in these items
- These results were not previously made available to AstraZeneca or to the Panel

- The promotional items at issue included claims around HbA1c, body weight and blood pressure reductions: the modelling study was restricted to HbA1c reduction only and so was not relevant to the claims about body weight or blood pressure effects
- The promotional items included comparative claims against sitagliptin: the model did not include comparative effects vs sitagliptin
- The results were at 26 weeks from treatment initiation. The promotional items at issue referred to results at 52 weeks.

AstraZeneca alleged that these results could not be extrapolated to substantiate the claims in the materials at issue relating to clinical benefits.

With regard to the phase 4 study, Rodbard *et al*:

- These data were available when the manuscript was submitted for publication on 21 March 2016, ie during the course of inter-company dialogue, yet were not previously made available to AstraZeneca or to the Panel: they were not referenced in the promotional items at issue
- The study examined patients on background therapy with metformin and sitagliptin. The claims made in the promotional items at issue related to patients either on no background therapy or on background therapy other than sitagliptin. These were not the same patient groups and therefore this study could not be used to substantiate the claims made in the promotional material at issue
- The promotional items included comparative claims against sitagliptin: the study did not include a sitagliptin arm and therefore could not be used to substantiate such claims
- This study did not include a comparative arm in which 300mg Invokana was given as a starting dose. It was therefore not possible to compare the efficacy of the two dosing regimens at issue on the basis of these results
- The results were at 26 weeks from treatment initiation. The promotional items at issue referred to results at 52 weeks.

AstraZeneca alleged that additional data and analysis which were not available when the promotional items in question were certified had been introduced and that this had the potential to confuse discussions around what claims could have been made at that time. The only relevance of this new information was to highlight that, when the items were certified, there were no data to substantiate efficacy claims for Invokana 300mg where it was used in accordance with the posology described in its SPC, ie with a starting dose of 100mg.

AstraZeneca alleged that the promotional items at issue were in breach of Clauses 7.2, 7.3, and 9.1 (Point 1), Clauses 7.4 and 9.1 (Point 2) and Clause 2 (Point 3).

**APPEAL BOARD RULING**

The Appeal Board noted that in the original complaint AstraZeneca alleged that promotional claims regarding Invokana 300mg based upon the pivotal studies were misleading as the starting dose in those studies was 300mg whereas the SPC required initiation on 100mg which could be increased to 300mg. In its appeal AstraZeneca's position changed as it now appeared to be of the view that the pivotal studies could be used provided that it was made clear that the results were obtained with a starting dose of 300mg which was different to that required in the SPC and this should be presented alongside data for the 100mg dose.

The Appeal Board did not consider that the cases cited by AstraZeneca were relevant as these related to the promotional use of 15 month data for a product where the SPC stated that treatment up to 12 months was recommended.

The Appeal Board noted the pharmacodynamic and pharmacokinetic data (Sections 5.1 and 5.2 of the SPC) that fasting plasma glucose reductions were near maximal after the first day of treatment and that steady state was reached after 4-5 days of treatment.

The Appeal Board considered on the very narrow grounds of the complaint that it was not necessarily inconsistent with the SPC to use studies with a starting dose of Invokana 300mg to support claims in the leavepiece as alleged. Similarly, the use of these references to substantiate claims for 300mg Invokana was not necessarily misleading as alleged. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2. The appeal on this point was unsuccessful.

With regard to the comparison with sitagliptin the Appeal Board noted its and the Panel's rulings above and decided that they were also relevant here. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.3. The appeal on this point was unsuccessful.

In the circumstances, the Appeal Board did not consider that there had been a failure to maintain high standards. The Appeal Board upheld the Panel's ruling of no breach of Clause 9.1. The appeal on this point was unsuccessful.

**2 Use of the word 'flexibility'**

The September 2015 journal advertisement was headed 'Invokana 100mg and 300mg efficacy and flexibility* at a single price'. A footnote in very small print at the bottom of the page stated '*The recommended starting dose of Invokana is 100mg once daily. In patients tolerating Invokana 100mg once daily, who have a eGFR ≥60mL/min/1.73m$^2$ and need tighter glycaemic control, the dose can be increased to 300mg'.

The heading was followed by hanging signs representing cost (a £ sign in a circle) and reductions in HbA1c, kg and mmHg. There were then sections headed 'Invokana 100mg' and 'Invokana 300mg'. The Invokana 100mg section included favourable comparison in HbA1c, weight and blood pressure reductions vs sitagliptin in dual therapy as add-on therapy to metformin referenced to Lavalle-González *et al*. The Invokana 300mg section included favourable comparison with HbA1c, weight and blood pressure reductions with sitagliptin in dual and triple therapy, as add-on to metformin and as add-on to metformin and

sulphonylurea. Each section contained comparisons between the Invokana dose and sitagliptin.

The same claim appeared on the front page of the October 2015 leavepiece which was also followed by the hanging signs.

**COMPLAINT**

AstraZeneca alleged that 'flexibility' also breached various clauses of the Code. The advertisement used 'flexibility' in its title and the equal prominence given to the 100mg and 300mg doses implied that 300mg could be initiated and/or administered interchangeably with 100mg. AstraZeneca alleged this was inconsistent with the SPC. This impression was not negated by the footnote in substantially smaller font near the bottom of the page which stated:

> 'The recommended starting dose of invokana is 100mg once-daily. In patients tolerating Invokana 100mg once-daily, who have an eGFR ≥60ml/min/1.73m$^2$ and need tighter glycaemic control, the dose can be increased to 300mg once-daily.'

AstraZeneca stated that the same was true for the October 2015 leavepiece.

AstraZeneca stated that in inter-company dialogue (letter of 3 February 2016) Janssen asserted that the advertisement was not misleading and was in accordance with the terms of the Invokana marketing authorization but did not explain. Janssen acknowledged AstraZeneca's comment on the size of the footnote related to the claim on flexibility and agreed to consider this for future advertisements. AstraZeneca contended that this did not address the fundamental issue in relation to the advertisement.

AstraZeneca alleged that use of the word 'flexibility' constituted promotion outside the scope of the marketing authorization in breach of Clause 3.2. AstraZeneca alleged that the claim was misleading and in breach of Clause 7.2. Furthermore, as it was not possible to substantiate claims around 'flexibility': this constituted a breach of Clause 7.4. This demonstrated a failure to maintain high standards and a breach of Clause 9.1 was alleged.

**RESPONSE**

Janssen refuted the allegations that 'flexibility' when read in context, was misleading, inaccurate and unable to be substantiated. 'Flexibility' in the cited Invokana materials did not infer flexibility to start Invokana at either dosage in patients with type 2 diabetes.

The full claim was: 'Invokana 100mg and 300mg efficacy and flexibility* at a single price.' Janssen submitted that the use of word 'flexibility' in the context of this claim was within the requirements of the Code and not in breach of Clauses 3.2, 7.2, 7.4 and 9.1.

In August 2015, both the 100mg and 300mg Invokana became available at the same listed price, removing some NHS imposed barriers to prescribe Invokana 300mg in patients who required tighter glycaemic control.

In light of this background, the context of this claim was to show that both doses of Invokana were now available at the same price - in other words health professionals could prescribe Invokana 100mg dose for initiation and then, if appropriate, increase to 300mg for patients who would benefit from tighter diabetes control without the concern of additional cost. This allowed flexibility to tailor the dose according to patients' individual needs, in line with the posology, without worrying about cost increasing in line with the increasing dose. 'Flexibility' was footnoted to the posology to give health professionals clear guidance in the dosing instruction when higher dose should be used.

Janssen noted that the font size varied deliberately in the claim with 'flexibility' in smaller font because the key point was the cost. The structure of the sentence was quite clearly such that the Invokana 100mg dose was initiated first, as per the SPC.

Janssen did not agree that use of the word 'flexibility' implied that Invokana 300mg dose could be initiated and/or administered interchangeably with the 100mg dose. Posology of how Invokana was recommended to be used was clearly stated in all Invokana materials as well as in the advertisement and the October 2015 leavepiece cited by AstraZeneca. Furthermore, there was no market evidence or physician feedback to suggest that doctors had been misled. As such Janssen refuted the allegations of breaches of Clauses 3.2, 7.2, 7.4 and 9.1.

Invokana 300mg had been granted a marketing authorization. Janssen had not identified any examples of where promoting the 300mg dose in accordance with the licence represented a breach of high standards. Janssen maintained the use of word 'flexibility' in the context of the material could be substantiated.

Janssen submitted that it took patient safety extremely seriously, and would never 'deliberately misrepresent the facts' regarding safety issues, as alleged. There was no rationale as to why the company would want to do this, or why Invokana 300mg dose would be recommended as an initiation dose. The Invokana 100mg dose was recommended as a precautionary measure and as such 300mg should only be considered in those who tolerated 100mg and required additional glycaemic control. This was made clear in Janssen's promotional material.

**PANEL RULING**

The Panel considered that the claim in the advertisement ('Invokana 100mg and 300mg efficacy and flexibility at a single price)' did not make it sufficiently clear where each dose fitted in to the treatment pathway. It might be likely that when prescribing for new patients health professionals might start by using the 100mg dose as set out in the SPC. The Panel did not accept Janssen's submission that the claim was qualified by the use of the asterisk and its explanation regarding the recommended starting dose. It was a well-accepted principle under the Code that claims should not be qualified by

footnotes, they should be capable of standing alone as regards accuracy etc.

The Invokana SPC was clear that the recommended starting dose was 100mg once daily. There was no indication in the posology section as to how long the 100mg starting dose should be used before increasing it to 300mg in appropriate patients.

The Panel considered that the claim 'flexibility' could be read as relating to the starting dose and not, as submitted by Janssen, that some patients started on 100mg could increase their dose to 300mg and this would not mean an increase in cost. The Panel considered that the claim was misleading and inconsistent with the SPC. The Panel ruled breaches of Clauses 3.2 and 7.2 of the Code. As far as substantiation was concerned the Panel accepted that there was data relating to both doses and in relation to starting with the 300mg dose as referred to in Point 1 above. The Panel thus ruled no breach of Clause 7.4. This ruling was appealed.

On balance, the Panel did not consider that the claim meant that high standards had not been maintained and no breach of Clause 9.1 was ruled. This ruling was appealed.

**APPEAL BY ASTRAZENECA**

AstraZeneca noted that the Panel had agreed that 'flexibility' claims for Invokana 100mg and 300mg were misleading and inconsistent with the SPC, ie that the claim implied that Invokana could be started at a dose of either 100mg or 300mg, and ruled breaches of Clauses 3.2 and 7.2. AstraZeneca alleged that there were no data to support efficacy claims for the 300mg dose when it was given in accordance with the posology stated in the SPC, ie when a patient was initiated at a dose of 100mg and subsequently escalated to a dose of 300mg. Thus, the claim, which had already been ruled to be misleading could not be substantiated and was in breach of Clause 7.4.

AstraZeneca alleged that to imply that Invokana could be started at a dose higher than that recommended in the SPC amounted to a failure to maintain high standards, in breach of Clause 9.1.

AstraZeneca referred in particular to the EPAR for Invokana which noted that patients should be started on the 100mg dose for safety:

> 'Thus, some conditions existed in which a starting dose of 100mg should be used for safety reasons since drop in blood pressure and volume depletion or its sequelae could be more pronounced upon onset of treatment. Therefore a starting dose of 100mg was recommended for all patients as a precautionary measure and to simplify posology' (page 104).
>
> 'As a precautionary measure, a starting dose of 100mg is recommended for all patients' (pages 111-112).

AstraZeneca alleged that the importance of starting Invokana at 100mg dose for safety reasons must be made clear.

**RESPONSE FROM JANSSEN**

Janssen accepted the Panel ruling that the claim flexibility could be read as relating to the starting dose and therefore accepted breaches of Clauses 3.2 and 7.2 of the Code. However, the dosing information was included in the advertisement as in all promotional materials:

> 'The recommended starting dose of Invokana is 100mg once-daily. In patients tolerating Invokana 100mg once-daily, who have an eGFR ≥60ml/min/1.73m$^2$ and need tighter glycaemic control, the dose can be increased to 300mg once-daily.'

Janssen submitted that it did not make claims that patients could be initiated on 300mg and as demonstrated above, there was evidence to support no difference in the efficacy if Invokana was given in accordance with SPC posology. Hence, efficacy claims of Invokana 300mg was capable of substantiation and high standards had been maintained.

Therefore, Janssen refuted breaches of Clauses 7.4 and 9.1.

**FINAL COMMENTS FROM ASTRAZENECA**

See AstraZeneca's final comments at Point 1 above.

**APPEAL BOARD RULING**

The Appeal Board noted the Panel's rulings of breaches of Clauses 7.2 and 3.2 had been accepted by Janssen. AstraZeneca's appeal related to the lack of data to support efficacy claims for Invokana 300mg when initiated at 100mg and subsequently increased to a dose of 300mg. The Appeal Board agreed with the Panel and accepted that there was data relating to both doses and in relation to starting with the 300mg dose as referred to in Point 1 above. It considered that in the circumstances there was data to substantiate the efficacy claims. The Appeal Board thus upheld the Panel's ruling of no breach of Clause 7.4. The appeal on this point was unsuccessful.

Again the Appeal Board noted the Panel's rulings of breaches of Clauses 7.2 and 3.2 of the Code as well as its ruling of no breach of Clause 7.4.

The Appeal Board did not consider that, in the circumstances, high standards had not been maintained and it upheld the Panel's ruling of no breach of Clause 9.1. The appeal on this point was unsuccessful.

**3 Seriousness of breaches**

**COMPLAINT**

AstraZeneca alleged that use of these promotional claims represented a deliberate attempt to misrepresent the facts. Furthermore, AstraZeneca noted that the EPAR for Invokana twice stated that patients should always be initiated on the 100mg dose for safety reasons.

'Thus, some conditions exist in which a starting dose of 100mg should be used for safety reasons since drop in blood pressure and volume depletion or its sequelae could be more pronounced upon onset of treatment. Therefore a starting dose of 100mg is recommended for all patients as a precautionary measure and to simplify posology.' (Page 104)

'As a precautionary measure, a starting dose of 100mg is recommended for all patients.' (Page 111)

AstraZeneca therefore alleged that use of the word 'flexibility' (Point 2) in this way had the potential to compromise patient safety. AstraZeneca alleged that Janssen's actions had the potential to bring discredit to, and reduce confidence in, the pharmaceutical industry in breach of Clause 2.

**RESPONSE**

Janssen submitted that the allegations raised by AstraZeneca were unfounded. Janssen promotional materials and claims were in alignment with the Code. As such, Janssen refuted the allegation of breach of Clause 2.

**PANEL RULING**

The Panel noted its rulings in Points 1 and 2 above. It did not consider that the use of the word 'flexibility' compromised patient safety such that Janssen had brought discredit upon or reduced confidence in the pharmaceutical industry. The Panel therefore ruled no breach of Clause 2 of the Code. This ruling was appealed.

**APPEAL BY ASTRAZENECA**

AstraZeneca appealed the Panel's ruling of no breach of Clause 2 in relation to all misleading claims that implied that Invokana could be initiated at a dose of 300mg and the cumulative breaches in this case. Clause 2 was reserved as a sign of particular censure and AstraZeneca alleged that claims that might impact the safety of patients fell in to this category.

**RESPONSE FROM JANSSEN**

Janssen reiterated that all promotional materials for Invokana included data on Invokana 100mg and 300mg. Janssen took patient safety extremely seriously and the materials always included information that patients should be initiated on 100mg Invokana in line with the approved posology. Janssen had not claimed that patients could be initiated on 300mg and as demonstrated above, there was evidence to support no difference in the efficacy if Invokana was given in accordance with SPC posology.

Hence, Janssen submitted that patient safety and high standards had been maintained so there had been no breach of Clause 2

**FINAL COMMENTS FROM ASTRAZENECA**

See AstraZeneca's final comments at Point 1 above.

**APPEAL BOARD RULING**

The Appeal Board noted its and the Panel's rulings in Points 1 and 2 above. It did not consider that the use of the word 'flexibility' compromised patient safety such that Janssen had brought discredit upon or reduced confidence in the pharmaceutical industry. The Appeal Board therefore upheld the Panel's ruling of no breach of Clause 2 of the Code. The appeal on this point was unsuccessful.

**Complaint received** **11 April 2016**

**Case completed** **21 July 2016**

**CASES AUTH/2840/4/16 and AUTH/2847/5/16**

# ANONYMOUS, NON CONTACTABLE v NOVARTIS and PFIZER

## Promotion of Ultibro Breezhaler and Seebri Breezhaler

**An anonymous, non contactable complainant complained about the promotion of long acting beta agonist/long acting muscarinic antagonists (LABA/LAMA) combination inhalers for the treatment of chronic obstructive pulmonary disease (COPD). The complainant noted that the medicines were licensed for the relief of COPD symptoms but appeared to have been additionally promoted to reduce exacerbations. The complainant stated that some LAMA inhalers had also similarly been promoted off-label. The complainant drew attention to, *inter alia*, Ultibro Breezhaler (indacaterol (LABA)/glycopyrronium (LAMA)) and Seebri Breezhaler (glycopyrronium (LAMA)) both co marketed by Novartis Pharmaceuticals UK and Pfizer.**

**Ultibro Breezhaler and Seebri Breezhaler were both indicated as maintenance bronchodilator treatments to relieve symptoms in adults with COPD.**

**The complainant noted that the first LABA/LAMA fixed combination to be licensed was Ultibro Breezhaler and stated that it was clear from its European Public Assessment Report (EPAR) that the Committee for Medicinal Products for Human Use (CHMP) turned down an application that included its use to reduce exacerbations, because its effects on such were too small to recommend such use. Ultibro Breezhaler was subsequently licensed only as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD and thus its promotion in relation to COPD exacerbation reduction was off-label. In relation to this case the complainant drew attention to a journal advertisement which stated that 'Ultibro Breezhaler can significantly reduce your patients' rate of moderate to severe exacerbations'. Similarly, the complainant alleged that a leavepiece contained an off-label claim for Seebri Breezhaler namely, '... significantly reduces the risk of first moderate/severe COPD exacerbation by 31%'. Neither contained any other information warning of the off-label aspects to the promoted use of the products.**

**The complainant stated that his/her colleagues had little awareness that LABA/LAMA combination inhalers or LAMA inhalers were being prescribed in an unlicensed manner. Also, formal recommendations for the use of these medicines in exacerbation reduction were increasingly appearing in local clinical guidelines which suggested that promotion of the medicines had not clearly communicated the off-label nature of this use. The complainant stated that the materials for the various inhalers to which he/she had drawn attention were most probably just the tip of the iceberg; he/she knew of numerous educational meetings/symposia with external speakers where exacerbation reduction data had been presented as part of product promotion.**

**A potential major concern for the complainant and his/her prescribing colleagues was that they might have unknowingly prescribed LABA/LAMA combination inhalers or LAMA inhalers to numerous COPD patients assuming that they were licensed for exacerbation reduction. The statement from the CHMP which considered exacerbation was therefore a sobering thought especially if COPD patients subsequently suffered exacerbations unexpectedly because their prescribed LABA/LAMA combination inhalers might not be effective enough as intimated by the CHMP assessment of Ultibro Breezhaler. COPD was characterised in part by airway inflammation and the extent of inflammation was progressive leading up to an exacerbation. None of the medicines in question contained an anti-inflammatory component. Another very important consideration was that prescribers were unaware from a medico-legal perspective that they would be solely liable for any adverse consequences suffered by patients which might arise.**

**The detailed response from Novartis and Pfizer is given below.**

**The Panel noted that both products were indicated as maintenance bronchodilator treatments to relieve symptoms in adult patients with COPD. Section 5.1 of the respective Ultibro Breezhaler and Seebri Breezhaler summaries of product characteristics (SPCs) referred to each medicine's positive impact on exacerbations of COPD. The Panel noted that Section 1.1 of the National Institute for Health and Clinical Excellence (NICE) Guideline on the management of COPD listed the symptoms of the disease which were, *inter alia*, exertional breathlessness, chronic cough, regular sputum production and wheezing. In Section 1.3 the exacerbation of COPD was described as a sustained worsening of the patient's symptoms from their usual stable state which was beyond normal day-to-day variations and was acute in onset. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidance similarly differentiated COPD symptoms and exacerbations. In the Panel's view, there was a difference between COPD symptoms and exacerbation of COPD although it accepted that patients with well controlled symptoms might be less likely to experience an exacerbation than patients with poorly controlled symptoms. In that regard the Panel considered that exacerbations might be referred to in the promotion of COPD maintenance therapy but that there was a difference between promoting a medicine for a licensed indication and promoting the benefits of treating a condition. In the Panel's view, reference to reduced COPD exacerbation must be set within the context of the primary reason to prescribe ie maintenance therapy to relieve symptoms.**

**The Panel noted that the Ultibro Breezhaler advertisement at issue included the sub-heading 'Ultibro Breezhaler offers benefits beyond**

**current standard COPD maintenance therapies' beneath which were four claims one of which was 'vs salmeterol/fluticasone Ultibro Breezhaler can significantly reduce your patients' rate of moderate or severe exacerbations', referenced to Zhong *et al* (2015), the LANTERN study. In that regard the Panel considered that the claim for a benefit vs salmeterol/fluticasone appeared to be a consequence of using Ultibro Breezhaler as a maintenance therapy and not the reason to prescribe *per se,* as alleged. Given the context in which it appeared, the claim was not misleading with regard to the licensed indication for Ultibro Breezhaler. No breaches of the Code were ruled including that high standards had been maintained.**

**These rulings also applied to the 'Wealth of data' leavepiece and on balance to the sales aid. No breaches of the Code were ruled.**

**Novartis also provided a copy of a leavepiece, 'What is the right treatment choice for your patients?'. Under a heading of 'Ultibro Breezhaler offers patients effective relief from symptoms of COPD at a price of £32.50' was boxed text entitled 'Reduces exacerbation risk beyond tiotropium (open label) and [salmeterol/fluticasone]' which reported the results from Zhong *et al*. The leavepiece, however, did not clearly state that Ultibro Breezhaler was a maintenance therapy to relieve COPD symptoms such that the boxed text would be read within the context of the licensed indication. In the Panel's view the leavepiece implied that Ultibro Breezhaler could be prescribed to reduce exacerbations rather than the reduction in exacerbations being a benefit of using the medicine as maintenance therapy. In the Panel's view the leavepiece was inconsistent with the particulars listed in the Ultibro Breezhaler SPC; it misleadingly implied that exacerbation reduction was a primary reason to prescribe Ultibro Breezhaler. Breaches of the Code were ruled including that high standards had not been maintained.**

**A speaker slide deck, 'Evolving science; Dual bronchodilation', examined the burden of COPD and the challenges of treatment and included an overview of clinical studies for, *inter alia,* Ultibro Breezhaler. The slide which introduced Ultibro Breezhaler (slide 54) clearly stated that it was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. A subsequent section on exacerbations referred to the positive data from the SPARK (vs glycopyrronium and tiotropium) and LANTERN (vs salmeterol/fluticasone (LABA/inhaled corticosteroid (ICS)) studies. Slide 80 within a subsequent section on health-related quality of life, was headed 'Summary: Ultibro Breezhaler significantly improved important patient outcomes vs monotherapies and LABA/ICS' and in that regard listed exacerbations. The second bullet point of the final concluding slide (slide 101) stated 'Once daily Ultibro Breezhaler demonstrated superior efficacy compared with placebo, its monocomponents indacaterol and glycopyrronium, the current standard of care (tiotropium) and LABA/ICS'. It was not stated what the superior efficacy related to. In the Panel's view, given the length of the slide deck and the number of topics discussed, it was possible that, after 101 slides, some viewers would have forgotten exactly what Ultibro Breezhaler was indicated for; some viewers might be left with the impression that Ultibro Breezhaler could be prescribed for the reduction of exacerbations *per se* which was not consistent with the particulars listed in its SPC. That the presentation implied that Ultibro Breezhaler could be used to reduce COPD exacerbations and was a primary reason to prescribe the product was misleading. Breaches of the Code were ruled including that high standards had not been maintained.**

**The Panel considered that the training course presentation could have benefitted from a more explicit statement as to the licensed indication for Ultibro Breezhaler and that any reduction in exacerbations was to be discussed as a benefit of maintenance therapy and not as a reason to prescribe *per se*. Nonetheless, on balance, the Panel did not consider that the material encouraged representatives to promote Ultibro Breezhaler for exacerbation reduction. No breaches were ruled.**

**The Panel noted that the Seebri Breezhaler leavepiece at issue stated on the front cover that the medicine was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. Page 2 of the leavepiece described a typical patient and stated that he 'wants a treatment that will help him breathe better in the morning…and throughout the day'. Page 3 of the leavepiece included the claim that, compared with placebo, Seebri Breezhaler 'Significantly reduces the risk of first moderate/severe COPD exacerbation by 31% (p=0.023)'. The Panel did not consider that the leavepiece promoted Seebri Breezhaler for the reduction of COPD exacerbation as alleged. Preceding claims largely discussed symptom control. The reference to exacerbations had been presented within the context of the licensed indication ie as a benefit of maintenance therapy and not the reason to prescribe *per se*. The Panel considered that the promotion of Seebri Breezhaler had been consistent with the particulars listed in the SPC. The leavepiece did not imply that exacerbation reduction was a primary reason to prescribe Seebri Breezhaler and so was not misleading in that regard. No breaches of the Code were ruled including that high standards had been maintained.**

**In response to the complainant's wider concerns about the promotion of Seebri Breezhaler, Novartis provided a copy of two internal training presentation. Overall the Panel considered that the presentations suggested that Seebri Breezhaler could be prescribed *per se* to reduce COPD exacerbations, for which the medicine was not indicated; both were ruled in breach of the Code including that high standards had not been maintained.**

**The Seebri Breezhaler sales aid contained a page which was headed 'How can you help delay the time to first moderate to severe COPD exacerbation for your patients' which appeared above a graph comparing the effect of Seebri Breezhaler with that of placebo. The claim at the bottom of the slide read**

**'Initiate Seebri Breezhaler to reduce your patients' risk of exacerbations'. Finally the Panel noted that although a set of Seebri Breezhaler speaker slides only briefly referred to the positive exacerbation data from Kerwin *et al* (2012) compared with placebo, those results were not put into context by any statement of the licensed indication for the medicine. The Panel considered that the sales aid and the speaker slides both suggested that Seebri Breezhaler could be prescribed *per se* to reduce COPD exacerbations, for which the medicine was not indicated; this was inconsistent with the particulars listed in the Seebri Breezhaler SPC. The materials implied that exacerbation reduction was a primary reason to prescribe Seebri Breezhaler. Breaches of the Code were ruled including that high standards had not been maintained.**

**The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel noted its rulings and comments above but considered that the matters were not such as to bring discredit upon, or reduce confidence in, the industry. No breach of Clause 2 was ruled.**

An anonymous, non contactable complainant complained about the promotion of long acting beta agonist/long acting muscarinic antagonists (LABA/LAMA) combination inhalers for the treatment of chronic obstructive pulmonary disease (COPD). The complainant referred to the fact that the medicines were licensed for the relief of COPD symptoms but appeared to have been additionally promoted to reduce exacerbations. The complainant stated that some LAMA inhalers had also similarly been promoted off-label. The complainant drew attention, *inter alia*, to Ultibro Breezhaler (indacaterol (LABA)/glycopyrronium (LAMA)) and Seebri Breezhaler (glycopyrronium (LAMA)) both co marketed by Novartis Pharmaceuticals UK Ltd and Pfizer Limited.

Ultibro Breezhaler and Seebri Breezhaler were both indicated as maintenance bronchodilator treatments to relieve symptoms in adult patients with COPD.

**COMPLAINT**

The complainant noted that the first LABA/LAMA fixed combination to be licensed was Ultibro Breezhaler and stated that although it was clear from its European Public Assessment Report (EPAR – dated 25 July 2013) that an application was originally submitted for the relief of COPD symptoms and the reduction of exacerbations, the Committee for Medicinal Products for Human Use (CHMP) subsequently stated the medicine's effects on reducing the rate of exacerbations were too small to recommend its use for such. Ultibro Breezhaler was eventually licensed as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The complainant stated that it could be concluded that Ultibro Breezhaler was not granted a licence at the time to recommend its use for reducing exacerbations and alleged, therefore, that promotion of Ultibro Breezhaler in relation to COPD exacerbation reduction was off-label. In relation to this case the complainant drew attention to a journal advertisement (ref UK/ULT/16-0028b (1) – February 2016) which stated that 'Ultibro Breezhaler can significantly reduce your patients' rate of moderate to severe exacerbations'.

Similarly, the complainant alleged that a leavepiece (ref SBR0003 – September 2014) contained an off-label claim for Seebri Breezhaler namely, '... significantly reduces the risk of first moderate/severe COPD exacerbation by 31%'.

Neither of the two items mentioned above contained any other information warning of the off-label aspects to the promoted use of the products.

The complainant stated having spoken to his/her peers it was evident that there was very little awareness amongst fellow colleagues that LABA/LAMA combination inhalers or LAMA inhalers were being prescribed in an unlicensed manner. Also, formal recommendations for the use of these products in exacerbation reduction were increasingly appearing in local clinical guidelines which suggested that promotion of the medicines had most likely missed an ethical obligation to also clearly communicate the off-label nature of this use, either in materials or as instruction to representatives. The complainant concluded that the materials for the various inhalers to which he/she had drawn attention were most probably just the tip of a large iceberg. The complainant was aware of numerous educational meetings/symposia involving external speakers where exacerbation reduction data had been discussed and presented as part of product promotion.

A potential major concern for the complainant and his/her prescribing colleagues was that unknowingly, they might have prescribed LABA/LAMA combination inhalers or LAMA inhalers to numerous COPD patients based on the assumption that the products were licensed for exacerbation reduction. The statement from the CHMP which considered exacerbation was therefore a sobering thought especially if treated COPD patients subsequently suffered exacerbations unexpectedly. This was because prescribing LABA/LAMA combination inhalers might not be effective enough as intimated by the CHMP assessment of Ultibro Breezhaler. COPD was characterised in part by airway inflammation and the extent of inflammation was progressive leading up to an exacerbation. None of the medicines in question actually contained an anti-inflammatory component. Another very important consideration was that prescribers were unaware from a medico-legal perspective that they would be solely liable for any adverse consequences suffered by patients which might arise.

In writing to Novartis and Pfizer the Authority asked them to respond to Clauses 2, 3.2, 7.2, 9.1 and 15.9. The edition of the Code would be that relevant at the time the materials were used.

**RESPONSE**

Novartis noted that Ultibro Breezhaler was indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD and denied that the claim 'Ultibro Breezhaler can significantly reduce your patients'

rate of moderate to severe exacerbations' constituted the off-label promotion because:

- The indication included symptomatic COPD patients regardless of exacerbation history or risk.
- Statistically significant reductions in the annualised rate of moderate to severe exacerbations and all COPD exacerbations (mild, moderate or severe) were described within Section 5.1 of the Ultibro Breezhaler summary of product characteristics (SPC). Statements regarding statistically significant reductions in the rate of exacerbations were therefore consistent with the particulars of the SPC.
- Two randomised controlled clinical trials had demonstrated significant reductions in exacerbations and so there was clinical evidence to substantiate the information. In the SPARK study (Wedzicha *et al* 2013), Ultibro Breezhaler statistically significantly reduced the annualised rate of moderate or severe COPD exacerbations by 12% compared with glycopyrronium ($p = 0.038$) and all COPD exacerbations (mild, moderate or severe) by 15% compared to glycopyrronium ($p = 0.001$). In addition, the LANTERN study (Zhong *et al* 2015) demonstrated a statistically significant 31% reduction in moderate to severe exacerbations for Ultibro Breezhaler vs salmeterol/fluticasone.

Furthermore, the complainant's example was only a component of the advertisement which was fully referenced and contained appropriate Code related requirements including (and not limited to) the prescribing information which clearly stated the licensed indication. Therefore, for all the reasons above, Novartis denied the complainant's allegation that the claim, 'Ultibro Breezhaler can significantly reduce your patients' rate of moderate to severe exacerbations', was off-label promotion.

In summary, Novartis submitted that the claim complied with the requirements of Clause 3.2, as it was in accordance with the terms of the Ultibro Breezhaler marketing authorisation and was consistent with the particulars and benefits described in its SPC. Novartis also submitted that the claim complied with Clause 7.2 in that the information was accurate, balanced, fair, objective and unambiguous and was based on an up-to-date evaluation of all the evidence available when the advertisement was published. Hence it would not mislead readers either directly or by implication, by distortion, exaggeration or undue emphasis.

With regards to compliance with Clause 15.9, Novartis did not believe it was relevant to this material. The item in question was an advertisement in a health professional journal. No representative briefing was required.

Novartis submitted that high standards had been maintained and that the Ultibro Breezhaler advertisement complied with the Code. Novartis denied a breach of Clause 9.1 and further denied that the material had brought the industry into disrepute, in breach of Clause 2.

Turning to the Seebri Breezhaler leavepiece, Novartis noted that it was indicated for maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Novartis did not consider that the claim that Seebri Breezhaler 'significantly reduces the risk of first moderate/severe COPD exacerbation by 31%' constituted off-label promotion because:

- The indication included symptomatic COPD patients regardless of exacerbation history or risk.
- Statistically significantly prolonged time to first moderate or severe exacerbation and reduction in the rate of moderate or severe COPD exacerbations (0.53 exacerbations/year vs 0.77 exacerbations/year, ($p < 0.001$)) were described within Section 5.1 of the Seebri Breezhaler SPC. Statements regarding statistically significant reductions in the rate of exacerbations were therefore consistent with the particulars of the SPC.
- The claim was supported by evidence from a randomised clinical trial which demonstrated a statistically significant 31% reduction in the risk of COPD exacerbations in terms of time to first moderate or severe COPD exacerbation compared with placebo (hazard ratio [HR] 0.69, 95% CI 0.500-0.949; ($p = 0.023$)) (D'Urzo *et al* 2011) which was cited in the leavepiece.

Furthermore the complainant's cited example was only a component of the leavepiece which was fully referenced and contained appropriate Code related requirements including (and not limited to) the prescribing information which clearly stated the licensed indication. Therefore, for all the reasons above, Novartis denied the complainant's allegation that the statement was off-label promotion.

In summary, Novartis submitted that the claim at issue, '... significantly reduces the risk of first moderate/severe COPD exacerbation by 31%', within the Seebri Breezhaler promotional material complied with Clause 3.2 as it was in accordance with the terms of the medicine's marketing authorization and was consistent with the particulars and benefits described in the Seebri Breezhaler SPC. Novartis further submitted that the claim complied with Clause 7.2 in that the information was accurate, balanced, fair, objective and unambiguous and was based on an up-to-date evaluation of all the evidence available when the leavepiece was used. Hence it would not mislead a reader either directly or by implication, by distortion, exaggeration or undue emphasis.

With regard to compliance with Clause 15.9, the leavepiece was comprised of excerpts from the Seebri Breezhaler sales aid for which training was completed face-to-face at the Seebri Breezhaler launch meeting in September 2014. The leavepiece was subsequently made available for trained representatives to use.

Novartis submitted that high standards had been maintained and the information contained in the Seebri Breezhaler leavepiece complied with the Code. Novartis denied that this was in breach of

Clause 9.1 and further denied that the leavepiece had brought the industry into disrepute, in breach of Clause 2.

With regard to the role of the LAMA inhalers (eg Seebri Breezhaler), LABA/LAMA combination inhalers (eg Ultibro Breezhaler) and LABA/ICS combination inhalers and their use in preventing COPD exacerbations Novartis explained that the natural history of COPD included a degree of symptom burden (typically breathlessness, cough and sputum production) punctuated with episodes of worsening of these symptoms (referred to as exacerbations). An exacerbation was defined in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines as 'an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication'.

LAMAs, LABA/LAMA fixed dose combinations and LABA/inhaled corticosteroid (ICS) fixed dose combinations were all licensed for the symptomatic treatment of patients with COPD as illustrated by the following examples:

- Spiriva (tiotropium - a LAMA inhaler) was indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD.

- Seebri Breezhaler (a LAMA inhaler) was indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

- Ultibro Breezhaler (a LABA/LAMA combination inhaler) was indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

- Seretide (salmeterol/fluticasone - a LABA/ICS combination inhaler) was indicated for the symptomatic treatment of patients with COPD, with a forced expiratory volume in 1 second (FEV1) < 60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who had significant symptoms despite regular bronchodilator therapy.

These medicine classes were recommended for use by the GOLD Guidelines and by the National Institute for Health and Care Excellence (NICE) therapeutic pathway for inhaled therapy for COPD in Clinical Guideline CG101. Recommendations were based on a patient's symptomatic response and preference, the medicine's adverse event profile and costs, as well as the potential to reduce exacerbations. LAMA and LABA/LAMA therapies were considered alternative options to LABA/ICS. Preference was not given to LABA/ICS by virtue of it containing an anti-inflammatory component (inhaled corticosteroid) and all treatment options had been shown to reduce exacerbations. The complainant was thus incorrect to suggest that there might be a concern in using LAMAs or LABA/LAMA combinations to reduce exacerbations because they did not contain an anti-inflammatory component. In fact, as described above, the LANTERN study demonstrated a statistically significant 31% reduction in moderate to severe exacerbations for Ultibro Breezhaler (LABA/LAMA) compared with salmeterol/fluticasone (LABA/ICS).

In summary Novartis submitted that its communications regarding the use of LAMA and LABA/LAMA combination treatment had been responsible, accurate, not misleading and based on an up-to-date evaluation of the latest clinical evidence. The data on reducing exacerbations for Ultibro Breezhaler and Seebri Breezhaler were substantiated and consistent with the particulars in their respective SPCs. Representatives were well-briefed on all promotional materials and high standards had been maintained at all times. The reputation of the industry had never been compromised. Novartis thus denied any breach of Clauses 3.2, 7.2, 15.9, 9.1 or 2 of the Code.

On receipt of Novartis' response, it became apparent that the medicines were co-promoted with Pfizer and the matter was taken up with Pfizer (Case AUTH/2847/5/16).

**RESPONSE FROM PFIZER**

Pfizer submitted that the initial response provided by Novartis was agreed by both Pfizer and Novartis as part of the Pfizer-Novartis Alliance and that any subsequent correspondence on the matter was to be considered as joint responses from both companies.

**FURTHER INFORMATION FROM NOVARTIS**

In response to a request for further information, Novartis submitted a copy of the relevant part of the training material covering exacerbations data for the Seebri Breezhaler sales aid.

Novartis submitted that a generally accepted definition of clinical practice guidelines was that they were systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. Published methods for development of valid guidelines differed in their detail but all were founded on the following three essential principles:

1 guidelines must be evidence based, with recommendations based on a systematic review, including critical appraisal, of published literature;

2 individual recommendations must be evidence-linked, using a recognised grading scheme that explicitly summarises the type and quality of evidence on which they were based; and

3 guideline development must be multidisciplinary, undertaken by a group in which all stakeholders, including patients or service users, for the clinical topic are represented.

Guidelines were usually produced at national or international level by medical associations or governmental bodies. Local healthcare providers might produce their own set of guidelines or adapt them from existing top-level guidelines. In developing local clinical guidelines, consideration would likely be given to issues such as local burden of disease,

the availability of effective and efficient healthcare interventions, evidence of variation in practice and evidence of current suboptimal performance.

While industry generated literature might be considered in the development of clinical guidelines, guidelines were independent, formal, evidence-based recommendations over which pharmaceutical companies had no editorial control.

Novartis disagreed with the complainant's assertion that the promotion of Ultibro Breezhaler and Seebri Breezhaler had most likely missed an ethical obligation.

Regarding the complainant's assertion of '… off-label nature of this use, …' Novartis refuted that statement and noted the approved indications for Ultibro Breezhaler and of Seebri Breezhaler in Section 4.1 (Therapeutic indications) of their respective SPCs, and also of the statements in Section 5.1 (Pharmacodynamic properties) about statistically significant reductions in exacerbation risk.

The GOLD 2016 Guidelines noted that the characteristic symptoms of COPD were chronic and progressive dyspnoea, cough, and sputum production that could be variable from day-to-day, and that an exacerbation of COPD was an acute event characterised by a worsening of the patient's respiratory symptoms that was beyond normal day-to-day variations, and led to a change in medication. An exacerbation was therefore part of the spectrum of symptomatology associated with COPD, and indeed, reduction of exacerbation risk in COPD was widely studied and widely reported.

Both Ultibro Breezhaler and Seebri Breezhaler were indicated as maintenance bronchodilator treatments to relieve symptoms in adults with COPD. The discussion of information and data included in Section 5.1 of each SPC specifically related to the patient population included in Section 4.1 of the same SPC and therefore did not constitute off-label promotion.

There were no restrictions in the Ultibro Breezhaler or Seebri Breezhaler indication in their respective SPCs regarding exacerbation history or risk, and therefore no reason why data relating to exacerbation risk reduction or other clinically relevant endpoints found in Section 5.1 should not be used in promotional materials.

Novartis provided copies of relevant current Ultibro Breezhaler and Seebri Breezhaler materials including presentations and representatives' briefing materials which referred to exacerbation reduction data.

**PANEL RULING**

The Panel noted that both Ultibro Breezhaler and Seebri Breezhaler were indicated as maintenance bronchodilator treatments to relieve symptoms in adult patients with COPD. Section 5.1 of the respective SPCs referred to each medicine's positive impact on exacerbations of COPD. The Panel noted that Section 1.1 of the NICE Guideline on the management of COPD listed the symptoms of the disease which were, *inter alia*, exertional breathlessness, chronic cough, regular sputum production and wheezing. In Section 1.3 of the Guideline, the exacerbation of COPD was described as a sustained worsening of the patient's symptoms from their usual stable state which was beyond normal day-to-day variations and was acute in onset. The GOLD guidance similarly differentiated COPD symptoms and exacerbations. In the Panel's view, there was a difference between COPD symptoms and exacerbation of COPD although it accepted that patients whose symptoms were well controlled might be less likely to experience an exacerbation of their condition than patients with poorly controlled symptoms. In that regard the Panel considered that reference to exacerbations might be included in the promotion of COPD maintenance therapy but that there was a difference between promoting a medicine for a licensed indication and promoting the benefits of treating a condition. In the Panel's view, any reference to reduced COPD exacerbation must be set within the context of the primary reason to prescribe ie maintenance therapy to relieve symptoms.

The Panel noted that Novartis and Pfizer had been asked to consider the requirements of Clauses 2, 3.2, 7.2, 9.1 and 15.9 and advised that the edition of the Code that would be relevant would be that which was in force when the materials were used. The Panel considered, however, that given the matters at issue, the relevant, substantial requirements of Clauses 2, 3.2, 7.2, 9.1 and 15.9 had not changed since the 2014 Code (the earliest Code relevant to the material at issue) and so all of the rulings below were made under the 2016 Code.

The Panel noted that the Ultibro Breezhaler advertisement at issue included the sub-heading 'Ultibro Breezhaler offers benefits beyond current standard COPD maintenance therapies' beneath which were four claims one of which was 'vs salmeterol/fluticasone Ultibro Breezhaler can significantly reduce your patients' rate of moderate or severe exacerbations' which was referenced to Zhong *et al*, the LANTERN study. In that regard the Panel considered that the claim for a benefit vs salmeterol/fluticasone appeared to be a consequence of using Ultibro Breezhaler as a maintenance therapy and not the reason to prescribe *per se*, as alleged. In that regard no breach of Clause 3.2 was ruled. Given the context in which it appeared, the claim was not misleading with regard to the licensed indication for Ultibro Breezhaler. No breach of Clause 7.2 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

In response to the complainant's wider concerns about the promotion of Ultibro Breezhaler, Novartis provided a copy of the Ultibro Breezhaler interactive sales aid (ref UK/ULT/15-0268b) which listed, in order, maintaining an active lifestyle, reducing breathlessness and reducing exacerbations as important when managing COPD patients. The Panel was concerned that it appeared that health professionals could choose only to learn about the reduction in exacerbations. The introductory slide to that section described exacerbation reduction as a priority of COPD management and detailed the consequences of exacerbations. The following slide

introduced the exacerbation data with the heading 'How can you control COPD symptoms while helping to reduce exacerbations?' This was followed by two slides headed 'Start a new chapter in improving symptoms' separated by a slide headed 'Start with a new chapter in reducing exacerbations'. All of the slides bore the product logo and a picture of the device. The Panel considered that this section of the sales aid was on the outer limits of acceptability and queried whether sufficient weight had been given to the licensed indication. That part of the exacerbations section which dealt with the comparison of Ultibro Breezhaler vs salmeterol/fluticasone, again reported the findings of Zhong *et al*.

A 'Wealth of data' leavepiece (ref UK/ULT/15-0270a) was headed on page 1 with 'If you have patients with COPD that are still symptomatic despite their maintenance therapy, there is something we'd like to bring to light …'. Page 3 was headed 'Ultibro Breezhaler offers benefits beyond current standard maintenance therapies' below which was a claim that, compared with tiotropium, Ultibro significantly reduced the rate of all exacerbations.

The Panel noted its comments and rulings above with regard to the Ultibro Breezhaler advertisement and considered that they applied to the 'Wealth of data' leavepiece and on balance to the sales aid. No breaches of Clause 3.2, 7.2 and 9.1 were ruled.

Novartis also provided a copy of a leavepiece (ref UK/ULT/15-0025) entitled 'What is the right treatment choice for your patients?'. Under a heading of 'Ultibro Breezhaler offers patients effective relief from symptoms of COPD at a price of £32.50' was boxed text entitled 'Reduces exacerbation risk beyond tiotropium (open label) and [salmeterol/fluticasone]' which reported the results from Zhong *et al* described above. The leavepiece, however, did not clearly state that Ultibro Breezhaler was a maintenance therapy to relieve COPD symptoms such that the boxed text would be read within the context of the licensed indication. In the Panel's view the leavepiece implied that Ultibro Breezhaler could be prescribed to reduce exacerbations rather than the reduction in exacerbations being a benefit of using the medicine as maintenance therapy. In the Panel's view the leavepiece was inconsistent with the particulars listed in the Ultibro Breezhaler SPC and a breach of Clause 3.2 was ruled. The leavepiece implied that that exacerbation reduction was a primary reason to prescribe Ultibro Breezhaler which was misleading. A breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

A speaker slide deck (ref UK/ULT/16-0025) entitled 'Evolving science; Dual bronchodilation' examined the burden of COPD and the challenges of treatment and included an overview of clinical studies for, *inter alia*, Ultibro Breezhaler. The slide which introduced Ultibro Breezhaler (slide 54) clearly stated that it was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. A subsequent section on exacerbations referred to the positive data from the SPARK (vs glycopyrronium and tiotropium) and LANTERN (vs salmeterol/fluticasone (LABA/ICS)) studies. Slide 80 within a subsequent section on health-related quality of life, was headed 'Summary: Ultibro Breezhaler significantly improved important patient outcomes vs monotherapies and LABA/ICS' and in that regard listed exacerbations. The second bullet point of the final concluding slide (slide 101) stated 'Once daily Ultibro Breezhaler demonstrated superior efficacy compared with placebo, its monocomponents indacaterol and glycopyrronium, the current standard of care (tiotropium) and LABA/ICS'. It was not stated what the superior efficacy related to. In the Panel's view, given the length of the slide deck and the number of topics discussed, it was possible that, after 101 slides, some viewers would have forgotten exactly what Ultibro Breezhaler was indicated for; some viewers might be left with the impression that Ultibro Breezhaler could be prescribed for the reduction of exacerbations *per se* which was not consistent with the particulars listed in its SPC. A breach of Clause 3.2 was ruled. That the presentation implied that Ultibro Breezhaler could be used to reduce COPD exacerbations and was a primary reason to prescribe the product was misleading and a breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Ultibro Breezhaler training course presentation (ref UK/ULT/15-0474) referred to COPD maintenance and that health professionals effectively control COPD symptoms through optimal bronchodilation as a cornerstone of COPD management. In a section entitled 'Ultibro Campaign Material "Benefits Beyond"', the structure of the sales aid as referred to above was discussed and a flow diagram included a box labelled 'Ultibro promise exacerbations'. Three subsequent slides discussed exacerbation data using the same slides as used in the sales aid. The Panel considered that the training presentation could have benefitted from a more explicit statement as to the licensed indication for Ultibro Breezhaler and that any reduction in exacerbations was to be discussed as a benefit of maintenance therapy and not as a reason to prescribe *per se*. Nonetheless, on balance, the Panel did not consider that the material encouraged representatives to promote Ultibro Breezhaler for exacerbation reduction. No breach of Clause 15.9 was ruled. The Panel considered that high standards had been maintained. No breach of Clause 9.1 was ruled.

The Panel noted that the Seebri Breezhaler leavepiece (ref SBR0003) at issue stated on the front cover that the medicine was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. Although the statement was in small type, it was visually prominent given that it was in black print on a white background. Page 2 of the leavepiece described a typical patient and stated that he 'wants a treatment that will help him breathe better in the morning… and throughout the day'. Page 3 of the leavepiece included the claim that, compared with placebo, Seebri Breezhaler 'Significantly reduces the risk of first moderate/severe COPD exacerbation by 31% (p=0.023)'. The Panel did not consider that the leavepiece promoted Seebri Breezhaler for

the reduction of COPD exacerbation as alleged. Preceding claims largely discussed symptom control. The reference to exacerbations had been presented within the context of the licensed indication ie as a benefit of maintenance therapy and not the reason to prescribe *per se*. The Panel considered that the promotion of Seebri Breezhaler had been consistent with the particulars listed in the SPC. No breach of Clause 3.2 was ruled. The leavepiece did not imply that exacerbation reduction was a primary reason to prescribe Seebri Breezhaler and so was not misleading in that regard. No breach of Clause 7.2 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

In response to the complainant's wider concerns about the promotion of Seebri Breezhaler, Novartis provided a copy of an internal training presentation (ref SBR0023). In an overview of COPD it was stated reduced rate of exacerbations were key issues for payers and clinicians. In an overview of the brands, a slide on positioning Seebri Breezhaler indicated that it was to be 'First line LAMA for all your COPD patients'. The two key messages were 'Initiate Seebri Breezhaler to help your patients breathe more easily during the mornings…and throughout the day' and 'Reduces your patients risk of exacerbations'. The presentation included a slide which stated 'Important Seebri Breezhaler is licensed as a maintenance therapy. You must not suggest it can be used as a rescue medication'. Representatives were not similarly reminded that they must not promote Seebri Breezhaler for reduction of exacerbations. A subsequent slide appeared to show a page similar to that contained within the sales aid referred to below with the claim, 'Initiate Seebri Breezhaler to reduce your patients' risk of exacerbations'. Overall the Panel considered that the presentation suggested that Seebri Breezhaler could be prescribed *per se* to reduce COPD exacerbations, for which the medicine was not indicated. It was particularly important to make this clear to representatives who might well be asked questions about exacerbation data. A second internal training presentation (ref UK/SBR/15-0215a) was similar in content although it did not contain the statement 'Important Seebri Breezhaler is licensed as a maintenance therapy. You must not suggest it can be used as a rescue medication'. Overall the Panel considered that the presentations suggested that Seebri Breezhaler could be prescribed *per se* to reduce COPD exacerbations, for which the medicine was not indicated; both were ruled in breach of Clause 15.9. The Panel considered that high standards had not been maintained; a breach of Clause 9.1 was ruled.

The Seebri Breezhaler sales aid (UK/SBR/15-0354a) contained a page which was headed 'How can you help delay the time to first moderate to severe COPD exacerbation for your patients' which appeared above a graph comparing the effect of Seebri Breezhaler with that of placebo. The claim at the bottom of the slide read 'Initiate Seebri Breezhaler to reduce your patients' risk of exacerbations'. Finally the Panel noted that although a set of Seebri Breezhaler speaker slides (ref UK/SBR/16-0012) only briefly referred to the positive exacerbation data from Kerwin *et al* (2012) compared with placebo, those results were not put into context by any statement of the licensed indication for the medicine. The Panel considered that the sales aid and the speaker slides both suggested that Seebri Breezhaler could be prescribed *per se* to reduce COPD exacerbations, for which the medicine was not indicated; this was inconsistent with the particulars listed in the Seebri Breezhaler SPC and a breach of Clause 3.2 was ruled. The materials implied that exacerbation reduction was a primary reason to prescribe Seebri Breezhaler. A breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel noted its rulings and comments above but considered that the matters were not such as to bring discredit upon, or reduce confidence in, the industry. No breach of Clause 2 was ruled.

During its consideration of the Ultibro Breezhaler material, the Panel noted that much of it referred to the findings of Zhong *et al*, ie a 31% reduction in the rate of moderate or severe exacerbations for Ultibro Breezhaler vs salmeterol/fluticasone (p=0.048). COPD exacerbations over 26 weeks, however, was only an exploratory objective of the study; the primary objective had been to demonstrate the non-inferiority of Ultibro Breezhaler to salmeterol/fluticasone in terms of postdose trough FEV1 at week 26. The exploratory nature of the exacerbation data was stated on some pieces by way of a footnote. In that regard the Panel queried whether exploratory data was robust enough to substantiate the prominent claims made and it also noted the advice contained in the supplementary information to Clause 7.2 that claims should be able to stand alone and in general should not be qualified by footnotes and the like. The Panel was further concerned to note that the data contained in the SPC with regard to COPD exacerbations showed a non-significant benefit for Ultibro Breezhaler vs salmeterol/fluticasone in that it was stated that number of moderate or severe COPD exacerbations/patient years was 0.15 vs 0.18 respectively (p=0.098). In that regard the Panel queried whether claims related to the statistically significant benefit for Ultibro Breezhaler vs salmeterol/fluticasone reported by Zhong *et al* were consistent with the non-significant benefit listed in the Ultibro Breezhaler SPC. The Panel requested that the Alliance be advised of its concerns in this regard.

**Complaint received** **25 April 2016**

**Case completed** **16 September 2016**

**CASE AUTH/2841/4/16**

# ANONYMOUS, NON CONTACTABLE v GLAXOSMITHKLINE

## Promotion of Anoro Ellipta

**An anonymous, non contactable complainant complained about the promotion of long-acting beta agonist/long-acting muscarinic antagonists (LABA/LAMA) combination inhalers for the treatment of chronic obstructive pulmonary disease (COPD). The complainant referred to the first medicine to be licensed within this class, Ultibro Breezhaler (indacaterol maleate and glycopyrronium bromide) noting that it was clear from its European Public Assessment Report (EPAR) that the Committee for Medicinal Products for Human Use (CHMP) turned down an application that included its use to reduce COPD exacerbations, because its effects in that regard were too small to recommend such use. Ultibro Breezhaler was subsequently licensed only as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD and thus its promotion in relation to COPD exacerbation reduction was off-label. The complainant cited other examples of what could be considered to be off-label promotion based on the CHMP ruling on LABA/LAMA combination inhaler indications and in that regard noted, *inter alia*, GlaxoSmithKline's product Anoro Ellipta (vilanterol/umeclidinium) for which, according to its EPAR, a specific licence for exacerbation reduction was never applied for.**

**Anoro was indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.**

**In relation to this case the complainant noted in particular that a MIMS webpage which reviewed Anoro Ellipta included the claim that COPD exacerbations were reduced by 50% compared with placebo. The complainant submitted that the item contained no information warning of the off-label aspects of the promoted use of the product.**

**The complainant concluded that as there was no specific indication for exacerbation reduction in the registration applications for Anoro Ellipta, the medicine was not licensed for use to reduce exacerbations in COPD patients and so promoting it to reduce COPD exacerbation reduction was off-label.**

**The complainant stated his/her colleagues had little awareness that LABA/LAMA combination inhalers or LAMA inhalers were being prescribed in an unlicensed manner. Also, formal recommendations for the use of these medicines in exacerbation reduction were increasingly appearing in local clinical guidelines which suggested that promotion of the medicines had not clearly communicated the off-label nature of this use. The complainant stated that the materials for the various inhalers to which he/she had drawn attention were just the tip of the iceberg; he/she knew of numerous educational meetings/symposia involving external speakers where exacerbation reduction data had been presented as part of product promotion.**

**A potential major concern for the complainant and his/her colleagues was that they might have unknowingly prescribed LABA/LAMA combination inhalers or LAMA inhalers to numerous COPD patients assuming that they were licensed for exacerbation reduction. The statement from the CHMP which considered exacerbation was therefore a sobering thought especially if COPD patients subsequently suffered exacerbations unexpectedly because their prescribed LABA/LAMA combination inhalers might not be effective enough as intimated by the CHMP assessment of Ultibro Breezhaler. COPD was characterised in part by airway inflammation and the extent of inflammation was progressive leading up to an exacerbation. None of the medicines in question contained an anti-inflammatory component. Another very important consideration was that prescribers were unaware from a medico-legal perspective that they would be solely liable for any adverse consequences suffered by patients which might arise.**

**The detailed response from GlaxoSmithKline is given below.**

**The Panel noted that Section 5.1 of the Anoro Ellipta summary of product characteristics (SPC) referred to its positive impact on exacerbations of COPD. The Panel noted that Section 1.1 of the National Institute for Health and Care Excellence (NICE) Guideline on the management of COPD listed the symptoms of the disease which were, *inter alia*, exertional breathlessness, chronic cough, regular sputum production and wheeze. In Section 1.3 of the Guideline, the exacerbation of COPD was described as a sustained worsening of the patient's symptoms from their usual stable state which was beyond normal day-to-day variations and was acute in onset. In the Panel's view, there was a difference between COPD symptoms and exacerbations of COPD although it accepted that patients whose symptoms were well controlled might be less likely to experience an exacerbation of their condition than patients with poorly controlled symptoms. In that regard the Panel considered that exacerbations might be referred to in the promotion of COPD maintenance therapy but that there was a difference between promoting a medicine for a licensed indication and promoting the benefits of treating a condition. In the Panel's view, reference to reduced COPD exacerbation must be set within the context of the primary reason to prescribe ie maintenance therapy to relieve symptoms.**

**The Panel noted that Anoro Ellipta was first authorised on 8 May 2014. The MIMS article referred to by the complainant was dated 24 June 2014 and headed 'In Depth – Anoro Ellipta: first LABA/LAMA combination inhaler for COPD'. The Panel noted GlaxoSmithKline's submission that it did not commission the MIMS article nor did it have any editorial control over it. The company submitted that it had no awareness of its inception or publication. GlaxoSmithKline had received confirmation from the editor that MIMS articles were produced independently. The Panel considered that as the article at issue was wholly**

**independent of GlaxoSmithKline, it did not come within the scope of the Code and no breach was ruled in that regard.**

**The Panel did not consider that either the primary care iPad presentation and its accompanying briefing material, nor other material, promoted Anoro Ellipta for the reduction of COPD exacerbation as alleged. Reference to exacerbations had been presented within the context of the licensed indication ie as a benefit of therapy and not the reason to prescribe *per se*. The Panel considered that the promotion of Anoro Ellipta had been consistent with the particulars listed in the SPC. The materials did not misleadingly imply that exacerbation reduction was a primary reason to prescribe Anoro Ellipta. Briefing materials did not present exacerbation data in such a way as to advocate a course of action which was likely to breach the Code. High standards had been maintained. No breaches of the Code were ruled.**

**The Panel noted that it had also been provided with copies of three certified presentations delivered by health professionals on behalf of GlaxoSmithKline. Slide 12 of a presentation entitled 'COPD – Latest therapies' stated that one of the aims of treatment was to reduce symptoms and increase the patient's quality of life and also to reduce exacerbations/ admissions and mortality. Slide 36, headed 'Exacerbations', stated, *inter alia*, that Anoro produced a 50% reduction in time to first exacerbation vs tiotropium. Slide 55 clearly stated the licensed indication for Anoro ie maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The following, and last 9 slides detailed clinical results for Anoro and gave a brief overview of the medicine. Reduction of exacerbations was not referred to on these slides. On balance, and notwithstanding one brief mention of exacerbation reduction in a set of 65 slides, the Panel did not consider that overall the presentation promoted Anoro for exacerbation reduction. No breach of the Code was ruled. The Panel, however, considered that the claim about reduced time to first exacerbation was misleading given GlaxoSmithKline's submission that clinical studies were not designed to evaluate the effect of Anoro on COPD exacerbations. A breach of the Code was ruled.**

**A second presentation about breathlessness in COPD, included a number of slides specifically about Anoro including one which referred to exacerbation data from a study comparing Anoro with tiotropium. The licensed indication for Anoro was not clearly stated anywhere in the presentation. Similarly, the final presentation 'Management and prevention of exacerbations of COPD', gave an overview of COPD, the effects of exacerbations on patients and the role of treatment in acute exacerbation. One slide headed 'LAMA-LABA' stated that Anoro reduced COPD exacerbations by 50% vs placebo and also vs tiotropium. Nowhere in the presentation was the licensed indication of Anoro stated. The Panel considered that in the absence of any statement to the contrary, some viewers might assume that Anoro could be prescribed *per se* to reduce COPD exacerbations for which the medicine was not licensed. In that regard the Panel considered that the presentations were not consistent with the particulars listed in the SPC. A breach of the Code was ruled which was upheld on appeal by GlaxoSmithKline. The Panel considered that although Anoro exacerbation data could be referred to, it was misleading to do so when the licensed indication for the medicine had not been clearly stated and there was no statement to the effect that clinical studies were not designed to evaluate the effect of Anoro on COPD exacerbations. A breach of the Code was ruled.**

**With regard to the three presentations, the Panel noted its rulings of breaches of the Code above and considered that high standards had not been maintained. A further breach of the Code was ruled.**

**The Panel noted its rulings and comments above about the presentations but considered that the matters were not such as to bring discredit upon, or reduce confidence in, the industry. No breach of Clause 2 was ruled.**

An anonymous, non contactable complainant complained about the promotion of long-acting beta agonist long-acting muscarinic antagonists (LABA/ LAMA) combination inhalers for the treatment of chronic obstructive pulmonary disease (COPD). The complainant referred to the first medicine to be licensed within this class, Ultibro Breezhaler (indacaterol maleate and glycopyrronium bromide) and stated that although it was clear from its European Public Assessment Report (EPAR – dated 25 July 2013) that an application was originally submitted for the relief of COPD symptoms and the reduction of exacerbations, the Committee for Medicinal Products for Human Use (CHMP) subsequently stated the medicine's effects on reducing the rate of exacerbations were too small to recommend its use for such. Ultibro Breezhaler was eventually licensed as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The complainant stated that it could be concluded that Ultibro Breezhaler was not granted a licence at the time to recommend its use for reducing exacerbations and alleged, that promotion of Ultibro Breezhaler in relation to COPD exacerbation reduction was off-label. The complainant provided a number of other examples of what could be considered to be off-label promotion based on the CHMP decision about LABA/LAMA combination inhaler indications and in relation to this case drew attention to GlaxoSmithKline's product Anoro Ellipta (vilanterol/ umeclidinium) for which, according to its EPAR, a specific licence for exacerbation reduction was never applied for.

Anoro was indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

**COMPLAINT**

The complainant drew particular attention to the MIMS webpage (http://www.mims.co.uk/depth-anoro-ellipta-first-laba-lama-combination-inhaler-copd/respiratory-system/article/1300220) which reviewed Anoro Ellipta and included the statement, 'COPD exacerbations were reduced by 50% with vilanterol/umeclidinium compared with placebo'. The item contained no information warning of the off-label aspects of the promoted use of the product.

The complainant submitted that as there was no specific indication for exacerbation reduction in the registration applications for Anoro Ellipta, it could be concluded that the medicine was not licensed for use to reduce exacerbations in COPD patients. Therefore promotion of Anoro Ellipta in relation to COPD exacerbation reduction was off-label.

The complainant stated having spoken to his/her peers it was evident that there was very little awareness amongst fellow colleagues that LABA/LAMA combination inhalers or LAMA inhalers were being prescribed in an unlicensed manner. Also, formal recommendations for the use of these medicines in exacerbation reduction were increasingly appearing in local clinical guidelines which suggested that promotion of the medicines had most likely missed an ethical obligation to also clearly communicate the off-label nature of this use, either in materials or as instructions to representatives. The complainant concluded that materials for the various inhalers to which he/she had drawn attention were probably just the tip of a large iceberg. The complainant was aware of numerous educational meetings/symposia involving external speakers where exacerbation reduction data had been discussed and presented as part of product promotion.

A potential major concern for the complainant and his/her prescribing colleagues was that unknowingly, they might have prescribed LABA/LAMA combination inhalers or LAMA inhalers to numerous COPD patients based on the assumption that they were licensed for exacerbation reduction. The statement from the CHMP which considered exacerbation was therefore a sobering thought especially if treated COPD patients subsequently suffered exacerbations unexpectedly. This was because prescribing LABA/LAMA combination inhalers might not be effective enough as intimated by the CHMP assessment of Ultibro Breezhaler. COPD was characterised in part by airway inflammation and the extent of inflammation was progressive leading up to an exacerbation. None of the medicines in question actually contained an anti-inflammatory component. Another very important consideration was that prescribers were unaware from a medico-legal perspective that they would be solely liable for any adverse consequences suffered by patients which might arise.

In writing to GlaxoSmithKline the Authority asked it to respond to Clauses 2, 3.2, 7.2, 9.1 and 15.9. The edition of the Code would be that relevant at the time the materials were used.

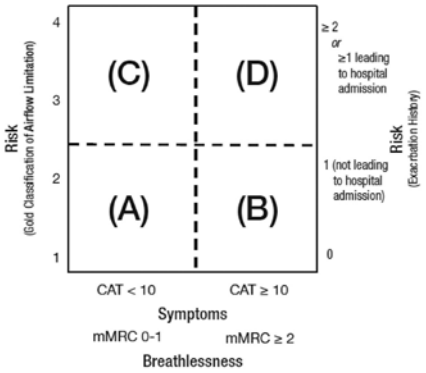
**RESPONSE**

By way of background, GlaxoSmithKline submitted that COPD was a heterogeneous disease, characterised by an irreversible airflow limitation that was usually progressive. The disease manifested in different ways in different patients, with different symptoms predominating. These symptoms could include breathlessness, cough, wheeze and sputum production. National Institute for Health and Care Excellence (NICE) Guidelines (Section 1.3.1) defined an exacerbation of COPD as 'a sustained worsening of the patient's symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset'. Differing symptoms, degrees of breathlessness, limitations to airflow, and risk of exacerbations gave rise to a heterogeneous patient population.

This heterogeneity was reflected in widely used patient classification systems, such as that found within the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines. GOLD was an international committee of respiratory medicine experts. Using its 'quadrant management strategy tool' (reproduced below) patients with COPD could be divided into four groups, based on their risk of exacerbations, lung function and degree of breathlessness.

**Table 4.2. Model of Symptom/Risk of Evaluation of COPD**

*When assessing risk, choose the highest risk according to GOLD grade or exacerbation history. (One or more hospitalizations for COPD exacerbations should be considered high risk.)*




| Patient Category | Characteristics | Spirometric Classification | Exacerbations per year | CAT | mMRC |
|---|---|---|---|---|---|
| A | Low Risk, Less Symptoms | GOLD 1-2 | ≤1 | < 10 | 0-1 |
| B | Low Risk, More Symptoms | GOLD 1-2 | ≤1 | ≥ 10 | ≥ 2 |
| C | High Risk, Less Symptoms | GOLD 3-4 | ≥ 2 | < 10 | 0-1 |
| D | High Risk, More Symptoms | GOLD 3-4 | ≥ 2 | ≥ 10 | ≥ 2 |

GOLD, Global Strategy for the Diagnosis, Management and Prevention of COPD, 2016.

GOLD classifications were widely used to define patient populations in COPD clinical trials, due to the international understanding and applicability of those categories.

The important role which exacerbations played within COPD was highlighted by Merinopoulou *et al* (2016) (44,201 patients) which demonstrated that all COPD patients were at risk of exacerbations. The authors reported that patients within all four GOLD categories experienced exacerbations. The rate of exacerbations varied from 0.83 exacerbations per person-year, in GOLD A (95% CI: 0.81–0.85) to 2.51 exacerbations per person-year, in GOLD D (95% CI: 2.47–2.55).

Given the range, and crossover of symptom manifestations experienced by COPD patients, it was important to capture different aspects of the disease within clinical studies as secondary endpoints. This allowed a full measure of a medicine's pharmacodynamic properties, and applicability to the patient population to be better understood.

The European Medicines Agency (EMA) provided guidance on the clinical investigation of medicines for the treatment of COPD and reflected the need to capture the heterogeneity of the disease in clinical studies:

> 'Different types of drugs may be developed for COPD which may provide symptomatic relief through improvement of airway obstruction, which may modify or prevent exacerbations or which may modify the course of the disease or modify disease progression .... Depending on the mechanism of action of the drug substance under evaluation, a complete characterisation of the effect of any therapy in COPD would require the inclusion of a number of different variables belonging to those domains expected to be affected by the study drug, because most treatments will produce benefits in more than one area.'

In conclusion, the heterogeneous nature of COPD meant that a number of different therapies were required; a complete characterisation of these medicines required assessment of a number of different clinical endpoints.

GlaxoSmithKline explained that Anoro Ellipta was an inhaled long-acting muscarinic antagonist/long-acting beta2 agonist (LAMA/LABA) combination product, which in the EU was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. It had been generally available in the UK since 24 June 2014.

Anoro was a long-acting, dual bronchodilator, which primarily acted to dilate the airways and improve airflow. This helped to relieve symptoms of COPD, including breathlessness. The primary outcome of Anoro Ellipta efficacy studies were therefore measures of lung function, such as FEV1 (forced expiratory volume in 1 second). Secondary endpoints included measures of breathlessness, quality of life, use of rescue medication, exacerbations, exercise endurance and lung volume.

The EPAR for Anoro Ellipta assessed that there was a place for the use of Anoro across all COPD patients as follows:

> 'Indication
> As all the efficacy studies predominantly included subjects from the GOLD category B (88%) and as consequence any conclusions drawn are likely to be applicable to this subset only. However the claimed indication would allow all four GOLD categories to be treated with the combination as a first line treatment. During the evaluation the Applicant was requested to justify the indication claimed. The Applicant did clarify that the estimate of 88% of subjects falling in to Group B was based on partial data (mMRC score and exacerbations). When all relevant data (including airflow limitation) was added, 58% subjects were group D and 42% were Group B. A reasonable proportion of subjects across the grade II-IV (GOLD grading based on spirometry) was represented in the studied population. Therefore it was accepted by the CHMP that the results are likely to be relevant to the broad COPD population.' (emphasis added)

In summary, the EPAR report concluded that the licence issued to Anoro allowed patients within all four GOLD categories, and hence the broad COPD population, to be treated with Anoro.

In line with the European Commission guidance document regarding the contents of the summary of product characteristics (SPC), Section 5.1 of the SPC should provide:

> 'limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials...'
>
> '...Such information on clinical trials should be concise, clear, relevant and balanced.'

In Section 5.1 of the EU SPC, exacerbation data for Anoro obtained from Phase 3a efficacy and safety studies, was documented:

> 'Anoro reduced the risk of a COPD exacerbation by 50% compared with placebo (based analysis of time to first exacerbation: Hazard Ratio (HR) 0.5, p=0.004*); by 20% compared with umeclidinium (HR 0.8, p=0.391); and by 30% compared with vilanterol (HR 0.7, p=0.121). From the three active-comparator studies, the risk of a COPD exacerbation compared with tiotropium was reduced by 50% in one study (HR 0.5, p=0.044) and was increased by 20% and 90% in two studies (HR 1.2, p=0.709 and HR 1.9, p=0.062 respectively). These studies were not specifically designed to evaluate the effect of treatments on COPD exacerbations and patients were withdrawn from the study if an exacerbation occurred. (A step-down statistical testing procedure was used in this study and this comparison was below a comparison that did not achieve statistical significance. Therefore, statistical significance on this comparison cannot be inferred).'

Exacerbations were a pre-defined secondary endpoint, captured within key phase 3 Anoro studies. This was consistent with the EMA clinical studies guidance that stated that:

> 'The rate of moderate or severe exacerbations is a clinically relevant endpoint related to the associated morbidity and mortality and the usually significantly increased health-care requirement. The frequency and/or severity of exacerbations are important outcome measures that should be considered in clinical studies in COPD.'

The inclusion of exacerbation data within Section 5.1 of the Anoro Ellipta SPC was therefore justified.

In order for clinicians and other key decision makers, to make informed choices about COPD treatments, they must be able to assess details of clinically relevant endpoints of efficacy and safety studies, including exacerbation data. This was supported by guidance from NICE:

> 'The choice of drug(s) should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and cost.'

This further supported the inclusion of exacerbation data within Section 5.1 of the Anoro Ellipta SPC. In addition, it highlighted the importance of making exacerbation data available for health professionals and other key decision makers, within the correct context, in order to help health professionals make informed choices about the most appropriate prescribing option for their patients.

GlaxoSmithKline referred to Clauses 3.2 and 7.2 of the Code and submitted given that exacerbation data was included in Section 5.1 of the Anoro Ellipta SPC, the inclusion of this data within promotional materials was not inconsistent with the particulars of the SPC, so long as the information given was not misleading. Inclusion of data, such as exacerbation rates within studies, played an important role to provide a balanced reflection of the evidence available.

GlaxoSmithKline noted that the complainant provided a single example of material, which he/she considered was 'off-label' promotion. The online article in MIMS at issue, dated June 2014, was a third party publication, which GlaxoSmithKline did not commission, and over which it had no editorial control. Indeed the company had no awareness of its inception or publication.

The editorial independence of MIMS from pharmaceutical companies was clear on its website:

> 'Each MIMS product monograph is compiled by our team of pharmacists based on the approved licence information. The monograph is an expert abbreviation of the full summary of product characteristics (SPC)...'

> 'MIMS is not influenced by marketing information from pharmaceutical companies and all products are included at the discretion of the editorial team. Coverage of new products and other prescribing news is decided solely by the editorial team.'

Furthermore, GlaxoSmithKline had also received confirmation from the editor of MIMS that:

> 'articles in MIMS are produced entirely independently. Each story is conceived and written solely by the editorial team, based on our opinion of what is interesting and relevant to MIMS audience, and we do not inform pharmaceutical companies of articles we plan to publish or consult with them on the content.'

In these circumstances, GlaxoSmithKline was not responsible for the content of the webpage, and therefore refuted any breaches of the Code in relation to it.

Notwithstanding the above, the statement within the article, referred to by the complainant, 'COPD exacerbations were reduced by 50% with vilanterol/umeclidinium compared with placebo' was factually correct, and referenced the Anoro SPC (Section 5.1).

Other than the MIMS article, no other material pertaining to GlaxoSmithKline was specifically highlighted or provided.

GlaxoSmithKline noted that the complainant stated that he/she was aware of 'numerous educational meetings/symposia involving external speakers where exacerbation reduction data had been discussed and presented as part of product promotion'. The complainant had not provided any specifics of those meetings, and it was unclear whether he/she referred to Anoro materials in this matter. GlaxoSmithKline was thus unable to comment specifically on this matter.

The complainant also stated that 'promotion of the above mentioned products have most likely missed an ethical obligation to also clearly communicate the offlabel nature of this use, either in materials or as instruction to sales representatives promoting the products'. The complainant had not provided any specifics of promotional or representative material, and it was unclear whether he/she referred to Anoro materials in this matter. GlaxoSmithKline was thus unable to comment specifically on this matter.

Notwithstanding the above, GlaxoSmithKline submitted that it had demonstrated that the presence of data relating to exacerbations within promotional material was acceptable, as it supported a balanced, fair, accurate and informed understanding of information relating to a medicine.

In conclusion, GlaxoSmithKline strongly believed that the promotion of Anoro was accurate, balanced, fair and objective and provided a clear overview of relevant information, in a manner that was not misleading, and could be substantiated. All data used, including exacerbation data, was in line with the marketing authorisation and not inconsistent with the SPC.

GlaxoSmithKline refuted any breach of Clauses 3.2, 7.2 and 15.9. In the absence of these breaches, the

company also refuted being in breach of Cause 9.1 and Clause 2, as it had maintained high standards and had not prejudiced patient safety.

In response to a request for further information, GlaxoSmithKline identified a number of materials which referred to exacerbation data. In each instance the data was consistent with Section 5.1 of the SPC as well as appropriately contextualised for the audience and situation.

The enclosed items were divided into a number of categories, depending on their intended use and audience.

Promotional materials

Exacerbation data did not form part of Anoro Ellipta core claims and was therefore not present in core promotional campaign materials or used proactively by representatives and so only a limited number of items fell within scope, and were summarised below. Those materials supported representatives in reactive conversations with health professionals and other key decision makers, about specific Anoro data. Where exacerbation data was included, it was consistent with that found in Section 5.1 of the Anoro SPC. This material ensured that representatives were adequately briefed on questions which might arise and enabled customers to remain informed about relevant data.

*Anoro Ellipta APACTs (acknowledge, probe, answer, confirm, transition) and Q&A (ref UK/UCV/0004/14d(2)).*

The position for representatives regarding exacerbation data was outlined under the question 'Why doesn't Anoro have exacerbation data like tiotropium?'. This was a document which was for internal use by representatives, and supported the representative in reactively answering health professionals' questions.

The statements; 'our Anoro Ellipta trial program was conducted in patients whose primary concern was shortness of breath (MRC ≥ 3). Patients were excluded from the trial program if they had been hospitalised with an exacerbation of COPD 12 weeks before the trials started', and, 'it is important to note that these studies were not specifically designed to evaluate the effect of treatments on COPD exacerbations and patients were withdrawn from the studies if an exacerbation occurred. In all studies absolute numbers of exacerbations were low' ensured that the data was appropriately contextualised by representatives. The statement 'No current bronchodilator licensed for the treatment of COPD has a label indication for exacerbation risk reduction' clarified the positioning of Anoro for the representatives. Anoro was positioned to relieve symptoms in adults with COPD, in line with Section 4.1 of the SPC. This was reinforced by the Anoro core claims used in promotional campaigns.

*Anoro market access document April 2016 (ref UK/UCV/0004/14z(4))*
*Anoro market access document April 2016 briefing document (UK/UCV/0004/14z(3)a(1)).*

The Anoro market access document was provided to a health professional, or key decision maker, to support market access reviewers by providing a more detailed overview of the wider body of evidence relevant to Anoro and information about the relevant therapy area. This was carried out in view of NICE Guidelines which stated that:

> 'The choice of drug(s) should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and cost.'

The section about exacerbations which it contained was taken directly from the Anoro SPC. Its inclusion was part of a balanced reflection of the evidence available. The statement 'Anoro Ellipta studies were specifically designed for breathless patients (MRC ≥ 3) and were not designed to evaluate the effect of treatments on COPD exacerbations' ensured that the reader was clear that the data did not come from exacerbation studies. It was also made clear that exacerbation rates were safety endpoints.

GlaxoSmithKline also provided a copy of the associated representative briefing document.

*Maleki-Yazdi Study Clinical Summary Booklet (ref UK/UCV/0160/14(1))*
*Maleki-Yazdi briefing video (ref UK/UCV/0164/14b).*

GlaxoSmithKline submitted that Maleki-Yazdi *et al* (2014) was a head-to-head clinical trial which compared the safety and efficacy of Anoro Ellipta with tiotropium. The data relating to exacerbation rates were found within Section 5.1 of the Anoro SPC. The 'clinical summary booklet' was provided to health professionals, at their request, with a reprint of the peer reviewed paper. The statement 'this study was not specifically designed to evaluate the effect of treatments on COPD exacerbations and patients were withdrawn from the study if an exacerbation occurred' ensured that readers were clear that this was not an exacerbation study.

The associated briefing video was for internal use only, and supported representatives by explaining and contextualising the data. It was not to be shared with health professionals and was viewed by representatives, alongside the printed materials.

*Duaklir competitor card (ref UK/RESP/0302/14k(2))*
*Ultibro Breezhaler briefing (UK/RESP/0302/14d).*

These competitor cards were for internal use by representatives only. They were not to be shared with health professionals. The information included was only discussed reactively with health professionals, in response to direct questions from them about data included in competitor materials.

Their development was in response to the use of exacerbation data in promotional campaigns for other products in the LAMA/LABA class. The exacerbation data relating to Anoro was taken directly from the Anoro SPC. The statement, 'the Anoro Ellipta trials were not specifically designed to evaluate the effect of treatments on COPD exacerbations. In all Anoro

Ellipta studies the absolute numbers of exacerbations were low', ensured that representatives were clear that these were not exacerbation studies.

*Anoro Ellipta SPC (ref UK/UCV/0041/14(3))*
*Anoro SPC training quiz (ref UK/RESP/0125/15).*

GlaxoSmithKline explained that representatives were provided with a copy of the Anoro Ellipta SPC to provide in specific circumstances, for example with samples if requested by a health professional. They were therefore required to read the SPC, and the associated quiz contained a question on exacerbation data, to ensure that they had reviewed the material and retained the information contained. The SPC was not used as a detail aid for conversations with customers, and as evident in the material provided above, all briefing regarding exacerbation data discussions were for reactive purposes only.

Promotional core claims documents

*Primary Care iPad campaign (ref UK/UCV/0011/16)*
*Primary Care iPad campaign briefing (ref UK/UCV/0011/16a)*
*Secondary Care iPad campaign (ref UK/UCV/0002/16)*
*Secondary Care iPad campaign briefing (ref UK/UCV/0002/16a)*
*Anoro Leavepiece (ref UK/UCV/0077/15a(1)).*

GlaxoSmithKline noted that exacerbation data did not form part of Anoro Ellipta core claims and was therefore not present in core promotional campaign materials used proactively by representatives. The company provided copies of the Anoro primary and secondary care campaigns, used by representatives in calls with health professionals, and the Anoro leavepiece, which could be left with health professionals for their reference. These materials did not refer to exacerbation data.

Medical materials

*MSL medical reactive deck - Bronchodilation and its role in preventing COPD exacerbations (ref UK/UCV/0077/14).*

*MEL deck – COPD: Time for a new NICE guideline? (ref UK/CPD/0006/15(4)).*

The medical scientific liaison (MSL) deck was a set of powerpoint slides that MSLs could use with customers to support reactive conversations answering specific questions from the health professional. This was carried out as scientific exchange and was non-promotional.

The MEL deck was a presentation given by specialist respiratory consultants, who were employees of GlaxoSmithKline and experts in the field, to a selective audience of health professionals. Specific exacerbation data was only given on a supplementary slide, which could be shown to health professionals if they had further questions about the topic.

External speaker presentations

*Ellipta Portfolio Slide Library (ref UK/RESP/0293/14(3))*
*Liz Sapey 4 June 2015 (ref UK/UCV/0021/15(1))*
*Sarah Cowdell 9 July 2015 (ref UK/UCV/0071/15)*
*Dr Mann 24 September 2015 (ref UK/UCV/0094/15).*

GlaxoSmithKline noted that the complainant broadly raised education meetings and symposia where external speakers had presented, although no GlaxoSmithKline meetings had been specified.

External speakers may elect to present pre-prepared slides produced by the company. Exacerbation data was included as a non-compulsory slide, should the speaker consider that this was relevant and important to the audience. It was made clear that 'exacerbations as a safety endpoint were measured in both our placebo controlled and active comparator trials vs. tiotropium' and 'the Anoro Ellipta clinical trial programme were not specifically designed to evaluate the effect of treatments on COPD exacerbations and patients were withdrawn from the studies if an exacerbation occurred'. This ensured the audience viewed the data within the appropriate context.

At company-sponsored events, external experts in COPD might present slides that were produced independently, by the expert. GlaxoSmithKline might provide data and images, if they were specifically requested by the speaker. Other than correcting factual inaccuracies, and ensuring that the material was in line with the Code, GlaxoSmithKline stated that it did not influence the content of these presentations. The slides were certified by the company. There were three instances where external experts' materials included exacerbation data relating to Anoro. In each instance, the data presented reflected that in Section 5.1 of the Anoro SPC. Anoro exacerbation data formed a small percentage of each presentation and was framed appropriately within wider disease and treatment discussions.

GlaxoSmithKline submitted that in conclusion, of the items enclosed, only thirteen referred to Anoro exacerbation data, reflecting a small percentage of the greater than 200 items of Anoro Ellipta representative and promotional materials produced.

GlaxoSmithKline explained that when exacerbation data had been used, it had been framed in an appropriate, transparent and responsible manner, and it was made clear that the studies referred to were not exacerbation studies.

GlaxoSmithKline submitted that as exacerbation data was included in Section 5.1 of the Anoro Ellipta SPC, the inclusion of this data in promotional materials was not inconsistent with the particulars of the SPC, and hence acceptable, providing that the information given was not misleading. Inclusion of data, such as exacerbation rates within studies, played an important role to provide a balanced reflection of the evidence available.

GlaxoSmithKline maintained that in order to allow clinicians and other key decision makers to make informed choices about COPD treatments, they must be able to assess details of clinically relevant endpoints of efficacy and safety studies, including

exacerbation data. This was supported by NICE guidance:

> 'The choice of drug(s) should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and cost.'

GlaxoSmithKline submitted that it was therefore appropriate to share this data within commercial and medical materials.

**PANEL RULING**

The Panel noted that Anoro Ellipta was indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Section 5.1 of the SPC referred to its positive impact on exacerbations of COPD. The Panel noted that Section 1.1 of the NICE Guideline on the management of COPD listed the symptoms of the disease which were, *inter alia*, exertional breathlessness, chronic cough, regular sputum production and wheeze. In Section 1.3 of the Guideline, the exacerbation of COPD was described as a sustained worsening of the patient's symptoms from their usual stable state which was beyond normal day-to-day variations and was acute in onset. In the Panel's view, there was a difference between COPD symptoms and exacerbations of COPD although it accepted that patients whose symptoms were well controlled might be less likely to experience an exacerbation of their condition than patients with poorly controlled symptoms. In that regard the Panel considered that reference to exacerbations might be included in the promotion of COPD maintenance therapy but that there was a difference between promoting a medicine for a licensed indication and promoting the benefits of treating a condition. In the Panel's view, any reference to reduced COPD exacerbation must be set within the context of the product's licensed indication and thus the primary reason to prescribe ie maintenance therapy to relieve symptoms.

The Panel noted that GlaxoSmithKline had been asked to consider the requirements of Clauses 2, 3.2, 7.2, 9.1 and 15.9 and advised that the edition of the Code that would be relevant would be that which was in force when the materials were used. The Panel considered, however, that given the matters at issue, the relevant, substantial requirements of Clauses 2, 3.2, 7.2, 9.1 and 15.9 had not changed since the 2014 Code (the earliest Code relevant to the material at issue) and so all of the rulings below were made under the 2016 Code.

The Panel noted that Anoro Ellipta was first authorised on 8 May 2014. The MIMS article referred to by the complainant was dated 24 June 2014 and headed 'In Depth – Anoro Ellipta: first LABA/LAMA combination inhaler for COPD'. It was stated on the MIMS website, *inter alia*, that each MIMS monograph was compiled by the MIMS team of pharmacists based on the approved licence information and the SPC. It was also stated that MIMS was not influenced by pharmaceutical companies; coverage of new products was decided solely by the editorial team. The Panel noted GlaxoSmithKline's submission that it did not commission the article nor did it have any editorial control over it. The company submitted that it had no awareness of its inception or publication. GlaxoSmithKline had received confirmation from the editor that MIMS articles were produced entirely independently. The Panel considered that as the article at issue was wholly independent of GlaxoSmithKline, it did not come within the scope of the Code and no breach was ruled in that regard.

The Panel noted GlaxoSmithKline's submission that exacerbation data did not form part of its core claims and thus was not present in its core promotional campaign materials or used proactively by its representatives. In that regard the Panel noted that the primary care iPad presentation posed the question 'What is important to you when prescribing a maintenance bronchodilator?' and did not refer to exacerbations. The accompanying briefing material referred to the appropriate positioning of LAMA/LABA as initial maintenance therapy. The secondary care presentation was similar and the relevant briefing material referred to the crucial role secondary care could play in the recommendation of Anoro Ellipta in primary care as initial maintenance therapy.

The Panel noted that most of the balance of the Anoro Ellipta materials provided were designed to support representatives in reactive conversations about specific Anoro Ellipta data. These materials referred to exacerbations but such data was usually within the context of a clear statement as to the licensed indication for the medicine and always accompanied by a statement to the effect that clinical studies were not designed to evaluate the effect of treatment on COPD exacerbations and that patients were withdrawn from the study if an exacerbation occurred e.g. the Anoro Ellipta APACTs and Q&A, the market access document and the Maleki-Yazdi Study Clinical Summary document. The briefing video on the latter referred to exacerbation data from the study but noted that it was not a primary endpoint; the summary statement at the end of the video made no reference to such data. The Portfolio COPD Ellipta Slide Library for speakers clearly stated the licensed indication for Anoro Ellipta on an introductory slide; there was no reference to its use to prevent COPD exacerbations. A non-compulsory slide did discuss time to first exacerbation data and whilst it did not include Anoro's licensed indication on the page it did indicate prominently and at the outset all of the study caveats mentioned above.

The MSL slide deck entitled 'Bronchodilation and its role in preventing COPD exacerbations' gave a general overview of the matter and was for reactive presentation by the GlaxoSmithKline medical team to support reactive conversations answering specific questions from a health professional. Two slides referred to Anoro and exacerbation data. One slide, entitled 'Why has GlaxoSmithKline not characterised [Anoro's] efficacy in patients at high risk of exacerbations?', included the explanation that as 12 month exacerbation studies had not been performed to generate robust exacerbation data, it was not possible to confirm the magnitude of benefit of Anoro on exacerbation. Whilst there was no statement of Anoro's licensed indication there was no evidence before the Panel that the presentation had been used

other than non-promotionally in response to a specific request about exacerbation data. The complainant bore the burden of proof in that regard.

The Panel did not consider that any of the materials referred to above promoted Anoro Ellipta for the reduction of COPD exacerbation as alleged. Reference to exacerbations had been presented within the context of the licensed indication ie as a benefit of therapy and not the reason to prescribe *per se*. The Panel considered that the promotion of Anoro Ellipta had been consistent with the particulars listed in the SPC. No breach of Clause 3.2 was ruled. The materials did not misleadingly imply that exacerbation reduction was a primary reason to prescribe Anoro Ellipta. No breach of Clause 7.2 was ruled. The primary and secondary care iPad briefing materials and the Maleki-Yazdi briefing video did not present exacerbation data in such a way as to advocate a course of action which was likely to breach the Code. No breach of Clause 15.9 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

The Panel noted that it had also been provided with copies of three presentations delivered by health professionals on behalf of GlaxoSmithKline; each presentation had been certified. Slide 12 of a presentation entitled 'COPD – Latest therapies' (ref UK/UCV/0071/15), stated that one of the aims of treatment was to reduce symptoms and increase the patient's quality of life and also to reduce exacerbations/admissions and mortality. Slide 36, headed 'Exacerbations', stated, *inter alia*, that Anoro produced a 50% reduction in time to first exacerbation vs tiotropium. Slide 55 clearly stated the licensed indication for Anoro ie maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The following, and last 9 slides detailed clinical results for Anoro and gave a brief overview of the medicine. Reduction of exacerbations was not referred to on these slides. On balance, and notwithstanding one brief mention of exacerbation reduction in a set of 65 slides, the Panel did not consider that overall the presentation promoted Anoro for exacerbation reduction. No breach of Clause 3.2 was ruled. The Panel, however, considered that the claim about reduced time to first exacerbation was misleading given GlaxoSmithKline's submission that clinical studies were not designed to evaluate the effect of Anoro on COPD exacerbations. A breach of Clause 7.2 was ruled.

A second presentation about breathlessness in COPD (ref UK/UCV/0021/15(1)), included a number of slides specifically about Anoro including one which referred to exacerbation data from a study comparing Anoro with tiotropium. The licensed indication for Anoro was not clearly stated anywhere in the presentation. Similarly, the final presentation (ref UK/UCV/0094/15) 'Management and prevention of exacerbations of COPD', gave an overview of COPD, the effects of exacerbations on patients and the role of treatment in acute exacerbation. One slide headed 'LAMA-LABA' stated that Anoro reduced COPD exacerbations by 50% vs placebo and also vs tiotropium. Nowhere in the presentation was the licensed indication of Anoro stated. The Panel considered that in the absence of any statement to the contrary, some viewers might assume that Anoro could be prescribed *per se* to reduce COPD exacerbations for which the medicine was not licensed. In that regard the Panel considered that the presentations were not consistent with the particulars listed in the SPC. A breach of Clause 3.2 was ruled. This ruling was appealed by GlaxoSmithKline. The Panel considered that although Anoro exacerbation data could be referred to, it was misleading to do so when the licensed indication for the medicine had not been clearly stated and there was no statement to the effect that clinical studies were not designed to evaluate the effect of Anoro on COPD exacerbations. A breach of Clause 7.2 was ruled.

With regard to the three presentations, the Panel noted its rulings of breaches of the Code above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel noted its rulings and comments above about the presentations but considered that the matters were not such as to bring discredit upon, or reduce confidence in, the industry. No breach of Clause 2 was ruled.

**APPEAL BY GLAXOSMITHKLINE**

GlaxoSmithKline appealed the Panel's ruling of a breach of Clause 3.2 with regard to the two presentations (refs UK/UCV/0021/15(1) and UK/UCV/0094/15).

GlaxoSmithKline submitted that the complainant's most pertinent concern was that 'Anoro Ellipta ... (is) not licensed for use to reduce exacerbations in COPD patients ... therefore promotion of Anoro Ellipta in relation to COPD exacerbation reduction is off-label'.

GlaxoSmithKline submitted that the use of Anoro Ellipta for the treatment goal of reducing the patient's risk of suffering a COPD exacerbation was not 'off-label', and was consistent with the licensed therapeutic indication (Section 4.1 of the SPC); it was also in line with national and international guidelines for the treatment of COPD, and was consistent with the manner by which patients with COPD, a heterogeneous disease, were managed by clinicians.

GlaxoSmithKline submitted that Section 4.1 of the Anoro Ellipta SPC, stated that:

> 'Anoro is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).'

GlaxoSmithKline submitted that this was the product's licence and guided a clinician to prescribe 'within label'.

GlaxoSmithKline submitted that symptoms and 'exacerbations' fell along a continuum in COPD. There was no diagnostic test or biomarker to define an 'exacerbation' of COPD. Widely accepted definitions of 'exacerbations' recognised this and referred to a

worsening of symptoms from a baseline of normal day-to-day variations, along this continuum, to an arbitrary threshold level. The modified Anthonisen criteria, a widely used definition for exacerbations in clinical trials, required an increase in symptoms for only two days.

'Respiratory symptoms were classified as "major" symptoms (dyspnea, sputum purulence, sputum amount) or "minor" symptoms (wheeze, sore throat, cough, and symptoms of a common cold which were nasal congestion/discharge). Exacerbations were defined as the presence for at least two consecutive days of increase in any two "major" symptoms or increase in one "major" and one "minor" symptom according to criteria modified from Anthonisen and colleagues.' (Seemungal *et al* 2000).

GlaxoSmithKline submitted that the European Respiratory Society/American Thoracic Society task force definition provided further clarification as to the continuum of worsening COPD symptoms and stratified exacerbation severity by the level of treatment which was required.

'- mild, which involves an increase in respiratory symptoms that can be controlled by the patient with an increase in the usual medication;
- moderate, which requires treatment with systemic steroids and/or antibiotics; and
- severe, which describes exacerbations that require hospitalisation or a visit to the emergency department' (Cazzola *et al* 2008).

GlaxoSmithKline submitted that national and international guidelines also acknowledge that the definition of an exacerbation of COPD was based on symptoms, and given the variability in the clinical presentation of individual patients, the definition consistently referenced the patient's baseline level of symptoms.

> 'An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication' (GOLD, Global Strategy for the Diagnosis, Management and Prevention of COPD, 2016).

> 'An exacerbation is a sustained worsening of the patient's symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum colour. The change in these symptoms often necessitates a change in medication' (NICE, Chronic obstructive pulmonary disease in over 16s: diagnosis and management, 2010).

GlaxoSmithKline submitted that studies also showed that symptom burden and exacerbations were intrinsically linked. In a survey of 2531 patients with COPD the correlation between breathlessness and exacerbations was assessed. It was found that patients with a higher burden of breathlessness experienced more frequent exacerbations (Punekar *et al* 2016).

GlaxoSmithKline submitted that if a patient's symptoms were relieved by Anoro Ellipta, then a sustained worsening in these symptoms was less likely and would be less severe, hence reducing the risk and severity of an exacerbation. Given that exacerbations and symptoms were intrinsically linked, it could not be stated that treating symptoms did not help prevent future exacerbations.

GlaxoSmithKline submitted that it was also important to recognise the heterogeneous nature of COPD. The majority of diagnosed COPD patients suffered from symptoms, which included breathlessness, cough, wheeze and sputum production. All patients were also at risk of suffering exacerbations, however the level of risk was different for different patients – this was distinctly different from a condition where some subgroups of patients had an exacerbating type of the disease, whilst others had a non-exacerbating type of the disease. GlaxoSmithKline submitted that this principle of COPD was clearly captured by the quadrant management strategy tool in the GOLD Guideline and reproduced above. The grid nature of this recognised that patients might have varying levels of symptom burden and risk, and that the combination of these which existed, helped determine which treatment class needed to be used.

GlaxoSmithKline submitted that the treatment options stipulated for categories A, B, C and D, recognised that all patients needed to be treated for their symptom burden and to reduce their risk of future exacerbations, however the specific class of medicine chosen changed depending on the level of symptoms and exacerbation risk.

GlaxoSmithKline submitted that GOLD Guideline supported the use of long-acting bronchodilators to reduce exacerbations in COPD patients.

> 'Both long-acting anticholinergic and long-acting beta2-agonist reduce the risk of exacerbations.'

> 'COPD exacerbations can often be prevented.... treatment with long-acting inhaled bronchodilators, with or without inhaled corticosteroids... are all interventions that reduce the number of exacerbations and hospitalizations.' (GOLD, Global Strategy for the Diagnosis, Management and Prevention of COPD, 2016).

GlaxoSmithKline submitted that due to this, the LAMA/LABA class was listed as a treatment choice for patients in GOLD groups B, C and D.

GlaxoSmithKline submitted that the Anoro EPAR concluded that there was a place for the medicine in treating patients across the continuum of all severities of disease, and in all GOLD groups.

> 'The claimed indication would allow all four GOLD categories to be treated with the combination as a first line treatment... it was accepted by the CHMP that the results are likely to be relevant to the broad COPD population' (EMA, European Public Assessment Report 2014).

GlaxoSmithKline submitted that the Anoro EPAR clarified that as 42% of subjects in Anoro clinical trials were in GOLD group B, and 58% were in GOLD group D, the licence granted allowed for all four GOLD categories to be treated with Anoro Ellipta as a first line treatment. A key difference between patients in GOLD B and D was an increase in exacerbation risk, and hence the EPAR confirmed that patients with an exacerbation risk could be prescribed Anoro.

GlaxoSmithKline submitted that NICE Guidelines also recognised that both symptoms (breathlessness) and reducing exacerbation risk were key treatment goals in managing COPD. As such, those suffering from either need to progress from short-acting therapy to long-acting maintenance therapy, which included bronchodilators (LAMA, LABA or LAMA + LABA).

GlaxoSmithKline noted that none of the COPD treatments licensed in the UK were indicated to reduce exacerbations. This included the licences of inhaled corticosteroids (ICS)/LABAs, which were widely recognised as the most established inhaled therapy class for exacerbation reduction in COPD patients.

GOLD Guidelines clearly stated that inhaled corticosteroids reduced exacerbations and positioned the ICS/LABA class as a first line treatment for patients with a high risk of exacerbations:

> 'Regular treatment with inhaled corticosteroids improves symptoms, lung function, and quality of life, and reduces the frequency of exacerbations in COPD patients with an FEV1 < 60% predicted.'
>
> 'Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients at high risk of exacerbations...Group C patients have few symptoms but a high risk of exacerbations. As first choice a fixed combination of inhaled corticosteroid/long-acting beta2-agonist or a long-acting anticholinergic is recommended.' (GOLD, Global Strategy for the Diagnosis, Management and Prevention of COPD, 2016).

GlaxoSmithKline submitted that this was in line with NICE Guidelines, which positioned ICS/LABAs as a recommended long-acting therapy for patients with airflow restriction who had exacerbations or persistent breathlessness, or in any COPD patient who remained breathless or had exacerbations despite long-acting bronchodilator therapy.

GlaxoSmithKline submitted that all ICS/LABAs had similar wording within their licences, and for simplicity it referred to the Seretide licence as the benchmark for this class. The rationale being that this was the first product licensed in this class, and it remained the product with largest market share in the class. Section 4.1 of the Seretide Accuhaler SPC stated:

> 'Seretide is indicated for the symptomatic treatment of patients with COPD, with a FEV1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.' (emphasis added).

GlaxoSmithKline submitted that it was clear that the licence for Seretide was for the treatment of symptoms of COPD. Given the recommended position of ICS/LABAs within guidelines, and the widespread use and promotion of this class for exacerbation reduction, the precedent was that an indication for the treatment of symptoms of COPD encompassed use for reducing exacerbation risk.

Notwithstanding the above, GlaxoSmithKline acknowledged that the exacerbation data from Section 5.1 of the Anoro SPC must be presented in a manner which did not mislead. It should be clear that this data was not a primary endpoint in the studies presented, and relevant detail should be provided on the population studied, e.g. low risk of exacerbations. It should also be clear what the full licensed indication for Anoro was, such that readers could contextualise the data within the broader licensed indication. Therefore GlaxoSmithKline accepted the breaches of Clauses 7.2 and 9.1.

In conclusion, GlaxoSmithKline strongly maintained that the use of Anoro Ellipta in COPD to improve symptom burden and reduce the risk of future exacerbations was not outside of the scope of the product indication. Such practice was also in line with national and international guidelines which reflected the way COPD patients were managed by health professionals. As such, GlaxoSmithKline submitted that the presentations in question did not breach Clause 3.2.

**APPEAL BOARD RULING**

The Appeal Board noted that that Anoro Ellipta was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. Although information regarding a reduced risk of COPD exacerbation was stated in Section 5.1 of the SPC, promoting any reduction in such risk had to be set within the context of using the medicine for its licensed indication. In particular, the Appeal Board noted GlaxoSmithKline's submission that including the exacerbation data in promotional materials was not inconsistent with the SPC provided that the information given was not misleading. GlaxoSmithKline had accepted the Panel's rulings that the two presentations were misleading.

The Appeal Board noted that neither presentation at issue contained a clear statement as to the licensed indication for Anoro Ellipta. In the Appeal Board's view, to present exacerbation data without that context invited the audience to assume that Anoro Ellipta could be used to reduce COPD exacerbation *per se*, for which the medicine was not licensed. The Appeal Board thus considered that the presentations were inconsistent with the Anoro Ellipta SPC and it upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was not successful.

**Complaint received** **22 April 2016**

**Case completed** **3 November 2016**

**CASE AUTH/2842/4/16**

# ANONYMOUS, NON CONTACTABLE v ASTRAZENECA

## Promotion of Duaklir Genuair

**An anonymous, non contactable complainant complained about the promotion of long acting beta agonist/long acting muscarinic antagonists (LABA/LAMA) combination inhalers for the treatment of chronic obstructive pulmonary disease (COPD). The complainant referred to the first medicine to be licensed within this class (Ultibro Breezhaler (indacaterol maleate and glycopyrronium bromide)) noting that it was clear from its European Public Assessment Report (EPAR) that the Committee for Medicinal Products for Human Use (CHMP) turned down an application that included its use to reduce COPD exacerbations because its effects in that regard were too small to recommend such use. Ultibro Breezhaler was subsequently licensed only as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD and thus its promotion in relation to COPD exacerbation reduction was off-label. The complainant cited other examples of what could be considered to be off-label promotion based on the CHMP ruling on LABA/LAMA combination inhaler indications and in that regard noted, *inter alia*, AstraZeneca's product Duaklir Genuair (formoterol/aclidinium) for which, according to its EPAR, a specific licence for exacerbation reduction was never applied for.**

**Duaklir Genuair was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD.**

**In relation to this case the complainant noted in particular a Duaklir Genuair leavepiece which contained the claim '... Duaklir has been shown to reduce moderate to severe exacerbations...' and a speaker slide set which included data on a competitor to Duaklir Genuair which stated '... Ultibro Breezhaler significantly reduces the rate of severe or moderate COPD exacerbations vs glycopyrronium over 64 weeks...'. The complainant submitted that neither of the above items contained any information warning of the off-label aspects of the promoted products.**

**The complainant concluded that as there was no specific indication for exacerbation reduction in the registration applications for Duaklir Genuair, the medicine was not licensed for use to reduce exacerbations in COPD patients and so promoting it to reduce COPD exacerbation reduction was off-label.**

**The complainant stated his/her colleagues had little awareness that LABA/LAMA combination inhalers or LAMA inhalers were being prescribed in an unlicensed manner. Also, formal recommendations for the use of these medicines in exacerbation reduction were increasingly appearing in local clinical guidelines which suggested that promotion of the medicines had not clearly communicated the off-label nature of this use. The complainant stated that the materials for the various inhalers to which he/she had drawn attention were probably just the tip of the iceberg; he/she knew of numerous educational meetings/symposia with external speakers where exacerbation reduction data had been presented as part of product promotion.**

**A potential major concern for the complainant and his/her colleagues was that they might have unknowingly prescribed LABA/LAMA combination inhalers or LAMA inhalers to numerous COPD patients assuming that they were licensed for exacerbation reduction. The statement from the CHMP which considered exacerbation was therefore a sobering thought especially if COPD patients subsequently suffered exacerbations unexpectedly because their prescribed LABA/LAMA combination inhalers might not be effective enough as intimated by the CHMP assessment of Ultibro Breezhaler. COPD was characterised in part by airway inflammation and the extent of inflammation was progressive leading up to an exacerbation. None of the medicines in question contained an anti-inflammatory component. Another very important consideration was that prescribers were unaware from a medico-legal perspective that they would be solely liable for any adverse consequences suffered by patients which might arise.**

**The detailed response from AstraZeneca is given below.**

**The Panel noted that Section 5.1 of the Duaklir Genuair summary of product characteristics (SPC) referred to its positive impact on exacerbations of COPD. In that regard the Panel considered that exacerbations might be referred to in the promotion of COPD maintenance therapy but that there was a difference between promoting a medicine for a licensed indication and promoting the benefits of treating a condition. In the Panel's view, reference to reduced COPD exacerbation must be set within the context of the primary reason to prescribe ie as a maintenance bronchodilator therapy to relieve symptoms.**

**The Panel noted that the leavepiece clearly stated on the front cover 'Twice daily LAMA/LABA combination of aclidinium/formoterol for your COPD patients who remain breathless and require improved symptom control, despite LAMA therapy'. Page 2 introduced Duaklir Genuair and was headed 'The confidence of two trusted molecules for your COPD patients who remain breathless and require improved symptom control, despite LAMA monotherapy'. In boxed text on page 3, the efficacy with regard to symptom control and bronchodilation was briefly referred to followed by 'Furthermore Duaklir has been shown to: reduce moderate or severe exacerbations vs placebo'. The gate folded flap which gave a brief summary of Duaklir Genuair did not refer to the exacerbation data. The Panel considered that the claim for reduced exacerbations vs placebo was presented as a consequence of**

**using Duaklir Genuair to control COPD symptoms and not as the reason to prescribe the medicine *per se*, as alleged. Given the context in which it appeared, the claim was not misleading with regard to the licensed indication for Duaklir Genuair. High standards had been maintained. No breaches of the Code were ruled.**

**The Panel noted that the complainant had drawn attention to data on slide 39 of a speaker slide set which stated 'Ultibro Breezhaler significantly reduces the rate of severe or moderate COPD exacerbations vs glycopyrronium over 64 weeks' above a bar chart. In that regard, the Panel noted that Ultibro Breezhaler was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD; it was not licensed to reduce COPD exacerbations. The licensed indication for Ultibro Breezhaler was not stated in the slide set although the introductory slide for that part of the presentation was headed 'Overview of newer bronchodilators treatment of COPD' and listed indacaterol and glycopyrronium separately. Nonetheless, the Panel considered that some might assume that Ultibro Breezhaler could be prescribed *per se* to reduce COPD exacerbations. Although Ultibro Breezhaler appeared to have been promoted for exacerbation reduction, it was not AstraZeneca's medicine and on this narrow point, no breach was ruled. The Panel considered that, on balance, the slide set gave a misleading impression about the licensed indication for Ultibro Breezhaler and in this regard high standards had not been maintained. Breaches of the Code were ruled**

**In response to the complainant's wider concerns about the promotion of Duaklir Genuair, the Panel noted that the speaker slide set referred to by him/her was a broad discussion on bronchodilators, steroids and the airways over 45 slides. The first slide made it clear that the presentation had been delivered at an AstraZeneca meeting. Although the components of Duaklir Genuair were separately listed on slide 32 as bronchodilators, none of the three specific Duaklir Genuair slides stated the licensed indication for the medicine; slides 33 and 34 detailed lung function and dyspnoea results respectively and then, with apparent equal emphasis, 35 featured a bar chart above which was the claim 'Duaklir was associated with a statistically significant reduction of 29% in the rate of moderate or severe exacerbations'. The Panel considered that in the absence of any statement as to the licensed indication for Duaklir Genuair, the exacerbation data might be viewed by some as the reason to prescribe the medicine as alleged rather than a benefit of using the medicine as maintenance therapy. The slide set was inconsistent with the particulars listed in the Duaklir Genuair SPC and was misleading with regard to the licensed indication for Duaklir Genuair and breaches of the Code were ruled including that high standards had not been maintained.**

**In the Panel's view the briefing materials did not show that representatives had been encouraged to promote Duaklir Genuair for reduction in COPD exacerbation as alleged. Any reference to such data was clearly set within the context of the licensed indication. No breach of the Code was ruled.**

**Neither an A4 card headed 'LABA/LAMA combination therapy in COPD' or a booklet about understanding patient-reported outcomes in COPD promoted Duaklir Genuair for reduction in COPD exacerbations. The pieces were not misleading as to the licensed indication for Duaklir Genuair. No breaches of the Code were ruled including that high standards had been maintained.**

**A third promotional piece entitled 'Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD; pooled analysis of symptoms and exacerbations from two six month, multicentre, randomised studies (ACLIFORM and AUGMENT)' did not clearly set out the licensed indication for Duaklir Genuair. Although symptom scores were discussed before exacerbations, the two were given equal emphasis. In that regard the Panel considered that some readers might assume that Duaklir Genuair could be prescribed, *per se*, to reduce COPD exacerbations for which the medicine was not licensed. This was inconsistent with the particulars listed in its SPC and was misleading about the licensed indication. Breaches of the Code were ruled including that high standards had not been maintained.**

**AstraZeneca had provided copies of 28 slides sets in addition to the one cited by the complainant. None of the slide sets clearly and unequivocally set out the licensed indication for Duaklir Genuair. Although exacerbation data was often referred to after data relating to symptom control, it appeared to be given the same emphasis. None of the slide sets stated that Duaklir Genuair was not licensed for reduction in exacerbations. One slide set listed as reasons to prescribe Duaklir Genuair, improved symptoms, reduced risk of rescue inhaler and reduced risk of exacerbation without making any distinction between symptom control and reduced exacerbations; a second slide set similarly listed 'Reduce exacerbations' in a list of the outcomes to be expected with therapy. A third slide set concluded that the place of LABA/LAMA in the treatment pathway was to address symptoms and exacerbations. The Panel considered that in the absence of any statement as to the licensed indication for Duaklir Genuair, the exacerbation data might be viewed by some as the reason to prescribe the medicine which was not in accordance with its SPC. Given the context in which the exacerbation data appeared, and the equal emphasis it appeared to have been given compared with symptom control, the slide sets were misleading with regard to the licensed indication for Duaklir Genuair. Breaches of the Code were ruled including that high standards had not been maintained.**

**The Panel noted its comments and rulings above and in particular it noted the extent to which AstraZeneca had facilitated independent speakers to present data on Duaklir Genuair without ensuring that its licensed indication was properly and unambiguously communicated to the audience, and further ensuring that exacerbation data was only referred to within the context of using the medicine to relieve COPD symptoms. The Panel was very concerned to note that speaker slides were only examined and not**

**formally certified given their promotional content and the inclusion of Duaklir Genuair slides which appeared to have been generated by AstraZeneca. This was of particular concern given their use at field force speaker meetings and the influence that local independent speakers would have on their colleagues. The first slide of each presentation clearly stated 'This is an AstraZeneca meeting'. Given the company's involvement and the context in which they were delivered, the presentations were clearly promotional and AstraZeneca was responsible for their content despite the disclaimer which appeared on every presentation that 'The views expressed by the speaker are not necessarily those of AstraZeneca'. In the Panel's view, facilitating the use by independent speakers on the company's behalf, of uncertified promotional presentations brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.**

An anonymous, non contactable complainant complained about the promotion of long acting beta agonist/long acting muscarinic antagonists (LABA/LAMA) combination inhalers for the treatment of chronic obstructive pulmonary disease (COPD). The complainant referred to the first medicine to be licensed within this class (Ultibro Breezhaler (indacaterol maleate and glycopyrronium bromide)) and stated that although it was clear from its European Public Assessment Report (EPAR – dated 25 July 2013) that an application was originally submitted for the relief of COPD symptoms and the reduction of exacerbations, the Committee for Medicinal Products for Human Use (CHMP) subsequently stated the medicine's effects on reducing the rate of exacerbations were too small to recommend its use for such. Ultibro Breezhaler was eventually licensed as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The complainant stated that it could be concluded that Ultibro Breezhaler was not granted a licence at the time to recommend its use for reducing exacerbations and alleged that promotion of Ultibro Breezhaler in relation to COPD exacerbation reduction was off-label. The complainant provided a number of other examples of what could be considered to be off-label promotion based on the CHMP ruling of LABA-LAMA combination inhaler indications and in that regard drew attention, *inter alia*, to AstraZeneca's product Duaklir Genuair (formoterol/aclidinium) for which, according to its EPAR, a specific licence for exacerbation reduction was never applied for.

Duaklir Genuair was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD.

**COMPLAINT**

In relation to this case the complainant drew particular attention to a Duaklir Genuair leavepiece (ref GL/ABF/1214/0063) which contained the claim '... Duaklir has been shown to reduce moderate to severe exacerbations...' and a speaker slide set (ref JRD 02 April 2015, prepared March 2015) which included data on a competitor to Duaklir Genuair which stated '... Ultibro Breezhaler significantly reduces the rate of severe or moderate COPD exacerbations vs glycopyrronium over 64 weeks...'. The complainant submitted that neither of the above items contained any information warning of the off-label aspects of the promoted products.

The complainant submitted that as there was no specific indication for exacerbation reduction in the registration applications for Duaklir Genuair, it could be concluded that the medicine was not licensed for use to reduce exacerbations in COPD patients. Therefore promotion of Duaklir Genuair in relation to COPD exacerbation reduction was off-label.

The complainant stated having spoken to his/her peers it was evident that there was very little awareness amongst fellow colleagues that LABA/LAMA combination inhalers or LAMA inhalers were being prescribed in an unlicensed manner. Also, formal recommendations for the use of these medicines in exacerbation reduction were increasingly appearing in local clinical guidelines which suggested that promotion of the medicines had most likely missed an ethical obligation to also clearly communicate the off-label nature of this use, either in materials or as instruction to representatives. The complainant concluded that the materials for the various inhalers to which he/she had drawn attention were most probably just the tip of a large iceberg. The complainant was aware of numerous educational meetings/symposia involving external speakers where exacerbation reduction data had been discussed and presented as part of product promotion.

A potential major concern for the complainant and his/her prescribing colleagues was that unknowingly, they might have prescribed LABA/LAMA combination inhalers or LAMA inhalers to numerous COPD patients based on the assumption that they were licensed for exacerbation reduction. The statement from the CHMP which considered exacerbation was therefore a sobering thought especially if treated COPD patients subsequently suffered exacerbations unexpectedly. This was because prescribing LABA-LAMA combination inhalers might not be effective enough as intimated by the CHMP assessment of Ultibro Breezhaler. COPD was characterised in part by airway inflammation and the extent of inflammation was progressive leading up to an exacerbation. None of the medicines in question actually contained an anti-inflammatory component. Another very important consideration was that prescribers were unaware from a medico-legal perspective that they would be solely liable for any adverse consequences suffered by patients which might arise.

In writing to AstraZeneca, the Authority asked it to respond to Clauses 2, 3.2, 7.2, 9.1 and 15.9. The edition of the Code would be that relevant at the time the materials were used.

**RESPONSE**

AstraZeneca noted that Duaklir Genuair was indicated to relieve symptoms in COPD patients. However, additional endpoint data derived from the pooled phase 3 clinical trials describing reductions in exacerbations were presented in Section 5.1 of

the summary of product characteristics (SPC) which stated:

> 'COPD exacerbation reductions
>
> Pooled efficacy analysis of the two 6-month Phase III studies demonstrated a statistically significant reduction of 29% in the rate of moderate or severe exacerbations (requiring treatment with antibiotics or corticosteroids or resulting in hospitalisations) with Duaklir Genuair compared to placebo (rates per patient per year: 0.29 vs. 0.42, respectively; p=0.036).
>
> In addition, Duaklir Genuair statistically significantly delayed the time to first moderate or severe exacerbation compared to placebo (hazard ratio=0.70; p=0.027).'

AstraZeneca thus considered that the presentation of this exacerbation data was in accordance with the terms of the marketing authorization for Duaklir, not inconsistent with the particulars listed in the SPC and was not in breach of Clause 3.2. Further, the leavepiece at issue was derived directly from a generic (general) leavepiece that was pre-vetted by the Medicines and Healthcare products Regulatory Agency (MHRA).

In a letter of 12 December 2014, the MHRA stated that it did not object to the leavepiece and accepted its use subject to unrelated minor considerations. One of the principal purposes of the MHRA pre-vetting was to ensure that promotional material complied with the marketing authorization for the product and as such AstraZeneca considered this further supported its position of no breach of Clause 3.2.

AstraZeneca submitted that the overall marketing strategy for Duaklir Genuair since its launch in 2015 had sought to ensure that the presentation of the outcomes from the two phase 3 clinical studies (ACLIFORM and AUGMENT) was balanced and fair with emphasis given to the primary endpoint of lung function (forced expiratory volume in 1 second (FEV1)) and the endpoints relating to the relief of symptoms. Study findings about exacerbations had been reported secondarily in line with the data in the SPC. This was demonstrated in the two items at issue along with the supporting briefing materials.

The leavepiece was part of the launch campaign for Duaklir Genuair in 2015 and was made available to the representatives at the launch conference in January and thereafter; it was widely used with health professionals but had not been used since June 2015 when the colour of the Duaklir Genuair device was changed from white and blue to white and orange.

AstraZeneca submitted that the exacerbation data from the pooled phase 3 clinical trials in the leavepiece were supported by the references cited and were balanced within the context of the item and sequence of statements, were accurate and were not misleading. AstraZeneca thus denied a breach of Clause 7.2.

The leavepiece was a small fold out design which consisted of a front page, a back page with prescribing information and three inner pages which showed information about the product. The central inner page bore the exacerbation data and began with a statement 'Help relieve the symptoms of COPD for your patients who need improved symptom control'. The subsequent statements on this page referred to the key primary and secondary endpoints from the clinical studies ie bronchodilation, breathlessness and overall symptom control, consistent with the licensed indication for the product.

The statement about exacerbations on the central page was shown as a bullet point placed third in a list within a text box. It was referenced to a poster which described the exacerbation findings from the pooled analysis of the two phase 3 clinical trials of Duaklir Genuair and read:

> 'Furthermore Duaklir has been shown to: reduce moderate to severe exacerbations vs. placebo.'

AstraZeneca submitted that the depiction of the exacerbation data from the phase 3 Duaklir Genuair clinical trials within the leavepiece was given fair prominence, was factual, accurate, balanced and not misleading and thus, not a breach of Clause 7.2.

With regard to the speaker slide set referred to by the complainant, AstraZeneca noted that it was written by an internationally renowned UK professor of respiratory medicine and approved for use at a number of representative run speaker meetings for health professionals. These slides were examined and approved in April 2015 before use by a medical nominated signatory in accordance with company policy. As the slides were examined, a certificate was not produced.

The presentation was to support a talk entitled 'Bronchodilation, Steroids and the Airway – What next?' The first 32 of the 45 slide deck discussed phenotype-based management of COPD and showed data from a number of published clinical trials. Slides 33 to 35 showed clinical data from the Duaklir Genuair phase 3 clinical studies in the following sequence:

- Slide 33 showed the findings for one of the co-primary endpoints, ie lung function at one hour post-morning dose compared with Duaklir Genuair's components and placebo. Further detailed speaker notes were available within the presentation.
- Slide 34 presented breathlessness findings as measured by the transitional dyspnoea index (TDI) and showed data from the pooled analysis and the two studies individually.
- Slide 35 depicted the exacerbations outcomes in the studies as a bar graph; the y axis showed the actual rates of exacerbations per patient per year and the x axis showed the two sets of data, 'all exacerbations' and 'moderate to severe exacerbations' for the placebo, aclidinium, formoterol and combination product. Risk ratio figures were shown between the combination

product and placebo and the p values for these differences was in notes below the graph which also defined moderate or severe exacerbation.

More detailed speaker notes for this exacerbation data graph stated:

> 'Analysis of the rate of exacerbations was assessed as a secondary outcome, based on the pooled data from ACLIFORM and AUGMENT (3,394 patients), as the studies were not powered to look at exacerbations, and as the study populations were not enriched for exacerbations, the rate of exacerbation was relatively low. As shown here, treatment with Duaklir was associated with a statistically significant reduction of 29% in the rate of moderate or severe exacerbations (based on healthcare resource utilisation [HCRU] criteria) compared with placebo ($p<0.05$) and a risk reduction of 24% for exacerbations of any severity, although this did not reach significance.'

The exacerbation data from the two pivotal phase 3 Duaklir Genuair clinical trials depicted in the slide presentation were supported by the references cited, were balanced within the context of the item, were accurate and were not misleading.

Following the slides showing Duaklir Genuair data were 4 slides from the Ultibro Breezhaler clinical study programme. Each slide accurately detailed the results of the study's primary endpoint with the sources of this information cited on each slide.

AstraZeneca stated that the overall presentation of data for LAMA/LABAs in the slides was not in breach of Clause 7.2.

With regard to supporting items for the representatives, AstraZeneca provided copies of the esales aid briefing guide (ref GL/ABF/0115/0184) and a table of marketing and educational materials available to representatives (ref GL/ABF/0115/0208).

The representatives underwent a comprehensive remote and face-to-face training programme in order to be fully trained and validated on the technical aspects of Duaklir Genuair. Furthermore, they received specific instructions as to how to present the exacerbation data from the two phase 3 pivotal clinical studies within the context of the overall campaign. AstraZeneca included two examples of certified briefing material, to illustrate how the representatives were specifically briefed to discuss exacerbation data for Duaklir Genuair.

The esales aid briefing guide contained the briefing for the overall promotion of Eklira (aclidinium) and Duaklir Genuair. The flow of the promotional messages for Duaklir Genuair was balanced and prioritised the discussion of its effects on symptom control and bronchodilation. Slide 46 of the briefing guide, listed the findings from the pivotal phase 3 Duaklir Genuair clinical studies relating to exacerbations as one of six key messages for the product and used the same language and references as the leavepiece at issue. The next 4 slides described the electronic sales aid screens to be used as the core flow for Duaklir Genuair and cited breathlessness, symptom control and lung function clinical study findings.

There were instructions that accompanied a screen available in the electronic sales aid which bore a bar graph depicting the pooled data from the phase 3 Duaklir Genuair clinical studies for moderate and severe exacerbations. Representatives were instructed that this was not a core page but could be used 'reactively in response to questions around exacerbations'.

Briefing of the leavepiece was within a document 'Marketing and Educational Materials Available to Representatives', which itemised all the materials available at launch. It stated that the leavepiece should be used as a post-call reminder or at meetings and set out the key messages to be taken from the item ie that Duaklir Genuair improved breathlessness, overall symptom control and bronchodilation vs aclidinium and formoterol given individually. Exacerbations outcomes were not cited as a key message to be taken from this item.

AstraZeneca noted that further details of the training programme for Duaklir Genuair representatives could be made available upon request.

In summary AstraZeneca submitted that representatives were suitably instructed on the technical aspects of Duaklir Genuair and how it should be promoted and it denied a breach of Clause 15.9 of the Code.

In response to a request for further information, AstraZeneca reiterated that it was confident that its depiction of the Duaklir Genuair exacerbation data was consistent with the particulars listed in the SPC and did not breach Clause 3.2. This was supported by the inclusion of the exacerbation findings in Section 5.1 of the SPC and the acceptance of similar representation of the data in the launch materials pre-vetted by the MHRA. Furthermore, the Duaklir Genuair exacerbation data from the phase 3 pivotal trials was given fair prominence, was factual, accurate, and balanced and hence not in breach of Clause 7.2.

AstraZeneca provided copies of all its current marketing items and associated briefing documents that referred to the Duaklir Genuair exacerbation data. The company submitted that in all of these documents, the exacerbation data from the pooled clinical studies was depicted in accordance with the terms of the Duaklir Genuair marketing authorization and consistent with the particulars listed in the SPC. The data was presented in a balanced and fair manner consistent with the depiction and emphasis given to this data from the original 2015 launch campaign, the leavepiece from which was cited by the complainant and discussed in detail above.

With regard to external speaker authored slide decks, AstraZeneca stated that its policy was to medically review such before use. These decks were then available for use for six months provided no alterations

were made. All current speaker decks to support Duaklir Genuair had been reviewed and of these, 28 cited the Duaklir Genuair exacerbation outcomes data and had thus been considered relevant to this case and a summary of each was provided. In all 28 decks the exacerbation data was depicted in accordance with the terms of the Duaklir Genuair marketing authorization and consistent with the particulars listed in the SPC and did not breach Clause 3.2.

In 25 of the 28 decks, including the presentation cited by the complainant, the Duaklir Genuair exacerbation data was presented after presentation of data on symptom control and/or lung function, and reflected a fair, balanced and accurate depiction of the evidence. Three decks presented the Duaklir Genuair exacerbation data in a different sequence, however, these decks were overall balanced and thus did not breach Clause 7.2. Two of the decks were variations of a deck written by the same author as detailed below:

- [named individual] March 2016

In this deck Duaklir Genuair exacerbation data was shown in slide 20 of 35 within the context of a presentation on the impact of COPD exacerbation of a number of licenced inhaled medicines. There then followed in slides 27-32 data on the outcomes from the Duaklir Genuair phase 3 studies on lung function, breathlessness, symptom control and quality of life.

- [named individual] February 2016 and April 2016

This deck of 66 slides presented various important clinical issues in COPD, including smoking cessation and pulmonary rehabilitation. Slide 40 introduced lung function and breathlessness/symptom control data from clinical studies of aclidinium. There then followed data from Duaklir Genuair clinical studies in slides 47-49. The Duaklir Genuair exacerbation data was presented from the pooled data and there followed data on symptom control and quality of life.

AstraZeneca denied breaches of Clauses 3.2 and 7.2 with regard to its current marketing materials and current externally authored slide decks for speaker meetings.

**PANEL RULING**

The Panel noted that Duaklir Genuair was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. Section 5.1 of the SPC referred to its positive impact on exacerbations of COPD. In that regard the Panel considered that reference to exacerbations might be included in the promotion of COPD maintenance therapy but that there was a difference between promoting a medicine for a licensed indication and promoting the benefits of treating a condition. In the Panel's view, any reference to reduced COPD exacerbation must be set within the context of the primary reason to prescribe ie as a maintenance bronchodilator therapy to relieve symptoms.

The Panel noted that AstraZeneca had been asked to consider the requirements of Clauses 2, 3.2, 7.2, 9.1 and 15.9 and advised that the edition of the Code that would be relevant would be that which was in force when the materials were used. The Panel considered, however, that given the matters at issue, the relevant substantial requirements of Clauses 2, 3.2, 7.2, 9.1 and 15.9 had not changed since the 2014 Code (the earliest Code relevant to the material at issue) and so all of the rulings below are made under the 2016 Code.

The Panel noted that the leavepiece at issue (ref GL/ABF/1214/0063) clearly stated on the front cover 'Twice daily LAMA/LABA combination of aclidinium/formoterol for your COPD patients who remain breathless and require improved symptom control, despite LAMA therapy'. Page 2 introduced Duaklir Genuair and was headed 'The confidence of two trusted molecules for your COPD patients who remain breathless and require improved symptom control, despite LAMA monotherapy'. In boxed text on page 3, the efficacy with regard to symptom control and bronchodilation was briefly referred to followed by 'Furthermore Duaklir has been shown to: reduce moderate or severe exacerbations vs placebo'. The gate folded flap which gave a brief summary of Duaklir Genuair did not refer to the exacerbation data. The Panel considered that the claim for reduced exacerbations vs placebo was presented as a consequence of using Duaklir Genuair to control COPD symptoms and not as the reason to prescribe the medicine *per se*, as alleged. In that regard no breach of Clause 3.2 was ruled. Given the context in which it appeared, the claim was not misleading with regard to the licensed indication for Duaklir Genuair. No breach of Clause 7.2 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

The Panel noted that the complainant had drawn attention to data on slide 39 in a speaker slide set (ref JRD 02 April 2015) which stated 'Ultibro Breezhaler significantly reduces the rate of severe or moderate COPD exacerbations vs glycopyrronium over 64 weeks' above a bar chart. In that regard, the Panel noted that Ultibro Breezhaler was indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD; it was not licensed to reduce COPD exacerbations. The licensed indication for Ultibro Breezhaler was not stated in the slide set although the introductory slide (slide 32) for that part of the presentation was headed 'Overview of newer bronchodilators treatment of COPD' and listed indacaterol and glycopyrronium separately. Nonetheless, the Panel considered that some might assume that Ultibro Breezhaler could be prescribed *per se* to reduce COPD exacerbations. Clause 1.2 of the Code defined promotion as any activity undertaken by a company which promoted the administration, consumption, prescription, purchase recommendation, sale supply or use of *its* medicines (emphasis added). Clause 3.2 prohibited the promotion of a medicine outwith the terms of its marketing authorization. Although Ultibro Breezhaler appeared to have been promoted for exacerbation reduction, it was not AstraZeneca's medicine and on this narrow point, no breach of Clause 3.2 was ruled. Clause 7 of the Code, however, referred to information, claims and comparisons

and in that regard applied to what a company stated about its own medicine and what it stated about competitors. The Panel considered that, on balance, the slide set gave a misleading impression about the licensed indication for Ultibro Breezhaler and it ruled a breach of Clause 7.2. High standards had not been maintained. A breach of Clause 9.1 was ruled.

In response to the complainant's wider concerns about the promotion of Duaklir Genuair, the Panel noted that the speaker slide set referred to by the complainant (ref JRD 02 April 2015), was a broad discussion on bronchodilators, steroids and the airways over 45 slides. The first slide made it clear that the presentation had been delivered at an AstraZeneca meeting. Although the components of Duaklir Genuair were separately listed on slide 32 as bronchodilators, none of the three specific Duaklir Genuair slides stated the licensed indication for the medicine; slides 33 and 34 detailed lung function and dyspnoea results respectively and then, with apparent equal emphasis, 35 featured a bar chart above which was the claim 'Duaklir was associated with a statistically significant reduction of 29% in the rate of moderate or severe exacerbations'. The Panel considered that in the absence of any statement as to the licensed indication for Duaklir Genuair, the exacerbation data might be viewed by some as the reason to prescribe the medicine as alleged rather than a benefit of using the medicine as maintenance therapy. The slide set was inconsistent with the particulars listed in the Duaklir Genuair SPC and in that regard a breach of Clause 3.2 was ruled. Given the context in which it appeared, the claim about exacerbation reduction was misleading with regard to the licensed indication for Duaklir Genuair and implied that exacerbation reduction was the primary reason to prescribe. A breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

AstraZeneca had provided a copy of the esales aid briefing guide (ref GL/ABF/0115/0184). The Panel noted that the emphasis from the outset (slide 41) was on the use of Duaklir for COPD patients who needed improved symptom control despite LAMA monotherapy; reference to exacerbation reduction was secondary to improvements in breathlessness, overall symptom control and bronchodilation. There was a pop-up screen detailing reductions in moderate or severe exacerbations but this was only to be used reactively in response to questions about exacerbations. The Table of Marketing and Educational Materials Available to Representatives listed all of the materials available each with a key visual, description and key messages. All of the key messages for Duaklir related to its use for additional symptom control, none referred to exacerbation reduction. In the Panel's view the briefing materials did not show that representatives had been encouraged to promote Duaklir Genuair for reduction in COPD exacerbation as alleged. Any reference to such data was clearly set within the context of the licensed indication. No breach of Clause 15.9 was ruled.

AstraZeneca provided copies of two further promotional pieces; an A4 card headed 'LABA/LAMA combination therapy in COPD' (ref 889,022.011, October 2015) and a booklet about understanding patient-reported outcomes in COPD (ref 951,333.011, February 2016). The booklet bore the product name and logo prominently in the top left of the front cover. Neither item discussed exacerbation data with specific reference to Duaklir. In that regard the Panel did not consider that either piece promoted Duaklir Genuair for reduction in COPD exacerbations. No breach of Clause 3.2 was ruled. The pieces were not misleading as to the licensed indication for Duaklir Genuair. No breach of Clause 7.2 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

A third promotional piece (ref 929,977.011, January 2016) provided by AstraZeneca was entitled 'Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD; pooled analysis of symptoms and exacerbations from two six month, multicentre, randomised studies (ACLIFORM and AUGMENT)'. The Panel noted that there was no clear statement in the body of the piece which clearly set out the licensed indication for Duaklir Genuair. Although symptom scores were discussed before exacerbations, the two were given equal emphasis. In that regard the Panel considered that some readers might assume that Duaklir Genuair could be prescribed, *per se*, to reduce COPD exacerbations for which the medicine was not licensed. This was inconsistent with the particulars listed in its SPC. A breach of Clause 3.2 was ruled. The piece was misleading about the licensed indication for Duaklir Genuair. A breach of Clause 7.2 was ruled. In the Panel's view, high standards had not been maintained. A breach of Clause 9.1 was ruled.

AstraZeneca had provided copies of 28 slides sets in addition to the one cited by the complainant. None of the slide sets clearly and unequivocally set out the licensed indication for Duaklir Genuair. Although exacerbation data was often referred to after data relating to symptom control, it appeared to be given the same emphasis. None of the slide sets stated that Duaklir Genuair was not licensed for reduction in exacerbations. One slide set (ref JRD 01 April 2016) listed as reasons to prescribe Duaklir Genuair, improved symptoms, reduced risk of rescue inhaler and reduced risk of exacerbation without making any distinction between symptom control and reduced exacerbations; a second slide set (ref December 2015 SWD) similarly listed 'Reduce exacerbations' in a list of the outcomes to be expected with therapy. A third slide set (ref February 2016 SWD) concluded by stating that the place of LABA/LAMA in the treatment pathway was to address symptoms and exacerbations. The Panel considered that in the absence of any statement as to the licensed indication for Duaklir Genuair, the exacerbation data might be viewed by some as the reason to prescribe the medicine which was not in accordance with its marketing authorization as alleged. In that regard a breach of Clause 3.2 was ruled. Given the context in which the exacerbation data appeared, and the equal emphasis it appeared to have been given compared with symptom control, the slide sets were misleading with regard to the licensed indication for Duaklir Genuair. A breach of Clause 7.2 was ruled.

High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted its comments and rulings above and in particular it noted the extent to which AstraZeneca had facilitated independent speakers to present data on Duaklir Genuair without ensuring that its licensed indication was properly and unambiguously communicated to the audience, and further ensuring that exacerbation data was only referred to within the context of using the medicine to relieve COPD symptoms. The Panel was very concerned to note that speaker slides were only examined and not formally certified given their promotional content and the inclusion of Duaklir Genuair slides which appeared to have been generated by AstraZeneca. This was of particular concern given their use at speaker meetings organised by the field force such as slide set 951,913.001 which was clearly promotional. In the Panel's view, this was of particular concern given the influence that local independent speakers would have on their colleagues. The first slide of each presentation clearly stated 'This is an AstraZeneca meeting'. Given the company's involvement and the context in which they were delivered, the presentations were clearly promotional and AstraZeneca was responsible for their content despite the disclaimer which appeared on every presentation that 'The views expressed by the speaker are not necessarily those of AstraZeneca'. In the Panel's view, facilitating the use by independent speakers on the company's behalf, of uncertified promotional presentations brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

**Complaint received** **25 April 2016**

**Case completed** **16 September 2016**

CASE AUTH/2843/4/16

# ANONYMOUS, NON CONTACTABLE v BOEHRINGER INGELHEIM

## Promotion of Spiriva

**An anonymous, non contactable complainant complained about the promotion of long-acting beta agonist/long-acting muscarinic antagonists (LABA/LAMA) combination inhalers for the treatment of chronic obstructive pulmonary disease (COPD). The complainant referred to the first medicine to be licensed within this class, Ultibro Breezhaler (indacaterol maleate and glycopyrronium bromide), noting that it was clear from its European Public Assessment Report (EPAR) that the Committee for Medicinal Products for Human Use (CHMP) turned down an application that included its use to reduce COPD exacerbations because its effects, in that regard, were too small to recommend such use. Ultibro Breezhaler was subsequently licensed only as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD and thus its promotion in relation to COPD exacerbation reduction was off-label. The complainant cited other examples of what could be considered to be off-label promotion based on the CHMP ruling on LABA/LAMA combination inhaler indications and stated that additionally some LAMA inhaler products also involved off-label promotion. With regard to the latter the complainant drew attention to, *inter alia*, Boehringer Ingelheim's product, Spiriva (tiotropium).**

**Spiriva was indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD.**

**In relation to this case the complainant noted in particular a Spiriva journal advertisement which stated, 'With a long-term record of success in reducing symptoms, exacerbations and hospitalisations vs placebo ...'.**

**The complainant stated that Spiriva was indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD ie identical to Ultibro Breezhaler and the advertisement did not contain any other information warning of the off-label aspects to the promoted use of the product.**

**The complainant stated that his/her colleagues had little awareness that LABA/LAMA combination inhalers or LAMA inhalers were being prescribed in an unlicensed manner. Also, formal recommendations for the use of these medicines in exacerbation reduction were increasingly appearing in local clinical guidelines which suggested that promotion of the medicines had not clearly communicated the off-label nature of this use. The complainant stated that materials for the various inhalers to which he/she had drawn attention were probably just the tip of the iceberg. The complainant knew of numerous educational meetings/symposia with external speakers where exacerbation reduction data had been presented as part of product promotion.**

**A potential major concern for the complainant and his/her prescribing colleagues was that they might have unknowingly prescribed the above mentioned medicines to numerous COPD patients assuming that they were licensed for exacerbation reduction. The statement from the CHMP which considered exacerbation was therefore a sobering thought especially if COPD patients subsequently suffered exacerbations unexpectedly because their prescribed LABA/LAMA combination inhalers might not be effective enough as intimated by the CHMP assessment of Ultibro Breezhaler. COPD was characterised in part by airway inflammation and the extent of inflammation was progressive leading up to an exacerbation. None of the medicines in question contained an anti-inflammatory component. Another very important consideration was that prescribers were unaware from a medico-legal perspective that they would be solely liable for any adverse consequences suffered by patients which might arise.**

**The detailed response from Boehringer Ingelheim is given below.**

**The Panel noted that Section 5.1 of the Spiriva summary of product characteristics (SPC) referred to its positive impact on exacerbations of COPD. The Panel noted that Section 1.1 of the National Institute for Health and Clinical Excellence (NICE) Guideline on the management of COPD listed the symptoms of the disease which were, *inter alia*, exertional breathlessness, chronic cough, regular sputum production and wheeze. In Section 1.3 the exacerbation of COPD was described as a sustained worsening of the patient's symptoms from their usual stable state which was beyond normal day-to-day variations and was acute in onset. The Global Initiative on Obstructive Lung Disease (GOLD) guidance similarly differentiated COPD symptoms and exacerbations. In the Panel's view, there was a difference between COPD symptoms and exacerbation of COPD although it accepted that patients with well controlled symptoms might be less likely to experience an exacerbation than patients with poorly controlled symptoms. In that regard the Panel considered that exacerbations might be referred to in the promotion of COPD maintenance therapy but that there was a difference between promoting a medicine for a licensed indication and promoting the benefits of treating a condition. In the Panel's view, reference to reduced COPD exacerbation must be set within the context of product's licensed indication and thus the primary reason to prescribe ie maintenance therapy to relieve symptoms.**

**The Panel noted that the advertisement included the claim, 'With a long-term record of success in reducing symptoms, exacerbations and hospitalisations vs placebo, Spiriva is a LAMA you can count on to help lead your COPD patients to everyday victories.' The Panel considered that the claim did not differentiate between the licensed**

**indication (reduction of symptoms) and the benefit of therapy (reduction of exacerbations). Other than in the prescribing information, the advertisement did not refer to the licensed indication for Spiriva and make it clear that this was the primary reason to prescribe. Reduction in COPD exacerbations appeared to be as much a reason to prescribe as reduction in symptoms. In that regard the Panel considered that the claim was inconsistent with the particulars listed in the Spiriva SPC and misleading with regard to the licensed indication for Spiriva. Breaches of the Code were ruled including that high standards had not been maintained.**

**The Panel noted that Boehringer Ingelheim also provided a copy of a slide deck used to train representatives and also used with and by health professionals. A benefit shown for Spiriva with regard to exacerbations was detailed in three slides, and in the summary slide one of the outcomes of the study (Tashkin *et al* 2008) was listed as 'Reduced exacerbations' and further details were provided. The data was not presented as being a benefit of using Spiriva to relieve COPD symptoms. The licensed indication for Spiriva was only stated in the prescribing information on the last slide.**

**The Panel again considered that Spiriva would be perceived as a medicine to reduce COPD exacerbations given that such use had been presented as a reason to prescribe *per se* and not as a benefit of using the medicine for its licensed indication. Although the SPC discussed reduction of exacerbation data, the Panel, noting the product's licensed indication, nonetheless considered that the slide deck was inconsistent with the particulars listed in the SPC. Slides that implied that exacerbation reduction was a primary reason to prescribe Spiriva were misleading. Breaches of the Code were ruled. In the Panel's view the slide deck which was used to train representatives, presented the exacerbation data in such a way as to advocate a course of action that was likely to breach the Code. Breaches of the Code were ruled including that high standards had not been maintained.**

**The Panel noted its comments and rulings above but did not consider that the matters were such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.**

An anonymous, non contactable complainant complained about the promotion of long-acting beta agonist/long-acting muscarinic antagonists (LABA/LAMA) combination inhalers for the treatment of chronic obstructive pulmonary disease (COPD). The complainant referred to the first medicine to be licensed within this class, Ultibro Breezhaler (indacaterol maleate and glycopyrronium bromide) and stated that although it was clear from its European Public Assessment Report (EPAR – dated 25 July 2013) that an application was originally submitted for the relief of COPD symptoms and the reduction of exacerbations, the Committee for Medicinal Products for Human Use (CHMP) subsequently stated the medicine's effects on reducing the rate of exacerbations were too small to recommend its use for such. Ultibro Breezhaler was eventually licensed as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The complainant stated that it could be concluded that Ultibro Breezhaler was not granted a licence at the time to recommend its use for reducing exacerbations and alleged, therefore, that promotion of Ultibro Breezhaler in relation to COPD exacerbation reduction was off-label. The complainant provided a number of other examples of what could be considered to be off-label promotion based on the CHMP decision about LABA/LAMA combination inhaler indications and stated that additionally some LAMA inhaler products also involved off-label promotion. With regard to the latter the complainant drew attention, *inter alia*, to Boehringer Ingelheim's product, Spiriva (tiotropium).

Spiriva was indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD.

**COMPLAINT**

In relation to this case the complainant drew particular attention to a Spiriva journal advertisement (ref UK/SPI-121330, Aug 2012) which stated, 'With a long-term record of success in reducing symptoms, exacerbations and hospitalisations vs placebo ...'.

The complainant stated that Spiriva was indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD ie identical to Ultibro Breezhaler and the advertisement did not contain any other information warning of the off-label aspects to the promoted use of the product.

The complainant stated having spoken to his/her peers it was evident that there was very little awareness amongst fellow colleagues that LABA/LAMA combination inhalers or LAMA inhalers were being prescribed in an unlicensed manner. Also, formal recommendations for the use of these medicines in exacerbation reduction were increasingly appearing in local clinical guidelines which suggested that promotion of the medicines had most likely missed an ethical obligation to also clearly communicate the off-label nature of this use, either in materials or as instructions to representatives. The complainant concluded that the materials for the various inhalers to which he/she had drawn attention were most probably just the tip of a large iceberg. The complainant was aware of numerous educational meetings/symposia involving external speakers where exacerbation reduction data had been discussed and presented as part of product promotion.

A potential major concern for the complainant and his/her prescribing colleagues was that unknowingly, they might have prescribed LABA/LAMA combination inhalers or LAMA inhalers to numerous COPD patients based on the assumption that they were licensed for exacerbation reduction. The statement from the CHMP which considered exacerbation was therefore a sobering thought especially if treated COPD patients subsequently suffered exacerbations unexpectedly. This was because prescribing LABA/LAMA combination inhalers might not be effective

enough as intimated by the CHMP assessment of Ultibro Breezhaler. COPD was characterised in part by airway inflammation and the extent of inflammation was progressive leading up to an exacerbation. None of the medicines in question actually contained an anti-inflammatory component. Another very important consideration was that prescribers were unaware from a medico-legal perspective that they would be solely liable for any adverse consequences suffered by patients which might arise.

When writing to Boehringer Ingelheim the Authority asked it to respond to Clauses 2, 3.2, 7.2, 9.1 and 15.9. The edition of the Code would be that relevant at the time the materials were used.

**RESPONSE**

Boehringer Ingelheim submitted that the journal advertisement at issue was produced in August 2012 and not used after August 2014. Boehringer Ingelheim noted that the claim that Spiriva HandiHaler had 'a long-term record of success in reducing symptoms, exacerbations, and hospitalisations vs placebo', was referenced to the Spiriva HandiHaler summary of product characteristics (SPC) and Tashkin *et al* (2008). With regard to Clauses 3.2 and 7.2, the Spiriva SPC stated that it was indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD. Section 5.1 of the SPC gave the following additional details:

> 'In a randomized, double-blind, placebo controlled trial of 1,829 patients with moderate to very severe COPD, tiotropium bromide statistically significantly reduced the proportion of patients who experienced exacerbations of COPD (32.2% to 27.8%) and statistically significantly reduced the number of exacerbations by 19% (1.05 to 0.85 events per patient year of exposure). In addition, 7.0% of patients in the tiotropium bromide group and 9.5% of patients in the placebo group were hospitalized due to a COPD exacerbation (p=0.056). The number of hospitalizations due to COPD was reduced by 30% (0.25 to 0.18 events per patient year of exposure)'.

The same section of the SPC also included data for exacerbation reduction, including hospitalisation, vs salmeterol:

> 'Compared with salmeterol, Spiriva increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; p<0.001). Spiriva also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; p<0.001)'.

Tashkin *et al* further supported the claim by showing a statistically significant reduction in symptoms (as measured by the St George's Respiratory Questionnaire) with tiotropium vs placebo throughout the four years of the trial. It showed that, vs placebo, 'tiotropium was associated with a reduction in the risks of exacerbations, related hospitalizations, and respiratory failure'. Boehringer Ingelheim further noted that Halpin *et al* (2016) cited numerous other trials from the years before the advertisement, which confirmed the effect of tiotropium on exacerbations. There was, therefore, supporting evidence for tiotropium's 'long-term record', both in terms of trial duration and the number of years of accumulated evidence.

Boehringer Ingelheim submitted that the information in the advertisement was accurate, fair and balanced. It was consistent with the Spiriva SPC, which included discussion of its effect on reduction of symptoms, exacerbations, and hospitalizations.

With regard to Clause 15.9, Boehringer Ingelheim submitted that as the complainant was anonymous and no specific details about representatives' activity were supplied it was difficult to offer a specific rebuttal. However, Boehringer Ingelheim provided field force training material in use at the time of the advertisement.

Given the above, Boehringer Ingelheim submitted that it had acted in full accordance with both the spirit and letter of the Code, and it denied breaches of Clauses 2, 3.2, 7.2, 9.1 and 15.9.

In response to a request for further information, Boehringer Ingelheim submitted that with regard to the general allegation that it had 'missed an ethical obligation to also clearly communicate the off-label nature of this [exacerbation prevention] use', it did not believe that the discussion of the role of Spiriva in exacerbation reduction was a recommendation for 'off-label' use nor was it inconsistent with the SPC. Boehringer Ingelheim provided evidence as follows:

1 The SPC stated that the indication for Spiriva HandiHaler was:

> 'As a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).'

To understand this licence statement fully, Boehringer Ingelheim clarified what symptoms of COPD were expected to be relieved by use of Spiriva. The company explained that COPD caused several key symptoms, as recognised by guidance created and accepted by clinicians ie the Global initiative for chronic Obstructive Lung Disease (GOLD – updated 2016) which stated:

> 'The characteristic symptoms of COPD are chronic and progressive dyspnea, cough, and sputum production that can be variable from day-to-day.'

These guidelines also recognised that exacerbations of COPD were understood as being a symptomatic phenomenon of COPD:

> 'An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.'

Boehringer Ingelheim noted that the GOLD guidance additionally advised that prescription of long-acting bronchodilators (such as tiotropium) was an appropriate part of management strategy to reduce exacerbations:

> 'COPD exacerbations can often be prevented. Smoking cessation, influenza and pneumococcal vaccines, knowledge of current therapy including inhaler technique, and treatment with long-acting inhaled bronchodilators, with or without inhaled corticosteroids, and possibly phosphodiesterase-4 inhibitors, are all therapies that reduce the number of exacerbations and hospitalizations.'

2 A similar symptom-based definition of 'exacerbation' in the context of COPD was used by the National Institute for Health and Care Excellence (NICE) (clinical Guideline 101 (2010)) which stated:

> 'A rapid and sustained worsening of symptoms beyond normal day-to-day variations.'

The NICE guidance additionally mentioned numerous settings where addition of a long-acting muscarinic antagonist such as tiotropium would be appropriate for reduction of exacerbation risk:

> '1.2.2.5: Offer once-daily long-acting muscarinic antagonist (LAMA) in preference to four-times-daily short-acting muscarinic antagonist (SAMA) to people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required.'
>
> '1.2.2.6: In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, offer the following as maintenance therapy:
> If [forced expiratory volume over 1 second] FEV1 ≥ 50% predicted: either long-acting beta2 agonist (LABA) or LAMA if FEV1 < 50% predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or LAMA.'
>
> '1.2.2.7: In people with stable COPD and an FEV1 ≥ 50% who remain breathless or have exacerbations despite maintenance therapy with a LABA:
> consider LABA+ICS in a combination inhaler
> consider LAMA in addition to LABA where ICS is declined or not tolerated.'
>
> '1.2.2.8: Offer LAMA in addition to LABA+ICS to people with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV1.'

Boehringer Ingelheim submitted that when clinicians prescribed a medicine for COPD, they therefore included reduction of exacerbations as an accepted element of management of symptoms. This approach was validated by national and international guidelines, and was consistent with the defined indication in Spiriva's SPC.

3 The SPC gave details of trial data for Spiriva related to exacerbations, compared with placebo and with the higher bar of an active comparator. Against placebo, the SPC stated:

> 'In a randomized, double-blind, placebo controlled trial of 1,829 patients with moderate to very severe COPD, tiotropium bromide statistically significantly reduced the proportion of patients who experienced exacerbations of COPD (32.2% to 27.8%) and statistically significantly reduced the number of exacerbations by 19% (1.05 to 0.85 events per patient year of exposure). In addition, 7.0% of patients in the tiotropium bromide group and 9.5% of patients in the placebo group were hospitalized due to a COPD exacerbation (p=0.056). The number of hospitalizations due to COPD was reduced by 30% (0.25 to 0.18 events per patient year of exposure).'

Against salmeterol, the SPC gave further details of Spiriva's exacerbation data involving a large number of patients:

> 'A one-year randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 microgram of SPIRIVA once daily with that of 50 microgram of salmeterol HFA pMDI twice daily on the incidence of moderate and severe exacerbations in 7,376 patients with COPD and a history of exacerbations in the preceding year.

A table summarising the exacerbation endpoints was provided. Compared with salmeterol, SPIRIVA increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; P<0.001). SPIRIVA also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001).'

In summary, Boehringer Ingelheim submitted that discussion of the use of Spiriva in exacerbation reduction was in keeping with the licence statement, in keeping with the data and content of the SPC, in keeping with use by clinicians and appropriately reflected in the recommendations of national and international guidelines. The product had not been promoted since 2014.

**PANEL RULING**

The Panel noted that Spiriva was indicated as a maintenance bronchodilator treatment to relieve symptoms in patients with COPD. Section 5.1 of the SPC referred to its positive impact on exacerbations of COPD. The Panel noted that Section 1.1 of the NICE Guideline on the management of COPD listed the symptoms of the disease which were, *inter alia*, exertional breathlessness, chronic cough, regular sputum production and wheeze. In Section 1.3 of the Guideline, the exacerbation of COPD was described as a sustained worsening of the patient's symptoms

from their usual stable state which was beyond normal day-to-day variations and was acute in onset. The GOLD guidance similarly differentiated COPD symptoms and exacerbations. In the Panel's view, there was a difference between COPD symptoms and exacerbation of COPD although it accepted that patients whose symptoms were well controlled might be less likely to experience an exacerbation of their condition than patients with poorly controlled symptoms. In that regard the Panel considered that reference to exacerbations might be included in the promotion of COPD maintenance therapy but that there was a difference between promoting a medicine for a licensed indication and promoting the benefits of treating a condition. In the Panel's view, any reference to reduced COPD exacerbation must be set within the context of product's licensed indication and thus the primary reason to prescribe ie maintenance therapy to relieve symptoms.

The Panel noted that Boehringer Ingelheim had been asked to consider the requirements of Clauses 2, 3.2, 7.2, 9.1 and 15.9 and advised that the edition of the Code that would be relevant would be that which was in force when the materials were used. The Panel considered, however, that given the matters at issue, the relevant substantial requirements of Clauses 2, 3.2, 7.2, 9.1 and 15.9 had not changed since the 2012 Code (the earliest Code relevant to the material at issue) and so all of the rulings below are made under the 2016 Code.

The Panel noted that the advertisement included the claim, 'With a long-term record of success in reducing symptoms, exacerbations and hospitalisations vs placebo, Spiriva is a LAMA you can count on to help lead your COPD patients to everyday victories.' The Panel considered that the claim did not differentiate between the licensed indication (reduction of symptoms) and the benefit of therapy (reduction of exacerbations). Other than in the prescribing information, the advertisement did not refer to the licensed indication for Spiriva and make it clear that this was the primary reason to prescribe. Reduction in COPD exacerbations appeared to be as much a reason to prescribe as reduction in symptoms. In that regard the Panel considered that the claim was inconsistent with the particulars listed in the Spiriva SPC. A breach of Clause 3.2 was ruled. The claim was misleading with regard to the licensed indication for Spiriva; a breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that Boehringer Ingelheim also provided a copy of a slide deck to be used to train representatives but also to be used with and by health professionals (ref UK/SPI-131788, February 2014) which post-dated the advertisement by 18 months. The slide deck detailed Tashkin *et al* (cited in the advertisement) which assessed whether Spiriva was associated with a decrease in the rate of decline of FEV1 over time in COPD patients who either had Spiriva or placebo added to their usual respiratory medicines. A benefit was shown for Spiriva with regard to exacerbations (a secondary objective of the trial) and this was detailed in three slides, and in the summary slide one of the outcomes of the study was listed as 'Reduced exacerbations' and further details were provided. The data was not presented as being a benefit of using Spiriva to relieve COPD symptoms. The licensed indication for Spiriva was only stated within the prescribing information on the last slide.

The Panel again considered that Spiriva would be perceived as a medicine to reduce COPD exacerbations given that such use had been presented as a reason to prescribe *per se* and not as a benefit of using the medicine for its licensed indication. Although the SPC did discuss reduction of exacerbation data, the Panel, noting the product's licensed indication, nonetheless considered that the slide deck was inconsistent with the particulars listed in the SPC. A breach of Clause 3.2 was ruled. Slides that implied that exacerbation reduction was a primary reason to prescribe Spiriva were misleading. A breach of Clause 7.2 was ruled. In the Panel's view the slide deck which was used to train representatives, presented the exacerbation data in such a way as to advocate a course of action that was likely to breach the Code. A breach of Clause 15.9 was ruled. In the Panel's view, high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such. The Panel noted its comments and rulings above but did not consider that the matters were such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. No breach of Clause 2 was ruled.

**Complaint received** **25 April 2016**

**Case completed** **16 September 2016**

**CASE AUTH/2844/5/16**

# VOLUNTARY ADMISSION BY AMDIPHARM MERCURY

## Email sent by representative

**Amdipharm Mercury Company (AMCo) voluntarily admitted a breach of the Code in that a representative sent an unapproved email promoting Lutrate (leuprorelin) to a prescribing advisor. Lutrate was indicated in the treatment of advanced prostate cancer.**

**AMCo stated that the email was discovered as a result of ongoing inter-company dialogue during which it had been brought to the company's attention that a budget impact model relating to cost savings for a specific clinical commissiong group (CCG) contained an error which seemed to have been confined to one territory. AMCo withdrew the model until it could be demonstated to work in all territories.**

**The representative concerned had noticed the error and sent revised and correct figures to the customer concerned. On further examination AMCo realised that the revised data itself was marginally incorrect (there was actually an additional cost saving available to the CCG). The inconsistency had since been fully explained to the customer with apologies from the company.**

**AMCo was disappointed that the representative's email included an unauthorized and unapproved claim which did not appear to be scientifically valid or clear. It was also inconsistent with the training provided to the sales force and fell short of the standards set for AMCo representatives.**

**The Panel noted AMCo's submission that the voluntary admission related to an email from an AMCo representative which included the claim 'Lutrate is available as a one month and three month formulation providing effective suppression and maintenance of testosterone to castration levels with the tolerability you would expect from each leuprorelin dose'. The Panel noted AMCo's admission that the claim was not scientifically valid and was confusing and ruled a breach of the Code. The claim could not be substantiated as acknowledged by AMCo and a further breach was ruled. Further breaches of the Code were ruled as the email had not been certified and high standards had not been maintained.**

**The Panel ruled no breach of the Code with regard to the frequency, timing and duration of calls by a representative on health professionals and others.**

Amdipharm Mercury Company (AMCo) Limited voluntarily admitted a breach of the Code in that a representative sent an unapproved email promoting Lutrate (leuprorelin) to a prescribing advisor.

Lutrate 1 month depot injection was indicated for palliative treatment of locally advanced or metastatic prostate cancer. Lutrate 3 month depot injection was indicated for palliative treatment of hormone dependent advanced prostate cancer.

**VOLUNTARY ADMISSION**

AMCo stated that it discovered the unapproved email sent by its representative following an internal investigation stemming from ongoing inter-company dialogue. The other pharmaceutical company had drawn AMCo's attention to a budget impact model (BIM) relating to cost savings for a specific clinical commissioning group (CCG) which contained an unaccountable error. The error seemed to have been confined to one territory after prescription cost anaylsis data was automatically imported in to the BIM. AMCo took a conservative approach to this inaccuracy and voluntarily withdrew the BIM until it could be demonstated to work in all territories. Additionally, AMCo provided clarification and reassurance to the other company on how the calculations were derived and the assumptions that were made in the model and was awaiting confirmation from it that the matter had been resolved.

AMCo informed the other company that the representative concerned had noticed the error and sent revised and correct figures to the customer in question. On further examination AMCo realised that the revised data itself was marginally incorrect (there was actually an additional £170 cost saving available to the CCG). The customer had since been informed with a full explanation regarding the inconsistency with the company's apologies.

AMCo was disappointed that the representative's email to the prescribing advisor contained an unauthorized and unapproved claim:

> 'Lutrate is available as a one month and three month formulation providing effective suppression and maintenance of testosterone to castration levels with the tolerability you would expect from each leuprorelin dose.'

This claim did not appear to be scientifically valid or clear and had not been approved for use in this manner. The statement was also inconsistent with the training provided to the sales force and fell short of the standards set for AMCo representatives.

Disciplinary action had been taken and further training had been delivered to the entire sales force. In addition, a formal memo had been sent to the whole UK field force highlighting the importance of ABPI compliant communications to customers and health professionals and clarification on the circumstances when approval/certification was required.

When writing to AMCo, the Authority asked it to respond in relation to Clauses 7.2, 7.4, 9.1 and 15.4 of the Code and in addition Clause 14.1.

**RESPONSE**

AMCo reiterated that the email was discovered in connection with on-going inter-company dialogue relating to the provision of inaccurate cost savings data to one customer. The error led to an underestimate of actual savings realisable. The customer had since been provided with the correct savings data and the other pharmaceutical company had been given details of the Lutrate BIM including all of the assumptions and updated information.

With regard to Clause 7.2, AMCo submitted that the unauthorized claim in the email did not specifically distort or mislead the reader as the claim itself did not seem to make sense; 'with the tolerability you would expect from every dose' therefore AMCo submitted that the reader was not misled but more likely confused by the statement, which in itself fell well below the high standards expected in communications with health professionals.

AMCo accepted that there appeared to be a breach of Clause 7.4 as the claim could not be substantiated. The company also accepted that high standards were not maintained in relation to this email in breach of Clause 9.1.

AMCo denied a breach of Clause 15.4 as the request to meet and discuss the budget impact model had been accepted by the customer along with a request for the representative to call back by telephone in two weeks. Other than this, one final email was sent by AMCo to alert the health professional of the error.

Since learning of this mistake, the entire sales force had been retrained and additionally sent a memo which highlighted the importance of ABPI compliant communications to customers and health professionals and clarified the circumstances when approval/certification was required.

AMCo trusted this set out the company's deep regret with respect to this voluntary admission and conveyed the seriousness with which it had taken this incident.

In response to a request for further information from the case preparation manager, AMCo submitted that prescribing information was included in both the email in question and the subsequent two corrective emails sent to the customer. AMCo had no additional comments in relation to Clauses 9.1 or 14.1.

**PANEL RULING**

The Panel noted AMCo's submission that the voluntary admission related solely to the email from an AMCo representative which included the claim 'Lutrate is available as a one month and three month formulation providing effective suppression and maintenance of testosterone to castration levels with the tolerability you would expect from each leuprorelin dose'. The Panel noted AMCo's submission that the claim was not scientifically valid or clear. The Panel found it difficult to understand AMCo's view that the claim in question was not misleading but was likely to confuse readers. The Panel noted that Clause 7.2 required, *inter alia*, that claims be accurate and unambiguous and that material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. The Panel noted AMCo's admission that the claim was not scientifically valid and was confusing and ruled a breach of Clause 7.2. The claim could not be substantiated as acknowledged by AMCo and a breach of Clause 7.4 was ruled. The promotional email had not been certified before it was sent to the prescribing advisor and a breach of Clause 14.1 was ruled.

The Panel noted that AMCo had been asked to respond to Clause 15.4 which required that representatives must ensure that the frequency, timing and duration of calls on health professionals, administrative staff in hospitals and NHS and other organisations, together with the manner in which they are made, do not cause inconvenience. The wishes of individuals on whom representatives wished to call and the arrangements in force at any particular establishment, must be observed. The Panel noted AMCo's submission that the request to meet and discuss the budget impact model had been accepted by the customer along with a request for the AMCo representative to call back by telephone in two weeks. The Panel ruled no breach of Clause 15.4; it covered the frequency and manner of calls on doctors and other prescribers which was not the subject of the voluntary admission and therefore not at issue in this case. The company had not been asked to respond in relation to Clause 15.2 and so the Panel could make no ruling in that regard.

The Panel noted that the email in question promoted Lutrate. The representative had created and disseminated his/her own piece of promotional material; it should have been certified in accordance with Clause 14.1. The Panel noted AMCo's submission that the claim was inconsistent with the training provided to the sales force and fell short of the standards set for AMCo representatives. Training provided by AMCo in January 2016 included a slide titled 'Field activities – Representatives' and stated that all emails needed to be certified. The Panel considered that the representative had not maintained high standards and a breach of Clause 9.1 was ruled.

**Complaint received** **11 May 2016**

**Case completed** **7 July 2016**

**CASE AUTH/2845/5/16** *NO BREACH OF THE CODE*

# CSL BEHRING v SWEDISH ORPHAN BIOVITRUM

## Charity ball

**CSL Behring complained about a charity ball held by Swedish Orphan Biovitrum (Sobi) and an advertisement/invitation for the event placed in the public domain on both Sobi's and a named charity's website. The advertisement stated, *inter alia*, the ticket price which included arrival drinks, a three course meal, table wine and entertainment. Sobi's contact details were provided for tickets and further information. It was stated at the bottom of the advertisement in small font that 'Proceeds will be distributed equally between the following three charities:' followed by their names and logos.**

**CSL Behring stated that the invitation failed to state who the event was for, health professionals, patients, spouses, patient organisations, families, or other. Without knowing who was invited, who attended and in what capacity and the proportion of the entire group they represented, it was impossible to label the meeting as a corporate event. CSL Behring submitted that the event fell within scope of the Code.**

**CSL Behring alleged that the event did not give the impression that it was primarily an educational event and that the hospitality was secondary to the purpose of the meeting. The event was wholly social and failed to maintain high standards and was therefore unacceptable. Moreover, the offer of entertainment, music, fun, wine and prizes was excessive. In addition, any hospitality must not be paid or facilitated by the company, and must not form part of the official programme of the meeting. CSL Behring alleged that it was not clear from the invitation exactly what Sobi had funded.**

**CSL Behring was particularly concerned about the involvement of one of the charities given the ongoing commercialisation and development of two of Sobi's medicines. CSL Behring alleged that Sobi had specifically targeted the audience in a therapy area where it had a vested interest and as the invitation failed to set out a clear agenda or indicate who should attend, the impression was one of disguised promotion.**

**CSL Behring stated that Sobi did not plan to track or monitor who had attended the event and therefore could not claim that the ball was a corporate event which fell outside the scope of the Code Breaches of the Code were alleged including a breach of Clause 2.**

**The detailed response from Sobi is given below.**

**The Panel noted Sobi's submission that the charity ball was a corporate event that fell outside the scope of the Code as it did not promote any of Sobi's medicines, nor did it target health professionals, other relevant decision makers or patients. The Panel considered that corporate events, including fund raising activities, were a legitimate activity for a pharmaceutical company to undertake. They were part of normal business practice. Whether a corporate event was covered by the Code would depend on the arrangements. Corporate events covered by the Code had to comply with it.**

**In the Panel's view, in order to fall outside the scope of the Code corporate events must not otherwise be meetings organised for health professionals, other relevant decision makers or patient organisation representatives and or their members, bearing in mind that meetings organised for such groups which were wholly or mainly of a social or sporting nature were unacceptable. Corporate events could include invited health professionals, other relevant decision makers or patient organisation representatives and/or members but must also include a significant proportion of other invited guests from a different background. Further, the capacity in which health professionals and others were invited to attend such events was an important factor. In the Panel's view inviting health professionals in their capacity as prescribers or as persons who recommended medicines to a corporate event with no educational or scientific input would be in breach of the Code. Such health professionals might be invited to attend in relation to their roles such as senior representatives of professional organisations, hospital trusts, primary care trusts, etc. The Panel noted that the reason that patient organisation representatives and/ or their members had been invited might also be relevant. The Panel noted that the event at issue was advertised through a number of channels and those who wanted to attend could purchase tickets. It appeared that no one was invited personally at Sobi's expense.**

**The Panel noted Sobi's submission that it organised the event with the help of three charities in order to raise funds for them and highlight their important work; Sobi would declare the amount donated to the charities in accordance with the Code. The Panel further noted that Sobi had provided significant administrative support and the confirmation letter sent to those who purchased tickets stated that it had payed part of the costs necessary to hire the venue and provide the catering and the evening's entertainment. This was in contrast to Sobi's submission that the cost of the tickets was more than the value of the hospitality and entertainment so all hospitality was paid for by the attendees. The amount paid by Sobi in that regard was unknown.**

**The Panel noted that the Code provided that pharmaceutical companies could interact with, *inter alia*, patient organisations to support their work. Taking all the circumstances into account the Panel considered that working with the patient organisations, including those that operated in a field in which Sobi had a commercial interest, to**

**raise money for those organisations was a matter covered by the Code.**

**The Panel noted that the event was open to anyone who wanted to buy a ticket. The attendee list showed a spread of attendees, primarily Sobi employees, patient organisations and healthcare agencies including partners, family and friends; overall the Panel did not consider that the ball was a meeting organised for health professionals or patient organisation members *per se*. Attendees had to purchase their own tickets. Sobi had not controlled who could buy tickets and in that regard attendees were not guests of the company. The Panel noted Sobi's submission that no health professionals attended the event at Sobi's invitation or expense and as far as Sobi was aware only three or four attendees might qualify as a health professional as defined in the Code and none prescribed Sobi products; they had attended as guests of the charities or other non-pharmaceutical companies that purchased tickets. The Panel considered, on balance that Sobi had organised a charitable event that was open to anyone who wished to purchase a ticket; it was not aimed at health professionals, other relevant decision makers or patient organisations *per se* and no breach of the Code was ruled.**

**The Panel noted Sobi's submission that the charity ball was a non-promotional event at which there was no direct or indirect promotion of Sobi's medicines. The Panel did not consider that the event was promotional nor were the raffle items offered as an inducement. In the exceptional circumstances of this case the Panel therefore ruled no breach of the Code.**

**The Panel noted its comments above and Sobi's submission that the event was non-promotional. In that regard, the event could not be disguised promotion and no breach of the Code was ruled.**

**The Panel did not consider that Sobi had failed to maintain high standards and so no breach of the Code was ruled. The Panel noted its rulings and further ruled no breach of Clause 2.**

CSL Behring complained about a charity ball held by Swedish Orphan Biovitrum Limited (Sobi).

**COMPLAINT**

CSL Behring referred to an advertisement/invitation for the ball placed in the public domain on both Sobi's and a named patient organisation's website. The advertisement depicted part of a tuxedo and was headed 'Sobi Charity Ball'. The date, time and venue were followed by the cost per person which was £65. The cost, according to the advertisement, included arrival drinks, a three course meal, table wine and entertainment. Sobi's contact details were provided for tickets and further information. Black tie was requested. It was stated at the bottom of the advertisement in small font that 'Proceeds will be distributed equally between the following charities:' followed by their names and logos. Although not stated on the invitation, the objective of the ball was to highlight and raise awareness of the challenges faced by those with rare diseases and the work that was being done to support them.

CSL Behring submitted that in inter-company dialogue it referred to the fact that although it was an established principle of the Code that corporate events were acceptable (Case AUTH/1604/7/04), Sobi needed to be clear who was attending the event and in what capacity. CSL Behring was unable to establish the clear nature and purpose of the charity event without knowing the intended audience; the invitation failed to specify that it was an event for health professionals, patients, spouses, patient organisations, families, or other. Without knowing details of who was invited, who actually attended, in what capacity, and the proportion of the entire group they represented, it was impossible to label the meeting as a corporate event and therefore CSL Behring submitted that it fell within scope of the Code. No programme or agenda was included or referred to in the invitation, nor was there an indication of what the evening would comprise of in terms of content such as presentations, education, etc. Rather, the invitation stated that potential attendees were invited to 'join in the celebrations at this "black tie" event – where you will enjoy welcome drinks, a delicious 3 course meal, table wine, music, fun and entertainment with fabulous prizes to be won and plenty of opportunities to support our charity'.

The overall impression of any meeting must be that it was primarily an educational event and that any hospitality provided was secondary and no more than what was expected to meet the purpose of the meeting. CSL Behring alleged that this charity event did not give that impression. CSL Behring submitted that the event was wholly social and failed to maintain high standards and was therefore unacceptable. Moreover, the offer of entertainment, music, fun, wine and prizes was excessive and in breach of Clause 18.1. In addition, any hospitality must not be paid or facilitated by the company, and must not form part of the official programme of the meeting. CSL Behring acknowledged that third parties were involved but considered that it was ultimately the company's responsibility. It was not clear from the invitation exactly what Sobi had funded.

CSL Behring stated that the event was clearly supported by three named charities and it was particularly concerned about the involvement of one of them given the ongoing commercialisation and development of two of Sobi's medicines. CSL Behring therefore alleged that Sobi had specifically targeted the audience in a therapy area where it had a vested interest and as the invitation failed to set out a clear agenda or indicate who should attend, the impression was one of disguised promotion in breach of Clause 12.

CSL Behring requested immediate withdrawal of all materials relating to the event and cancellation of the event with written communication to all relevant internal and external stakeholders. This did not take place and on 24 March 2016, CSL Behring received written acknowledgement from Sobi that its charity ball would raise funds for three charities,

with which it had long-standing relationships and highlight the important work done by them. Sobi stated that the event was not intended to promote its medicines, or to target health professionals; the event was open to anyone who wished to purchase a ticket. Sobi itself would not pay for anyone to attend; even its personnel who planned to attend had to purchase their own tickets. Sobi stated that it publicised the event by word of mouth to family, friends and business partners, as well as trade and industry media. The charities for which the event would raise money also publicised the event through their networks and membership and Sobi gave them posters to place in their offices. Finally, members of the steering committee used social media to publicise the event to their individual networks. Sobi claimed that because they did not target the event specifically at health professionals or other relevant decision makers, it fell outside the scope of the Code and thus could not be in breach of Clauses 9.1, 18.1 or 22.1 of the Code and since there was no breach of those clauses, there could be no breach of Clause 2. Therefore, Sobi refused to cancel the ball or withdraw any materials relating to the event.

CSL Behring did not consider that Sobi's response adequately addressed its concerns. Although Sobi stated that the event was open to anyone who wished to purchase a ticket, this was not apparent from the posters and other publicity. In addition, it was not clear who developed these posters and other publicity and what involvement, if any, Sobi had in that. This was confounded by the fact that Sobi admitted publicising the event by word of mouth to family, friends and business partners, as well as trade and industry media. Reference to 'business partners' and 'trade media' was ambiguous and could include health professionals. Also, as the charities advertised the event through their own networks and membership, this could have included health professionals and definitely failed to exclude this group. If health professionals were to attend, no statement or disclaimer was made on the advertisement indicating that they should do so in a non-prescribing capacity.

CSL Behring noted that the charity ball took place and Sobi had failed to supply a list of attendees and the capacity within which they attended. In essence, it was clear that Sobi made no plans to track or monitor who had attended the event and therefore could not claim the event was a corporate one that fell outside the scope of the Code.

CSL Behring alleged breaches of Clause 2, discredit to, and reduction of confidence in, the industry through provision of excessive hospitality, Clause 9.1, failing to maintain high standards, Clause 18.1, gifts, rewards or hospitality, the use of competitions, quizzes and Clause 22.1, meetings, hospitality and sponsorship.

**RESPONSE**

Sobi explained that the charity ball was designed to raise funds for three charities with which Sobi had long-standing relationships and to highlight the important work done by them. Sobi submitted that it organised the event with the full knowledge and assistance of the three charities. The event was not intended to and did not promote any of Sobi's medicines, nor did it target health professionals or patients and as a non-promotional event that did not target or involve health professionals Sobi considered that it fell outside the scope of the Code.

Sobi submitted that it had the initial idea for the charity ball which was conceived as a non-promotional, corporate event to raise money for the three charities. This was apparent from the posters and other publicity materials which made no reference to any of Sobi's products. In the confirmation letter sent to those who purchased tickets it was made clear that it was a non-promotional charitable event that Sobi employees voluntarily supported by purchasing tickets at the purchase price and attended in their own time and not in a promotional capacity. Those points were reiterated at the event itself. Sobi did not give any presentations about its products or any other topic which could be construed as being promotional in nature. Sobi did not have any booths or displays at the event, nor did it distribute any promotional or non-promotional materials at the event.

The event was organised with help from the three charities. A steering committee of four Sobi employees and a representative from each of the three charities volunteered to plan and implement the event.

Sobi publicised the event by word of mouth to family, friends and business partners, such as recruitment, advertising and communications agencies. Sobi understood that the charities also publicised the event through their networks and membership. Sobi gave them some posters to place in their offices and Sobi employees and charity members used social media to publicise the event to their personal networks.

Sobi submitted that the intended audience included its employees, business partners such as agencies that provided services to Sobi, and their respective guests. The charities involved were able to generate ticket sales through their own networks. Sobi submitted that it did not target health professionals or other relevant decision makers. No health professionals attended the event at Sobi's invitation or expense and as far as Sobi was aware, of the approximately 150 individuals that attended, only three or four might qualify as a health professional as defined in the Code and none were prescribers of Sobi products; they had attended as guests of the charities or other non-pharmaceutical companies that purchased tickets. Sobi submitted that those health professionals were academic and therefore unlikely to be active prescribers or did not operate in the specialist therapeutic areas for which Sobi marketed products. Sobi did not pay for any attendees; even its own employees, with the exception of two steering committee members, had to buy their own tickets.

Sobi submitted that the cost of each ticket was £65 which was more than the value of the hospitality and entertainment provided. The combination of

ticket sales and fundraising on the night more than covered the entire cost of the event so Sobi did not subsidise the event in any way. The profits of the night were shared equally by the three charities. In addition, Sobi pledged to donate an amount equivalent to 50% of the total costs of the event and donated £5,224.16 to be shared equally between the three charities which would be publicly disclosed in due course in accordance with the requirements of Clause 27.7.

Sobi submitted that hospitality comprised a three course meal accompanied by wine and soft drinks. Music was provided by a local band and there was a raffle with prizes donated by Sobi employees, Sobi business partners, local business or people connected with the three charities (a list of prizes was provided). In addition, one of the charities arranged for four children, whom it supported, to give a short demonstration of a dance that they have developed. The children used dance as a form of exercise and to help them express themselves which had proven very valuable as part of their disease management. The children and their parents or carers were provided with a light buffet in a separate room at the venue before leaving.

Sobi stated that the Code applied to the promotion of medicines to health professionals and other relevant decision makers as well as to non-promotional information about prescription only medicines made available to the public. It also applied to hospitality provided to health professionals and other relevant decision makers, whether or not in a promotional context. The Sobi charity ball did not involve the promotion of any Sobi's products or the dissemination of non-promotional information about Sobi's products. This event was not targeted at health professionals or other relevant decision makers and Sobi did not provide any hospitality to such persons and as a result submitted that the event fell outside of the scope of the Code.

Sobi noted that Case AUTH/1604/7/04 confirmed that corporate events were in general acceptable under the Code. That case concerned three separate corporate events which had been attended by health professionals as guests and at the expense of a pharmaceutical company. In that case, the Panel explained that corporate events were a legitimate activity for pharmaceutical companies to undertake and whether the event came within the scope of the Code would depend on the arrangements. In particular, to be exempt from the Code, events must not otherwise be meetings organised for health professionals or appropriate administrative staff. The Panel ruling for Case AUTH/1604/7/04 also confirmed that the corporate events that included health professionals could be exempt from the Code, provided that a significant proportion of other guests were from a different background and health professionals were invited to attend in a capacity other than mere prescribers or persons who could recommend medicines.

Sobi reiterated that the charity ball was not targeted at health professionals or other relevant decision makers and, while a small number of the guests invited by the charities or other organisations present might meet the definition of health professionals under the Code, none were there as guests of or at the invitation of Sobi or in a capacity as a prescriber of one of Sobi's medicines. Applying the principles set out in Case AUTH/1604/7/04, the event fell outside the scope of the Code.

Clause 14.1 of the Code required companies to certify the compliance of promotional materials with the Code, while certain other educational, patient support and similar materials required certification under Clause 14.3. Since the event was non-promotional and no materials relating to diseases, therapy areas or Sobi's medicines were disseminated before or during the event, all materials relating to the event, such as the posters, tickets and confirmation letters fell outside the scope of the certification requirements under the Code. Nonetheless, applying the principle described in the supplementary information to Clause 14.3, Sobi sought to examine and approve all items planned for public dissemination to ensure they did not contravene the Code. Those materials were reviewed and approved through the electronic approval system. All other items not planned for wide public dissemination (ie tickets and confirmation letter to guests) were not approved electronically but were examined before use.

Sobi noted that whilst in its view the charity ball fell outside the scope of the Code, for completeness it responded to each of the alleged breaches.

**Clause 12**

Sobi noted that CSL Behring argued that as the event involved a charity which was active in a therapy area for which Sobi marketed and developed prescription only medicines, the event was somehow disguised promotion in breach of Clause 12. Clause 12 concerned materials and activities that were disguised so that while appearing to be non-promotional they were in fact promotional. Sobi reiterated that the ball did not involve the promotion of any of its products, nor did it involve the dissemination of non-promotional information about its products. Further, Sobi did not provide any hospitality to health professionals, either free of charge or as an inducement to prescribe or recommend Sobi's products. Rather, this was a non-promotional, corporate event, which did not target health professionals or other relevant decicion makers. Given that no promotion of, or even reference to, any Sobi's products had occured in connection with the charity ball, the event could not constitute disguised promotion and be in breach of Clause 12.

**Clause 18.1**

Sobi noted that Clause 18.1 prohibited the supply, offer or promise of gifts, pecuniary advantages or benefits to health professionals or other relevant decision makers in connection with the promotion of medicine or as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. In the context of Clause 18.1, CSL Behring had referred to the use of competitions

and quizzes. The supplementary information to Clause 18.1 provided that use of competitions, quizzes and such like, and the giving of prizes, were unacceptable methods of promotion.

Sobi submitted that the charity ball was a non-promotional, corporate event at which there was no direct or indirect promotion of Sobi's medicines. The event did not target health professionals and as far as Sobi was aware none of the small number of health professionals who attended prescribed Sobi's medicines. Consequently there could not have been any inducement for such health professionals to prescribe, supply, administer, recommend, buy or sell any medicine. In any event, since all attendees other than the steering committee were required to purchase a ticket which cost more than the value of the hospitality and Sobi did not pay for anyone to attend, Sobi had not given any benefit to any person, let alone to a health professional or other relevant decision maker. Further, since the event fell outside the scope of both Clause 18.1 and the Code in general, there could not have been a breach of Clause 18.1 or any of the guidance contained in the supplementary information to Clause 18.1.

**Clause 22.1**

Sobi noted Clause 22.1 provided that (i) companies must not provide hospitality to health professionals and other relevant decision makers except in connection with appropriate meetings, (ii) meetings must be held at an appropriate venue, (iii) hospitality must be strictly limited to the main purpose of the event, (iv) the level of subsistence must be appropriate and proportionate, (v) the costs involved must not extend beyond health professionals and other relevant decision makers.

Sobi reiterated that the charity ball was a non-promotional corporate event that did not target health professionals or other relevant decision makers. The very few health professionals that attended the ball did not do so in their capacity as prescribers and, as far as Sobi was aware, they did not prescribe Sobi's medicines. Applying the principles from Case AUTH/1604/7/04 discussed above, it was clear that this corporate event fell outside the scope of Clause 22.1 and the Code more generally so there could not have been a breach of Clause 22.1.

Further, Sobi did not provide hospitality to anyone let alone a health professional. Clause 22.1 made it clear that the costs involved in an event covered by Clause 22.1 must not exceed the level which recipients would normally adopt when paying for themselves. In this case, admission to the event was by ticket only and Sobi did not pay for anyone to attend. The cost of the ticket was more than the value of the hospitality and entertainment, so all hospitality was paid for by the attendees.

**Clause 9.1**

Sobi noted that Clause 9.1 required that high standards be maintained at all times. It was, however, unclear from the complainant exactly in which regard Sobi had failed to maintain high standards. Sobi noted that the supplementary information to Clause 9.1 stated that the special nature of medicines and the professional audience to which the material was directed required that standards for the promotion of medicine were higher than those which might be acceptable for general advertising. That suggested that the high standards referred to in Clause 9.1 related to the promotion of prescription medicines.

Sobi submitted that it had maintained high standards at all times, in that the organisation of the event was conducted appropriately, the materials and publicity surrounding such a corporate, non-promotional event (which was therefore outside the scope of the Code) were appropriate and all attendees were made fully aware of its non-promotional nature. Since the event fell outside the scope of the Code and did not involve any direct or indirect promotion of any of Sobi's medicines, it followed that there could not have been a breach of Clause 9.1.

**Clause 2**

Sobi noted that CSL Behring alleged a breach of Clause 2 'through provision of excessive hospitality'. Sobi submitted that a breach of Clause 2 was a sign of particular censure for events that brought discredit upon, or reduced confidence in, the pharmaceutical industry. Sobi submitted that as the charity ball fell outside the scope of the Code and Sobi had not breached Clause 18.1 or any of the provisions of the Code relating to hospitality, there could be no breach of Clause 2 relating to such hospitality.

**PANEL RULING**

The Panel noted that the provisions of Clause 22 of the Code applied to meetings organised for health professionals regardless of whether the meetings were promotional or not. Clause 22.1 of the Code permitted companies to provide appropriate hospitality to members of the health professions and other relevant decision makers in association with scientific and promotional meetings. Hospitality must be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion. The costs incurred must not exceed the level which recipients would normally adopt if paying for themselves. It must not extend beyond members of the health professions or other relevant decision makers. The supplementary information stated that the impression created by the arrangements must be borne in mind. Meetings organised for groups of doctors, other health professionals and/or other relevant decision makers etc which were wholly or mainly of a social or sporting nature were unacceptable. The relevant supplementary information also made it clear that the requirements of the Code did not apply to the provision of hospitality other than that referred to in, *inter alia*, Clause 27.2 and the supplementary information to Clause 26.2. The latter made it clear that meetings organised for or attended by members of the public, journalists and patient organisations must comply with Clause 22. Clause 27.2 stated that

Clause 22 applied to pharmaceutical companies supporting patient organisation meetings. The Panel noted that the charity ball was not a patient organisation meeting sponsored by Sobi.

The Panel firstly had to consider whether the charity ball was covered by the Code. The Panel noted Sobi's submission that the charity ball was a corporate event that fell outside the scope of the Code as it did not promote any of Sobi's medicines, nor did it target health professionals, other relevant decision makers or patients. The Panel considered that corporate events, including fund raising activities, were a legitimate activity for a pharmaceutical company to undertake. They were part of normal business practice. Whether a corporate event was covered by the Code would depend on the arrangements. Corporate events covered by the Code had to comply with it.

The Panel noted that both parties had referred to Case AUTH/1604/7/04. Whilst that case provided useful guidance, breaches of the Code were ruled in that case in relation to corporate events to which health professionals had been personally invited and paid for by a pharmaceutical company. This was not the case with the Sobi charity ball.

In the Panel's view, in order to fall outside the scope of the Code corporate events must not otherwise be meetings organised for health professionals, other relevant decision makers or patient organisation representatives and or their members, bearing in mind that meetings organised for such groups which were wholly or mainly of a social or sporting nature were unacceptable. Corporate events could include invited health professionals, other relevant decision makers or patient organisation representatives and/or members but must also include a significant proportion of other invited guests from a different background. Further, the capacity in which health professionals and others were invited to attend such events was an important factor. In the Panel's view inviting health professionals in their capacity as prescribers or as persons who recommended medicines to a corporate event with no educational or scientific input would be in breach of the Code. Such health professionals might be invited to attend in relation to their roles such as senior representatives of professional organisations, hospital trusts, primary care trusts, etc. The Panel noted that the reason that patient organisation representatives and/or their members had been invited might also be relevant. The Panel noted that the event at issue was advertised through a number of channels and those who wanted to attend could purchase tickets. It appeared that no one was invited personally at Sobi's expense.

The Panel noted Sobi's submission that it organised the event with the help of three charities who were represented on the steering committee in order to raise funds for them and highlight their important work. The profits were shared equally by the three charities. In addition, Sobi pledged to donate an amount equivalent to 50% of the total costs of the event to be shared equally between the three charities; Sobi would declare the amount donated to the charities in accordance with Clause 27.7. In addition the Panel noted that Sobi had provided non-financial support; its contact details had appeared on all the materials, ticket payments were made via the company's charity account, it issued tickets and corresponded with guests. Significant administrative support had therefore been provided. It was not known who had paid for printing costs. In addition the Panel noted the confirmation letter sent to those who purchased tickets stated that Sobi had provided part of the costs necessary to hire the venue and provide the catering and the evening's musical entertainment. This was in contrast to Sobi's submission that the cost of the tickets was more than the value of the hospitality and entertainment so all hospitality was paid for by the attendees. The amount paid by Sobi in that regard was unknown.

The Panel noted that Clause 27.1 provided that pharmaceutical companies could interact with, *inter alia*, patient organisations to support their work. Taking all the circumstances into account the Panel considered that working with the patient organisations, including those that operated in a field in which Sobi had a commercial interest, to raise money for those organisations was a matter covered by the Code.

The Panel then had to decide whether the charity ball was in breach of the Code as alleged bearing in mind its comment above that corporate events were a legitimate activity. The Panel noted that the event was open to anyone who wanted to buy a ticket although as might be anticipated, given the advertising channels, it appeared to be largely attended by those with a professional connection to the company or therapy area and their friends and colleagues. Overall there were 163 attendees including Sobi staff. According to Sobi three or four might be described as health professionals and were not prescribers of Sobi's products. The Panel did not know whether these individuals could recommend products. The Panel noted that there was a spread of attendees, primarily Sobi employees, patient organisations and healthcare agencies. Those attending under the Sobi or patient organisation banner included partners, family and friends. For instance for one patient organisation 6 attendees had a formal role at the organisation, such as trustees or staff, whilst 10 were family or friends and 3 were connected with its marketing and public relations agency. Overall the Panel reviewed the full attendee list and considered that the charity ball was not a meeting organised for health professionals or patient organisation members *per se*. Attendees even Sobi's own employees with the exception of two steering committee members, were required to purchase their own tickets. Sobi had not controlled who could buy tickets and in that regard attendees were not guests of the company although it had organised the ball and met certain costs. The Panel noted Sobi's submission that no health professionals attended the event at Sobi's invitation or expense and as far as Sobi was aware only three or four attendees might qualify as a health professional as defined in the Code and none prescribed Sobi products; they had attended as guests of the charities or other non-pharmaceutical companies that purchased tickets. The Panel considered, on balance that Sobi had

organised a charitable event that was open to anyone who wished to purchase a ticket; it was not aimed at health professionals, other relevant decision makers or patient organisations *per se* and no breach of Clause 22.1 was ruled.

The Panel noted that Clause 18.1 stated that no gift, pecuniary advantage or benefit might be supplied, offered or promised to members of the health professions or to other relevant decision makers in connection with the promotion of medicines or as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine, subject to the provisions of Clauses 18.2 and 18.3. The supplementary information to Clause 18.1 provided that use of competitions, quizzes and such like, and the giving of prizes, were unacceptable methods of promotion. The Panel noted Sobi's submission that the charity ball was a non-promotional event at which there was no direct or indirect promotion of Sobi's medicines. The Panel did not consider that the event was promotional nor were the raffle items offered as an inducement. In the exceptional circumstances of this case the Panel therefore ruled no breach of Clause 18.1.

The Panel noted that CSL Behring had cited Clause 12 although not included it in its list of alleged breaches. Nonetheless, the Panel considered that there was an allegation of disguised promotion and Sobi had responded to it. The Panel noted its comments above and Sobi's submission that the event was non-promotional. In that regard, the event could not be disguised promotion and no breach of the Code was ruled.

The Panel did not consider that Sobi had failed to maintain high standards and so no breach of Clause 9.1 was ruled. The Panel noted its rulings and further ruled no breach of Clause 2.

**Complaint received** **12 May 2016**

**Case completed** **18 August 2016**

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**CASE AUTH/2848/5/16**

# VOLUNTARY ADMISSION BY FERRING

## Representative-facilitated letter

**Ferring Pharmaceuticals voluntarily admitted that one of its sales managers encouraged the representatives in his/her team to facilitate their local hospital to send a letter to local primary care practices encouraging the use of DesmoMelt (sublingual desmopressin) instead of Desmospray (desmopressin nasal spray). Ferring acknowledged that the sales manager's action, which was an entirely a local initiative, was inappropriate and constituted disguised promotion.**

**In accordance with Paragraph 5.6 of the Constitution and Procedure, the Director treated the matter as a complaint.**

**The detailed response from Ferring is given below.**

**The Panel noted Ferring's submission that without its consent or approval, an area sales manager had drafted a letter for hospital consultants to send to local GPs recommending the use of DesmoMelt for primary nocturnal enuresis and discouraging the use of desmopressin nasal spray. The drafted text was, in effect, a piece of promotional material.**

**Regardless of the fact that no letters had been sent to GPs, the provision of the draft text, handwritten on a piece of notepaper, to the hospital consultants meant that they had been handed a piece of disguised promotional material and a breach of the Code was ruled.**

**The Panel considered that the creation of a piece of promotional material by an area sales manager, and its subsequent provision to health professionals, demonstrated an extremely poor understanding of the Code; it appeared that numerous clauses had not been complied with. The Panel considered that the representatives had not maintained a high standard of ethical conduct and breaches of the Code were ruled.**

**The Panel noted its rulings and comments above but considered that, on balance, and given the very limited reach of the material at issue (no letters were sent), the area sales manager's conduct was not such as to bring discredit upon, or reduce confidence in, the industry. No breach of Clause 2 was ruled.**

Ferring Pharmaceuticals Ltd made a voluntary admission about the conduct of one of its representatives.

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 Ferring.

**VOLUNTARY ADMISSION**

Ferring stated that a sales manager encouraged the representatives in his/her team to facilitate their local hospital to send a product-related letter to local primary care practices. The letter was to be signed by the relevant hospital consultant and specifically encouraged GPs to use one particular formulation of a Ferring product instead of another. The activity was entirely a local initiative and came to the company's attention after an ex-employee raised concerns.

Ferring acknowledged that this activity was inappropriate and in breach of Clause 15.2. Because the letter was effectively disguised promotion, it also acknowledged that the activity was in breach of Clause 12.1.

Ferring was asked to provide the PMCPA with any further comments in relation to the requirements of Clauses 2, 9.1, 12.1 and 15.2.

**RESPONSE**

Ferring submitted that it had a range of products to treat enuresis (bedwetting), including DesmoMelt, (sublingual desmopressin) for the treatment of primary nocturnal enuresis and Desmospray (desmopressin nasal spray), which was indicated, *inter alia*, for the treatment of nocturia.

Desmospray was previously indicated for primary nocturnal enuresis, but this indication was removed by the Medicines and Healthcare products Regulatory Agency (MHRA) in September 2007 due to concerns over safety in children. Ferring noted that there were generic versions of Desmospray available and whilst the Ferring sales team promoted DesmoMelt because of its more child-friendly delivery, both Desmospray and generic desmopressin sprays remained available because of their other indications.

In April 2016 a former representative emailed Ferring to raise concerns about the actions of his/her local area sales manager.

The area sales manager, who managed a small team and also had account responsibilities, had established a local initiative with the urology key account specialist. Ferring understood this had the combined objectives of communicating a genuine patient safety concern – hyponatremia in children was a serious adverse event – and boosting sales of DesmoMelt. The sales manager directed his/her representative to facilitate a letter from the local hospital to certain local GP practices. The letter was written by the area sales manager in draft (handwritten on note paper) and stated:

'Dear x

It has been brought to the attention of the XXXXX continence service that there is a disproportionate

amount of desmopressin spray/Desmospray being issued from your surgery. Please find attached information relating to the licence removal for the treatment of primary nocturnal enuresis and why we recommend the use of Desmomelt (desmopressin oral lyophilisate) instead.

We would be grateful if you would disseminate this information amongst the GPs in your surgery and make the appropriate changes.

[Signed relevant consultants in department].'

The representative was expected to ask the local enuresis team in the local hospital to send the text on hospital letterhead to local GP practices that had high levels of Desmospray usage, indicating that it might still be being used for the withdrawn indication of primary nocturnal enuresis. The dictated text did not include any mention of Ferring's initiation of the content.

Ferring stated that whilst it could be argued that the action had a legitimate role in communicating the recent withdrawal of the Desmospray licence for safety reasons, the manner of the unsanctioned activity and the commercial motivation were obviously foremost in its considerations.

Ferring was aware that one hospital generated a letter which was signed by one of the two hospital consultant signatories. However, the letter was not sent to any GP practice as it was withdrawn from the hospital office by a colleague of the same (ex-) representative that had arranged for its creation – the same (ex-) representative that subsequently raised the matter with Ferring.

Ferring was aware that a second letter was requested from the paediatric clinical director at another hospital although no further action was taken in relation to this and no letter was sent.

Across the two hospitals, fifteen practices were identified as potential recipients of the intended letter however no letters were sent from either hospital.

The letter and safety issue were only relevant to urology, hence the activity was isolated to this speciality.

Ferring provided an email from the ex-representative to Ferring and a scanned copy of the handwritten note passed to the ex-representative from the sales manager.

Ferring noted that the ex-representative's email implied that one of its senior managers might be aware of the area sales manager's initiative. Ferring confirmed that during interviews, that senior manager categorically denied any knowledge of the activity. Ferring accepted that the actions of the area sales manager were in breach of Clause 15.2.

The letter would have constituted disguised promotion. However, no letters were actually sent from the hospital and none were received by any GP practice, Ferring did not believe a breach of Clause 12.1 actually occurred.

Ferring reassured the PMCPA that the area sales manager's actions were not endorsed or approved by Ferring. Ferring aspired to achieve the highest standards of conduct and it submitted it was badly let down by this individual. However, it was unable to interview him/her to determine any missing context and information which might be relevant (a detailed explanation was provided).

Since the matter came to light, Ferring had engaged the services of compliance specialists to work closely with the sales management team to reinforce the importance of securing approval for local initiatives so that they could be appropriately assessed for Code compliance. The entire sales team had also been retrained on the Code and the inappropriateness, in particular, of unapproved local activities.

**PANEL RULING**

The Panel noted Ferring's submission that without its consent or approval, an area sales manager had drafted a letter for hospital consultants to send to local GPs recommending the use of DesmoMelt for primary nocturnal enuresis and discouraging the use of Desmospray/desmopressin spray. Desmospray had not been licensed for use in primary nocturnal enuresis since September 2007 (the change in the licence was not recent as stated by Ferring). The drafted text was, in effect, a piece of promotional material.

Regardless of the fact that no letters had been sent to GPs, the provision of the draft text, handwritten on a piece of notepaper, to the hospital consultants meant that they had been handed a piece of disguised promotional material. A breach of Clause 12.1 was ruled.

The Panel considered that the creation of a piece of promotional material by an area sales manager, and its subsequent provision to health professionals, demonstrated an extremely poor understanding of the Code; it appeared that numerous clauses had not been complied with. The Panel considered that the representatives had not maintained a high standard of ethical conduct. A breach of Clause 15.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such. The Panel noted its rulings and comments above but considered that, on balance, and given the very limited reach of the material at issue (no letters were sent), the area sales manager's conduct was not such as to bring discredit upon, or reduce confidence in, the industry. No breach of Clause 2 was ruled.

**Complaint received** **26 May 2016**

**Case completed** **22 July 2016**

**CASE AUTH/2849/6/16**

# A CONSULTANT ONCOLOGIST AND A PHARMACIST v LILLY

## Oncology handbook

**A consultant oncologist, and a pharmacist, complained in June 2016 about an error which appeared in the 8th edition of the Handbook of Systemic Treatments for Cancer and related to the use of Alimta (pemetrexed) marketed by Eli Lilly and Company. The complainants had recently received a letter from Lilly about the medically significant error.**

**The complainants stated that they had previously received emails from Lilly indicating that copies of the handbook could be ordered through the company's oncology website which promoted its products and such resources. The website currently mentioned the handbook, but access to it had been disabled without any explanation. When queried, the Lilly representative explained that it was because of the error and an updated 9th edition was being developed by Lilly. The complainants had received copies of the two previous editions of the same handbook.**

**The complainants stated that whilst the error identified raised an important question about the reliability, quality and standard of materials disseminated by Lilly, the purpose of their complaint was to also raise a serious concern regarding the veracity, accuracy and transparency of the disclaimer that appeared on these handbooks which suggested that Lilly had no role whatsoever in the development of the handbooks and that all aspects of the publication, including editorial control, were fully owned and retained by the publisher. However, if this were so, one would have anticipated that an erratum, such as the one received, would have been issued by the publisher. As Lilly issued the erratum, the complainants assumed that Lilly did in fact retain editorial control over the contents of the entire handbook, its distribution and also forwarded the erratum to all UK recipients of the handbook. This would also be consistent with the fact that no other pharmaceutical company had ever provided or sponsored the handbooks despite many of their medicines being referred to in them. It appeared that the commercial arrangement between Lilly and the publisher was dubious and less than transparent and excluded the wider dissemination of the valuable medical educational resource by Lilly's competitors thereby facilitating the promotion of only Lilly and its products. Notably, some contributors to the handbooks appeared to be closely associated with Lilly and had previously supported its other commercial interests.**

**The complainants stated that it was likely that the handbook contained other medically significant errors and inaccuracies that could jeopardise patient safety.**

**The detailed response from Lilly appears below.**

**The Panel noted that a company could sponsor material, produced by a third party, which mentioned its own products, and not be liable under the Code for its contents, but only if, *inter alia*, there had been a strictly arm's length arrangement between the parties.**

**With regard to the disclaimer the Panel noted that the handbook had originally been conceived and published by Lilly with the help of key pharmacy staff at a named hospital. Lilly outsourced production of the 8th edition to a third party as the complexity of the information had increased but it maintained close association with relevant pharmacy staff at the hospital; two of the three authors had contributed to previous editions. A flowchart showing the review and edit process noted that new monographs would be included with the agreement of Lilly and one of the authors based on criteria used for the 7th edition. In the Panel's view, there was no arm's length arrangement between the parties. The handbook was initiated and its production managed by Lilly. Lilly submitted that it took full responsibility for the handbook.**

**The Panel noted that although the handbook had been updated by a third party, Lilly was responsible under the Code for its contents. Lilly's involvement with the handbook was obvious. The Panel noted that the statement on page 3 of the handbook that 'Lilly's role as sponsor of this handbook, has been limited to checking the factual accuracy of information on Lilly products and ensuring compliance with the [Code]' should have more accurately reflected the extent of the company's involvement. Nonetheless, it was abundantly clear from the references to Lilly on the front and back covers and numerous inside pages that it was a Lilly-sponsored item and on balance, the Panel ruled no breach of the Code which was upheld on appeal by the complainants.**

**With regard to Lilly's products, the Panel noted that the drug monographs appeared in alphabetical order of the non-proprietary name of the medicine. Only two monographs were for Lilly products. None of the 108 monographs detailed the responsible pharmaceutical company, such detail was given in a list of references. There was nothing to distinguish the monographs for Lilly medicines from those of any other pharmaceutical company. Overall, the Panel did not consider that, given the presentation of the monographs, the handbook was disguised promotion of Lilly's products as alleged and no breaches were ruled including no breach of Clause 2. These rulings were upheld on appeal by the complainants.**

**The Panel noted Lilly's submission that it had not informed health professionals about the error in the handbook when the complaint was submitted in early June. The Panel also noted that the complainants referred to a 'medically significant error relating to the use of Alimta' which Lilly, in its response, assumed was about the dosing of Vitamin $B_{12}$ which the complainants confirmed in response to a request for further information. According to**

**Lilly, a letter was sent to health professionals in mid June 2016 after a third party had comprehensively reviewed the 8th edition of the handbook following receipt of this complaint. The Panel noted that that letter to health professionals stated that there were multiple omissions and errors in the handbook but did not specifically refer to the Vitamin $B_{12}$ dosing error. The Panel noted Lilly's submission that it was advised of this particular error in March 2016 and removed the handbook from its website the same day. Lilly staff were briefed by email three days later to destroy copies of the handbook. If customers asked about the error they were to be told that the handbook was being updated and they could have a new version once re-approved. The briefing detailed the Vitamin $B_{12}$ dosing error.**

**The Panel considered that the inclusion of the error which listed the intramuscular dose of Vitamin $B_{12}$ at 1g instead of 1mg when used before and during treatment with Alimta meant that the information in the handbook was inaccurate, misleading and not capable of substantiation. Breaches of the Code were ruled as acknowledged by Lilly including that high standards had not been maintained.**

**The Panel noted that a ruling of a breach of Clause 2 was used as a sign of particular censure. An example of an activity likely to be in breach of Clause 2 and listed in the supplementary information, was prejudicing patient safety. Whilst the Panel was concerned to note the Vitamin $B_{12}$ dosing error within the handbook, it also noted that the presentation of Vitamin $B_{12}$ (hydroxocobalamin) injection was such that in order to administer 1g, as incorrectly stated in the handbook, health professionals would have to open 1000 ampoules. In the Panel's view it was thus unlikely that such a dosing error leading to an overdose would occur. The Panel considered that Lilly had taken reasonable steps when it was notified of the error in March; it removed the handbook from its website and briefed all customer-facing teams. In mid June, however, following receipt of an interim report revealing additional errors and omissions in the handbook, Lilly wrote to all oncology health professionals requesting the immediate withdrawal and destruction of the handbook. The Panel noted its comments above and did not consider that the circumstances warranted a ruling of a breach of Clause 2. Following an appeal by the complainants the Appeal Board considered that any dosing error, regardless of its magnitude and no matter how unlikely it was to occur, was a serious matter. In addition, the error was in association with one of Lilly's medicines which the company should have identified. In the Appeal Board's view that the dosage error existed at all was such as to reduce confidence in the industry being able to produce complex material to the required quality standards. A breach of Clause 2 was ruled.**

A consultant oncologist, and a pharmacist, complained about an error which appeared in the 8th edition of the Handbook of Systemic Treatments for Cancer (ref UKONC00326, February 2014) and related to the use of Alimta (pemetrexed) marketed by Eli Lilly and Company Limited; the handbook was provided to the complainants' team by a Lilly representative. The complainants had recently received a letter from Lilly about the medically significant error.

'Lilly Oncology' appeared in the bottom right hand corner of the front and back covers of the handbook and the back cover also referred to 'A Medical Education Goods and Services item by Lilly Oncology UK'. Page 3 included a note from the publisher which stated that Lilly's role as sponsor was limited to checking the factual accuracy of information on Lilly products and ensuring compliance with the Code.

**COMPLAINT**

The complainants stated that they had previously also received email newsletters from Lilly indicating that copies of the handbook could be ordered through the company's oncology website which promoted its products and such resources. This website currently mentioned the handbook, however, access to the handbook seemed to have been disabled without any explanation or any reference to the Alimta related error. On enquiry from the complainants the Lilly representative explained that it was because of the error and an updated 9th edition was being developed by Lilly. The complainants had also previously received copies of the 6th and 7th editions of the same handbook.

The complainants stated that whilst the error identified raised an important question about the reliability, quality and standard of materials disseminated by Lilly, the purpose of their complaint was to also raise a serious concern regarding the veracity, accuracy and transparency of the disclaimer that appeared on these handbooks which suggested that Lilly had no role or involvement whatsoever in the development of the handbooks and that all aspects of the publication, including editorial control, were fully owned and retained by the publisher.

The complainants questioned the latter arrangement because if this were so, one would have anticipated that any erratum, such as the one received, would have been issued by the responsible party, ie the publisher, to all recipients of the publication, as was usual practice. As Lilly, not the publisher, issued the erratum, the complainants assumed that Lilly did in fact retain editorial control over the contents of the entire handbook, its distribution and also forwarded the erratum to all UK recipients of the handbook. This would also be consistent with the observation that no other pharmaceutical company had ever provided or sponsored the handbooks despite many of their medicines being referred to in them. It appeared that the commercial arrangement between Lilly and the publisher excluded the wider dissemination of the valuable medical educational resource by Lilly's competitors thereby facilitating the promotion of only Lilly and its products. Notably, it also appeared that various contributors to the handbooks were closely associated with Lilly and had previously supported its other commercial interests.

The complainants stated that they would be grateful if this matter could be addressed to Lilly as it was likely that the handbook also contained other medically significant errors and inaccuracies that

could jeopardise patient safety and because of the dubious and less than transparent nature of the historical and current collaboration between the publisher and Lilly.

In response to a request for further information the complainants stated that unfortunately they had not retained the letter at issue as they had stopped using the handbook in question. The complainants stated that the letter was widely disseminated to oncologists and related to an error in that a significant overdose of Vitamin $B_{12}$ was recommended when using Alimta.

The complainants stated that they stopped using the handbook because of the above and concern that there were other potential errors therein. The complainants were also concerned that the contents of the handbook were not up-to-date in relation to newly licensed products available for the treatment of the cancers referred to in it. For example the omission of medicines such as nivolumab (lung cancer) and ramucirumab (gastric cancer) was misleading and did not reflect the purpose of the handbook which was to be an authoritative reference text which provided relevant, accurate and up-to-date information on medicine for various cancers.

The complainants presumed that Lilly's medical or medical information department would have the necessary information regarding what was communicated.

When writing to Lilly, the Authority asked it to consider the requirements of Clauses 2, 9.1, 7.2, and 7.4 in relation to the error and Clauses 2, 9.10, 9.1 and 12.1 in relation to the disclaimer.

**RESPONSE**

Lilly submitted that the 8th edition was a non-promotional, medical educational item as stated on the back cover and was not an independent textbook. Lilly accepted full responsibility for the 8th edition and all previous editions of the handbook.

Lilly noted that the complainants referred to a recently received letter from Lilly which highlighted an error with respect to dosing Vitamin $B_{12}$ and pemetrexed. Following a thorough internal investigation Lilly could not explain how the complainants received such a letter, as no correspondence had been sent to any health professional or other person when the complaint was submitted. However, Lilly took this issue very seriously and was grateful to the complainants for drawing this matter to the PMCPA's and Lilly's further attention.

Lilly stated that the 8th edition was published in February 2014, two years after the publication of the 7th edition. The first edition was published by Lilly in collaboration with the named hospital around 20 years earlier and each subsequent edition had always been produced in consultation with key pharmacy staff at that hospital. The handbook was conceived and published by Lilly to assist health professionals in their day-to-day patient management by providing concise information as guidelines for the administration of medicines commonly used for the treatment of cancer. Subsequent editions included new anticancer agents as these came to market. The 7th edition included additional information to support the care of cancer patients such as the 'Oncology/Haematology Helpline Triage Tool' developed by the UK Oncology Nursing Society and endorsed by MacMillan Cancer Support. This information was also included in the 8th edition.

The handbook was widely distributed by Lilly to cancer treating institutions in the NHS. Chemotherapy nurses and cancer nurse specialists were the primary users and feedback consistently confirmed that the handbook, in its various editions, was a well-regarded and valued resource among health professionals.

Given the enduring heritage of the handbook since its first edition, many health professionals routinely referred to it as the 'Lilly Chemo Handbook' or even the 'Lilly Handbook' such had been the recognition of its value and long-term production by Lilly. As the complexity of information included increased, Lilly Oncology decided in 2013 to outsource the production of the 8th edition to a third party, while maintaining the close association with key pharmacy staff at the named hospital. Two of the three authors (as acknowledged on page 2 of the handbook) were from that hospital. The third author was a lead chemotherapy nurse from a Cancer Network.

A copy of the letter notifying health professionals about the errors was provided as were the instructions to representatives about the distribution, content and withdrawal of the handbook. The withdrawal letter was dated 16 June 2016. It advised that there were multiple errors and omissions in the handbook and that all copies (whichever edition) should be destroyed.

Lilly stated that the 8th edition was reviewed and approved through the certification process and subsequently certified by two signatories. Various comments were made during this review, however, regrettably nothing was noted in relation to the error noted by the complainants. On the draft version of the 8th edition there were Lilly comments made with regard to ensuring clarity that this was a Lilly publication. In addition, questions were raised about the inclusion of 'Very Rare' and 'Unknown' side-effects in light of the handbook being a summary of the summary of product characteristics (SPC). Comments were also made regarding the online version of the 8th edition and links to the electronic medicines compendium (eMC) in the list of SPC references. Further comments were made about inclusion of dates of first authorisation in the SPC references.

Lilly provided copies of relevant documents which described the extent of its influence over the handbook and a detailed account of Lilly's role in relation to the creation of the handbook.

The contract with the third party was by way of a master services agreement and associated work order. As set out in the work order, the information contained in the 8th edition was to consist of the chemotherapy pathway, nursing guidelines, summaries of more than 80 oncology agents and

an educational/practical appendix section. As prior editions of the handbook had proven to be a valuable resource for health professionals, there was a recognised need to continue to produce an updated copy to reflect changes in SPCs and guidelines.

Lilly oncology decided to partner with the third party to ensure an efficient and sustainable delivery. The third party took over the editorial management including ongoing content updates.

The third party subcontracted relevant and key health professionals to clinically validate the updated content and new content developed by the third party, and to further improve the features of the 8th edition. The intended work on the 8th edition was set out in a flowchart, which showed that the 8th edition was to include 24 new medicine monographs, and 86 existing monographs (2 were removed).

For the 8th edition, the third party was to use its editorial teams which included oncology pharmacists.

The authors of the 8th edition were paid by the third party.

The handbook was distributed by Lilly to healthcare organisations and health professionals in oncology in response to direct requests to Lilly switchboard, by post or email to Lilly; or requested via the Lilly oncology website or via requests made to Lilly's salesforce. In addition, health professionals could download the handbook from the Lilly oncology website. When the handbook was provided by sales representatives the Lilly procedure for a medical educational good or service would be followed ensuring that it was provided during a non-promotional call.

The 8th edition was first distributed after an oncology sales force meeting (March 2014). Lilly's oncology medical liaison ran a session for representatives and marketing on introducing the 8th edition of the handbook, outlining recall of the 7th edition and availability of the 8th edition.

Lilly was notified of the error with respect to the dosing of Vitamin $B_{12}$ for pemetrexed by a nurse on Friday, 18 March 2016. The error listed the dose of Vitamin $B_{12}$ as 1g instead of 1000mcg (1mg). Medical information reported the error to the oncology medical team. That same day the handbook was removed from the Lilly oncology website. The oncology team also prepared a briefing on the withdrawal of the handbook for all customer-facing teams, this was sent by email on Monday, 21 March. Following review of previous editions, Lilly established that the error in the dosing of Vitamin $B_{12}$ for pemetrexed was unique to the 8th edition.

Following receipt of the complaint, Lilly commissioned a third party, to assist in a complete and comprehensive review of the 8th edition for any further errors. In light of an interim report showing there were other errors and omissions on 16 June, Lilly sent a letter from the business unit director, Lilly Oncology to all oncology health professionals in its customer database instructing the immediate withdrawal and destruction of all copies of the handbook.

Lilly submitted that in order to prevent future errors in clinical summaries, Lilly oncology would not publish further editions of the handbook.

The letter explaining the nature of the error dated 16 June 2016, was sent to over 3000 oncology health professionals. Emails were sent on 18 June to all oncology health professionals for whom Lilly held a current permission to email. Following approval and certification on 27 June, the letter was made available at all relevant locations on the Lilly oncology website.

Lilly accepted that the highlighted error identified in the 8th edition with respect to dosing Vitamin $B_{12}$ and pemetrexed meant it had breached Clauses 7.2, in that the information was not accurate; 7.4, as the information in the handbook could not be substantiated; and 9.1, as Lilly had not maintained high standards in relation to the Code. Lilly took these breaches very seriously and would now unreservedly accept the Panel's ruling on Clause 2 should it so rule in this regard.

Lilly referred to the disclaimer in the 8th edition (page 3) that:

> 'Welcome to the 8th edition of the Lilly Handbook of Systemic Treatments for Cancer (2014).
>
> The intent of this handbook is to assist healthcare professionals in their day-to-day patient management by providing concise information and guidelines for the administration of commonly used pharmacological agents for the treatment of cancer.
>
> The contents of this handbook have been developed collaboratively by nurse and pharmacist teams at the [named hospital, named authors] on behalf of Eli Lilly and Company Ltd ("Lilly") and the publisher.
>
> Lilly's role, as the sponsor of this handbook, has been limited to checking the factual accuracy of information on Lilly products and ensuring compliance with the PMCPA Code of Practice for the Pharmaceutical Industry.
>
> Save for the above, and the compilation of the "Appendices" section, the updated contents of the handbook have been developed independently by the authors in collaboration with the publisher.
>
> The monographs in this handbook were compiled from manufacturers' summaries of product characteristics (SPCs) and other established resources. Some of the information presented may reflect local practice and the clinical expertise of the healthcare professionals involved. The monographs of the products contained herein are not intended to be a substitute for the manufacturers' SPCs. Only adverse events deemed to be of particular relevance are included. The publisher has tried to ensure that the information contained in this handbook is accurate and up-to-date at the time of publication. **It is the user's responsibility to check for any variation in the product SPC subsequently**. These

can be found at www.medicines.org.uk/emc. It is important not to use copies of the handbook that are out of date or pass on old editions.

The practice guidance presented in this handbook is offered as recommendations, and does not diminish the requirement for clinical judgment. Readers are strongly advised to check these recommendations against their local protocols and guidelines and to make their own further enquiries of manufacturers or specialists in relation to particular drugs, treatments or advice. Lilly, the publisher and the authors cannot accept liability for errors or omissions, and disclaim any liability arising out of the use of this handbook in practice.'

In relation to Clause 12.1, Lilly submitted that the handbook was a Lilly medical educational good or service which could be requested, downloaded or provided to healthcare organisations and health professionals in the field of oncology as described above.

In relation to Clause 9.10, Lilly submitted its sponsorship of the handbook was clear and transparent, (paragraph 3 of the disclaimer quoted above and on both the front and back cover of the handbook). Furthermore, the 8th edition was Lilly's copyright and the footer on each odd numbered page read 'Lilly Handbook of Systemic treatments for Cancer 8th Edition'. Therefore, Lilly respectfully submitted that it did not breach Clauses 9.10 or 12.1 with respect the disclaimer and that it maintained high standards in accordance with Clause 9.1 and therefore had not breached Clause 2.

In response to a request for further information, Lilly submitted that it had previously set out the corrective steps that it took immediately following the original notification on 18 March 2016 of an error in the 8th edition of the handbook. The corrective steps included commissioning a comprehensive review of the handbook by an independent third party. Lilly provided confidential copies of both the interim report and the final report prepared by the third party.

Lilly reassured the PMCPA that it recognised the seriousness of the obligations that the Code placed upon pharmaceutical companies in relation to the accuracy of industry sponsored publications. Lilly wished to engage with the PMCPA with full transparency in its consideration of this matter.

Lilly noted the history of the handbook as set out above. Lilly now recognised that, by the 8th edition, the objectives and content of the handbook had grown in scope and ambition to such an extent that it was beyond the sponsoring capabilities of a pharmaceutical company. The number of products included and the differences in interpretation between the hospital editorial team, health professionals and indeed the third party review team meant that the handbook was not an appropriate industry sponsored medical educational good or service. It should not have been commissioned, it should not have been certified, and it should not have been distributed. Lilly submitted that it would not produce further editions of the handbook.

On 16 June 2016 Lilly received an interim report from the third party revealing additional errors and omissions in the handbook to that identified in the complaint. In light of that report, Lilly sent a letter on the same day to all oncology health professionals on its database requesting the immediate withdrawal and destruction of all copies of the handbook. That was followed by an email to all oncology health professionals, for whom Lilly had email permission, including to members of the UK Oncology Nursing Society who subsequently disseminated it to its wider membership.

Following the interim report, Lilly requested that the third party proceed immediately with its comprehensive review of the entire handbook.

Lilly immediately put in place a communications plan to address any external enquiries received by medical information regarding the withdrawal of the handbook. To date Lilly had not received any enquiries related to individual patient safety. If enquiries about individual patient safety were received, Lilly had an action plan in place to ensure they would be reported in the appropriate way to the Medicines and Healthcare products Regulatory Agency (MHRA).

In addition to the actions taken above, Lilly reassured the PMCPA that it was committed to ensuring that incidents of this type did not occur again.

**PANEL RULING**

The Panel noted that it was possible for a company to sponsor material, produced by a third party, which mentioned its own products, and not be liable under the Code for its contents, but only if, *inter alia*, there had been a strictly arm's length arrangement between the parties. In practical terms the arrangements must be such that there could be no possibility that the pharmaceutical company had been able to exert any influence or control over the final content of the material. Factors which might mean there had not been a strictly arm's length arrangement would include, but not be restricted to:

- Initiation of the material, or the concept for it, by the pharmaceutical company
- Influence from the pharmaceutical company on the content/balance/scope of the material
- Choice/or direct payment of the authors by the pharmaceutical company
- Influence from the pharmaceutical company on the list of persons to whom the material was sent.

With regard to the disclaimer the Panel noted Lilly's submission regarding the history of the handbook, it was originally conceived and published by Lilly with the help of key pharmacy staff at the hospital. Lilly outsourced production of the 8th edition to a third party as the complexity of the information had increased but it maintained close association with relevant pharmacy staff at the hospital; two of the three authors had contributed to previous editions. A flowchart showing the review and edit process noted that the list of new monographs to be included would be agreed with Lilly and one of the authors based on criteria used for the 7th edition. In the

Panel's view, there was no arm's length arrangement between the parties. The handbook was initiated and its production managed by Lilly. Lilly submitted that it took full responsibility for the 8th Edition and all previous editions of the handbook.

The Panel noted Lilly's submission about the number of medicines/treatments included in the handbook and that it was designed to be comprehensive. Each even page of the book was dated February 2014.

The Panel noted that the handbook, although updated by a third party, had been initiated and managed by Lilly which was responsible under the Code for its contents. The preface on page 4 stated that the handbook was a Lilly initiative and through the use of bright red font on pages 3 and 4 and tear out cards on the following page, Lilly's involvement with the handbook was obvious. The Panel noted the requirements of Clause 9.10 and considered that the statement on page 3 of the handbook that 'Lilly's role as sponsor of this handbook, has been limited to checking the factual accuracy of information on Lilly products and ensuring compliance with the PMCPA Code of Practice for the Pharmaceutical Industry' should have more accurately reflected the extent of the company's involvement. Nonetheless, it was abundantly clear from the various references to Lilly on the front and back covers, pages 3 and 4 and all odd numbered pages that it was a Lilly-sponsored item and on balance, the Panel ruled no breach of Clause 9.10.

With regard to Lilly's products, the Panel noted that the medicine monographs appeared in alphabetical order of the non-proprietary name of the medicine. Only two monographs were for Lilly products. None of the 108 monographs detailed the responsible pharmaceutical company, such detail was given in a list of references. There was nothing to distinguish the monographs for Lilly medicines from those of any other pharmaceutical company. Overall, the Panel did not consider that, given the presentation of the monographs, the handbook was disguised promotion of Lilly's products as alleged and no breach of Clause 12.1 was ruled. This ruling was appealed by the complainants.

The Panel noted its rulings above and ruled no breach of Clauses 9.1 and 2. These rulings were appealed by the complainants.

The Panel noted that the complaint dated 28 May was received on 3 June 2016. The Panel noted Lilly's submission that it had not informed health professionals about the error in the handbook when the complaint was submitted. The Panel also noted that the complainants referred to a 'medically significant error relating to the use of Alimta' which Lilly, in its response, assumed was about the dosing of Vitamin $B_{12}$ which the complainants confirmed in response to a request for further information. According to Lilly, a letter was sent to health professionals on 16 June 2016 after it had commissioned a third party to conduct a comprehensive review of the 8th edition of the handbook following receipt of this complaint. The Panel noted that that letter to health professionals stated that there were multiple omissions and errors in the handbook but did not specifically refer to the Vitamin $B_{12}$ dosing error. The Panel noted Lilly's submission that it was advised of this particular error on 18 March 2016 and it removed the handbook from the Lilly oncology website the same day. Lilly staff were briefed by email on 21 March to destroy copies of the handbook. If customers asked about the error they were to be informed that the handbook was being updated and they could have a new version once re-approved. The briefing gave details about the Vitamin $B_{12}$ dosing error.

The Panel considered that the inclusion of the error which listed the intramuscular dose of Vitamin $B_{12}$ at 1g instead of 1mg when used before and during treatment with Alimta meant that the information in the handbook was inaccurate, misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled as acknowledged by Lilly. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was used as a sign of particular censure. An example of an activity likely to be in breach of Clause 2 and listed in the supplementary information, was prejudicing patient safety. Whilst the Panel was concerned to note the Vitamin $B_{12}$ dosing error within the handbook, it considered that such an overdose was unlikely to occur as Vitamin $B_{12}$ (hydroxocobalamin) was supplied in 1ml ampoules each containing 1mg. In order to administer 1g, as incorrectly stated in the handbook, health professionals would have to open 1000 ampoules. In the Panel's view it was thus unlikely that such a dosing error leading to an overdose would occur. The Panel considered that Lilly had taken reasonable steps when it was notified of the error in March; it removed the handbook from the Lilly oncology website and briefed all customer-facing teams. On 16 June, however, following receipt that day of an interim report revealing additional errors and omissions in the handbook to that identified in this complaint, Lilly sent a letter to all oncology health professionals on its database requesting the immediate withdrawal and destruction of all copies of the handbook. That was followed by an email to all oncology health professionals, for whom Lilly had email permission, including to members of the UK Oncology Nursing Society who, Lilly submitted, subsequently disseminated it to its wider membership. The Panel noted its comments above and did not consider that the circumstances warranted a ruling of a breach of Clause 2. This ruling was appealed by the complainants.

During consideration of this case the Panel noted that the supplementary information to Clause 18.1, Textbooks, stated that in appropriate circumstances independently produced medical/educational publications such as textbooks could be given for health professionals to use in accordance with Clause 19.1 – Medical and Educational Goods and Services – but they must not be given to individuals. The Panel noted that the handbook in question was not independently produced, it was clearly initiated and sponsored by Lilly and included information about its medicines. The Panel thus queried whether the handbook could be given as

a medical or educational good or service. Further, it appeared that, contrary to Code requirements regarding provision of medical and educational goods or services, the handbook had been given to individuals. Tear out cards stated 'Do you know someone who would like a copy of the handbook? Hand them this card to order one free of charge'.

The Panel further noted that the 8th edition handbook was certified on 14 March 2014; it was still in use in June 2016. In that regard, the Panel noted that the Code stated that material still in use must be certified at intervals of no more than two years to ensure continued compliance with the Code. The Panel noted that all material had to be up-to-date and current and in that regard it noted the complainant's additional comments that some cancer medicines were not included in the handbook. These comments appeared to be a fresh allegation that the handbook was not up-to-date. If the complainants wanted this allegation considered they would have to submit a new complaint (Case AUTH/2872/9/16).

Although noting that the handbook had been withdrawn, the Panel requested that its concerns be drawn to Lilly's attention.

**APPEAL FROM THE COMPLAINANTS**

The complainants noted that Lilly had stated, unsurprisingly, that it had accepted 'unreservedly' that it had brought the industry into disrepute and breached Clause 2 of the Code. It was therefore unclear why the Panel had not accepted this admission and ruled accordingly. The complainants alleged that it appeared that this pre-emptive self-censure had led the Panel to completely absolve Lilly from any sanction or responsibility or liability to uphold the Code. The latter was particularly surprising given the unequivocal and unforced admission from Lilly that '… the handbook was not an appropriate industry sponsored medical educational good or service. It should not have been commissioned, it should not have been certified, and it should not have been distributed'. The complainants were genuinely unclear as to what more the Code deemed necessary to invite a breach of Clause 2 of the Code. Given the latter and the seriousness of the issues, the complainants respectfully requested that the Appeal Board consider a breach of Clause 2, in respect of their entire complaint.

The complainants further did not accept Lilly's contention that the handbook was non-promotional and provided as a medical education good or service. In this regard the complainants noted that the handbook was available for download on the Lilly oncology website which was a promotional platform for Lilly's products. On various pages of the website the handbook was directly associated with hyperlinks which promoted the availability of 'ALIMTA Literature' and 'Alimta Abbreviated Prescribing Information'. This was exemplified by the screenshots which were accessed on 17 June 2016 (provided) and appeared to contravene the requirements of the Code in respect of the need to dissociate the provision of a medical education good or service and product promotion.

The complainants alleged that it was therefore evident that Lilly was covertly using the handbook as a tool to help promote products such as Alimta which was, as such, disguised promotion in breach of Clauses 2, 9.10 and 12.1.

In response to a request to confirm if they were appealing Clause 9.1 or 9.10 or both, the complainants stated that they wanted to include Clauses 9.1 and 9.10 in their appeal. Although Lilly had disclosed its sponsorship of the handbook, the complainants alleged that it was evident from the Panel's ruling that the disclaimer was not sufficiently clearly worded so as to inform the reader that the handbook was not developed independently by the publishers as suggested. Lilly's involvement was not at 'arms-length'.

**COMMENTS FROM LILLY**

Lilly noted that in its ruling, the Panel was clear that the circumstances of the complaint, the nature of Lilly's remedial action, and the unlikely impact on patient safety meant that a ruling of a breach of Clause 2 was not warranted. Lilly submitted that this was the correct decision, and respectfully requested that the Appeal Board uphold the ruling of the Panel.

Lilly noted that the complainants' appeal alleged specifically that the Panel's ruling on Clause 2 was inappropriately influenced by Lilly's original admissions and the Chemotherapy Handbook was a promotional item being used covertly to promote Lilly's medicines.

Lilly submitted that its interactions with the Panel had been full, transparent and had enabled the Panel to consider this matter thoroughly and without any undue influence. This had been Lilly's intention throughout, and Lilly remained committed to the integrity of the complaints process.

Lilly noted that in its original response, it did not accept unreservedly that it had brought the industry into disrepute and breached Clause 2. The letter stated that Lilly would unreservedly accept the Panel's ruling on Clause 2. The Panel ruled no breach of Clause 2 which Lilly unreservedly accepted.

Lilly submitted that the handbook was conceived and published by it with the help of pharmacy staff at a named hospital to assist health professionals in their day-to-day patient management by providing concise information and guidelines for the administration of commonly used pharmaceutical agents for the treatment of cancer. The 8th Edition included all approved cancer medicines available in the UK at the end of November 2013.

Lilly submitted that as the Panel noted in its ruling, '…the medicine monographs appeared in alphabetical order of the non-proprietary name of the medicine. Only two monographs were for Lilly products. None of the 108 monographs detailed the responsible pharmaceutical company, such detail was given in a list of references. There was nothing to distinguish the monographs for Lilly medicines from those of any other pharmaceutical company'.

Lilly submitted that its oncology portal provided a resource for health professionals to access promotional and non-promotional items. All links on the portal to the handbook were deactivated on Friday, 18 March 2016. As the Panel agreed, the Chemotherapy Handbook was not a promotional item, and Lilly was not acting 'covertly' in its sponsorship and dissemination of it. Lilly submitted that no disguised promotion had taken place.

Lilly had accepted throughout this case that it should not have sponsored the 8th Edition in the form in which it was published. Lilly submitted that the Panel's ruling in this case was thorough, correct, and unsparing in its assessment of Lilly's shortcomings. Lilly requested that the Panel's decision be upheld.

**FINAL COMMENTS FROM THE COMPLAINANTS**

The complainants submitted that by stating its willingness to unreservedly accept the Panel's rulings, Lilly had effectively attempted to pre-empt the likelihood of an adverse ruling; indeed, if this were not its intention then there was no obvious reason to state its position in advance of any decision by the Panel. Lilly could simply have accepted, 'unreservedly', the Panel's rulings after the fact. Lilly also clearly indicated that the handbook was not really fit for purpose and so clearly recognised its failings and the gravity of the situation and the likelihood of a breach of Clause 2 being ruled and to this end has attempted to mitigate against this particular sanction.

The complainants alleged that a handbook being used promotionally and produced to such a dangerously low standard that even its sponsor noted in retrospect that it should not have been commissioned, certified or distributed must surely bring disrepute.

The complainants invited the Appeal Board to review the findings of the third party's report which was not provided to them by the Panel but whose comments suggested that the handbook contained many other significant errors.

The complainants alleged that the handbook was associated with promotion of Alimta as evidenced by the direct and close association of Alimta related materials and the handbook. Lilly seemed to rely on counter arguments based on the semantics of the terms disguised and covert. However, there was no getting away from the fact that use of the handbook, classified as a medical education good and service, was not completely disassociated with the promotion of Alimta on the Lilly oncology portal. This association was a form of disguised promotion of Alimta given that the nuances of the Code requirements related to the provision of a MEGS were unlikely to be immediately appreciated or obvious to those health professionals who might not be aware of the Code's requirements in this particular regard. There was also no statement to the contrary on the screenshots to explain this distinction to the viewer.

Finally the complainants alleged that whilst the links to the handbook might have been deactivated on 18 March the fact remained that the screen shots provided clearly evidenced that Lilly referred to the handbook and Alimta on this website prior to and well after this date.

**APPEAL BOARD RULING**

The Appeal Board noted the Panel's ruling above and agreed that it was abundantly clear in the handbook from the various references to Lilly on the front and back covers, pages 3 and 4 (all in red) and all odd numbered pages that it was a Lilly-sponsored item and the Appeal Board therefore upheld the Panel's ruling of no breach of the Clause 9.10. The appeal on this point was unsuccessful.

The Appeal Board noted that the 108 monographs included in the handbook appeared in alphabetical order of the non-proprietary name of the medicine. Only two monographs were for Lilly products. None of the monographs detailed pharmaceutical companies, such detail was given in a list of references at the back of the handbook. There was nothing to distinguish the monographs for Lilly medicines from those of any other pharmaceutical company.

The Appeal Board did not consider that, given the presentation of the monographs, the handbook was disguised promotion of Lilly's products as alleged. The Appeal Board upheld the Panel's ruling of no breach of Clause 12.1. The appeal on this point was unsuccessful.

Given its rulings above the Appeal Board upheld the Panel's rulings of no breach of Clauses 9.1 and 2. The appeal on this point was unsuccessful.

The Appeal Board noted Lilly's submission at the appeal that the handbook would be used in conjunction with other data sources, notably SPCs. However, screen shots of the Lilly website provided by the complainants showed that the handbook was described as a '…definitive guide to assist you and your colleagues in your day-to-day management of patients with cancer…'. In that regard the Appeal Board considered that the handbook would be regarded by at least some users, as a one-stop document.

The Appeal Board noted that the complainants had only referred to one specific error in the handbook ie that the intramuscular dose of Vitamin $B_{12}$ to be given in assocation with Alimta therapy was 1g instead of 1mg. The Appeal Board noted the magnitude of the error and that such an excessive dose of Vitamin $B_{12}$ was unlikely to be administered given the number of ampoules that would have to be opened. Nonetheless, the Appeal Board considered that any dosing error, regardless of its magnitude and no matter how unlikely it was to occur, was a serious matter. In addition, the error was in association with one of Lilly's medicines and the company should have picked it up. In the Appeal Board's view, that the dosage error existed at all was such as to reduce confidence in the industry being able to produce complex material to the required quality standards. A breach of Clause 2 was ruled. The appeal on this point was successful.

**Complaint received** **3 June 2016**

**Case completed** **7 November 2016**

**CASE AUTH/2850/6/16**

# ANONYMOUS, NON-CONTACTABLE v SUNOVION

## Disparagement at a meeting

**An anonymous, non-contactable complainant complained about comments made at a meeting organised by Sunovion Pharmaceuticals Europe. The meeting was one of a series for clinical psychiatrists and related professionals. Sunovion marketed Latuda (lurasidone) an antipsychotic used in the treatment of schizophrenia.**

**The complainant alleged that a presenter's suggestion that anyone should feel guilty if they prescribed olanzapine disparaged the medicine and the psychiatrists who prescribed it. An experienced psychiatrist knew that for some service users, olanzapine was actually the best treatment for them. The complainant stated that everyone was different and they should be free to take all factors into account and to prescribe within their clinical judgement as recommended by national guidelines without being made to feel guilty.**

**The detailed response from Sunovion is given below.**

**The Panel noted that a Sunovion employee gave a presentation which included comparisons of Latuda with other atypical antipsychotics. Although weight gain was referred to as a common side-effect of Latuda, data was presented which showed that weight gain with olanzapine was greater. Sunovion's response included comments from two company attendees who remembered that the presenter had questioned why clinicians were continuing to use olanzapine. The company attendees referred to these comments being made in relation to changes in weight. The complainant made no mention of weight gain in this context. The Panel noted the difficulty of dealing with allegations regarding what was said at a meeting. However, on the evidence before it, the Panel considered that, on the balance of probabilities, the presenter had suggested clinicians should feel guilty if they prescribed olanzapine. This was a medicine licensed to treat schizophrenia and clinically significant weight gain was listed as an adverse event. The company acknowledged that the presenter had been disparaging although he/she had no recollection of being so.**

**The Panel considered that comments about clinicians feeling guilty about prescribing any medicine for its licensed indication disparaged those health professionals and their clinical and scientific opinions. The Panel therefore ruled a breach of the Code. The Panel also ruled that high standards had not been maintained.**

**The presenter was not a representative as defined by the Code and thus the Panel ruled no breach in this regard.**

An anonymous, non-contactable complainant complained about a meeting organised by Sunovion Pharmaceuticals Europe Ltd in Cardiff in April 2016 and in particular about comments made by a company presenter. The meeting was one of the 'HOPE' ('honest opinions personal experiences') series of meetings for clinical psychiatrists and related professionals. Sunovion marketed Latuda (lurasidone) an antipsychotic agent used in the treatment of schizophrenia.

**COMPLAINT**

The complainant stated that during a presentation at the 'HOPE' meeting the company employee suggested that anyone should feel guilty if they prescribed olanzapine. The complainant alleged that this disparaged the medicine and the psychiatrists who prescribed it. An experienced psychiatrist knew that for some service users, olanzapine was actually the best treatment for them. The complainant stated that everyone was different and they should be free to take all factors into account and to prescribe within their clinical judgement as recommended by the National Institute for Health and Care Excellence (NICE) without being made to feel guilty for their choice.

When writing to Sunovion, the Authority asked it to respond in relation to Clauses 8.2, 9.1 and 15.2.

**RESPONSE**

Sunovion submitted that the 2016 'HOPE' meeting series comprised three high quality educational meetings held in April. A total of 142 delegates attended the series; 71 attended the Cardiff meeting. The 'HOPE' programme had run since 2014 and feedback from delegates had been very good; Sunovion received overwhelming positive comments on the quality and content of these meetings eg 92% of delegates who attended one of the three meetings in 2016 and completed an event feedback form, rated the overall impression of the event programme as excellent or good.

The overall approach for the 'HOPE' meetings was to inform, educate and encourage discussion among an audience of peers. In this spirit, exchanges were dynamic and interactive, and reflected the speakers' profound involvement in the areas discussed. Delegate feedback on this format was very positive; one delegate at the Cardiff meeting commented in their feedback form that 'The best presentations were when there was the most interactivity with the audience'.

The meeting content was highly scientific; it included efficacy and safety data on a range of antipsychotic agents including Latuda and olanzapine and referred to authoritative independent recommendations.

Sunovion provided a copy of the meeting invitation, agenda and the presentation. The presentations, agenda and invitations were certified by Sunovion.

The Sunovion presenter was one of seven speakers and this presentation lasted 45 minutes from a total presentation content of 3 hours and 45 minutes.

Sunovion stated that the presenter was certain that he/she would not have deliberately stated or intended to imply that doctors should feel guilty about prescribing olanzapine. The presenter clearly understood that there were circumstances where the use of olanzapine was entirely appropriate and he/she had often prescribed it.

The presentation, 'A Review of Latuda (lurasidone) efficacy & tolerability registration studies', included results from published clinical trials involving Latuda, olanzapine and a number of other licensed medicines. In addition, one slide referenced the Maudsley Prescribing Guidelines in Psychiatry. The presentation contained only published/data on file scientific information and made no claims regarding prescribing olanzapine or otherwise. The presenter believed that where any informal verbal statement regarding the use of olanzapine was made, it was in reference to weight gain. If any concern had been raised about the impression given by his/her comments at the meeting it would have immediately been corrected.

Sunovion submitted that it had interviewed two other company attendees; their recollections of dialogue made during the presentation were as follow:

> Participant A: The presenter made a remark along the lines of 'how can you clinicians consciously continue to prescribe olanzapine' phrased in context of weight gain, the remark was made in the course of the speakers' commentary and not in response to a question from the audience and a speaker at his table noted that 'you should not say that'.
>
> Participant B: A statement was made by the presenter along the lines of 'for those who feel guilty prescribing olanzapine'; this was in the context of weight loss. A speaker who shared a table with me gave me a look, made a comment about the ABPI clauses and said 'can he say that?'.

Sunovion stated that all materials for the Cardiff meeting were reviewed and certified as compliant with the Code. Whilst the presenter had no recollection of commenting on the prescribing of olanzapine, and was certain that no comment would have been intentionally made, it was apparent that other company attendees recollected that something was said that could have been interpreted in a way that was not intended. This appeared to be a single sentence in a 45 minute presentation and within the broader context of an 8 hour event of seven presenters.

Sunovion noted that 81% of delegates who attended one of the three 'HOPE' meetings in 2016 and completed an event feedback form, rated the presentation as very useful or useful and a further 13% as fairly useful.

Sunovion stated that the presenter did not intend to disparage the practice of health professionals and apologised for any unintended consequences.

On the basis of the investigation described above, Sunovion acknowledged a breach of Clause 8.2. The presentation was developed by the speaker with other Sunovion Pharmaceuticals Europe and Sunovion staff and he/she was therefore very familiar with the content and objectives of the session. In addition, in advance of the first 2016 'HOPE' meeting, the presenter attended a full run through by all speakers.

With reference to Clause 9.1, Sunovion stated that this was an isolated one-off comment, at a single meeting in a series of high quality educational events which had been well received by clinicians. All content and materials were reviewed and certified and none contained or advocated anything which disparaged another product or competitor; Sunovion submitted that all 'HOPE' materials were accurate, fair and balanced and on that basis it refuted any breach of Clause 9.1.

Sunovion also refuted any breach of Clause 15.2 which referred specifically to high standards on the part of representatives. The presenter's role did not meet the Code definition of a representative ie 'a representative calling on members of the health professions and other relevant decision makers in relation to the promotion of medicines'.

Sunovion stated it was committed to self-regulation and strongly supported the Code. The company accepted responsibility for the incident described above and greatly regretted this unplanned and informal comment at a highly interactive meeting. Sunovion reiterated that there was no intention to disparage a third party.

**PANEL RULING**

The Panel noted that the meeting was organised by Sunovion and it was clearly a promotional meeting. The presentation 'A review of Latuda efficacy & tolerability registration studies' included comparisons of Latuda with other atypical antipsychotics. Although weight gain was referred to as a common side-effect of Latuda, data was presented which showed that weight gain with olanzapine was greater. Latuda prescribing information was included on the agenda, invitation and the presentation. It appeared from the company response that two company attendees remembered that the presenter had raised the issue of continuing to use olanzapine and questioning why clinicians were continuing to do this. The company attendees referred to these comments being made in relation to changes in weight. The complainant alleged that the presenter suggested that clinicians should feel guilty if they prescribed olanzapine but made no mention of weight gain in this context. The Panel noted the difficulty of dealing with allegations regarding what was said at a meeting. However, on the evidence before it, the Panel considered that, on the balance of probabilities, the presenter had suggested clinicians should feel guilty if they prescribed olanzapine. This was a medicine licensed to treat schizophrenia and clinically significant weight gain was listed as an adverse event. Sunovion acknowledged that the presenter had been disparaging although he/she had no recollection of being so.

The Panel considered that comments about clinicians feeling guilty about prescribing any medicine for its licensed indication disparaged those health professionals and their clinical and scientific opinions. The Panel therefore ruled a breach of Clause 8.2. The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The presenter was not a representative as defined by Clause 1.7 and thus Clause 15.2 did not apply and the Panel ruled no breach.

**Complaint received** **13 June 2016**

**Case completed** **13 July 2016**

# ANONYMOUS CONTACTABLE v NOVO NORDISK

## Alleged promotion of Tresiba to the public

**An anonymous, contactable complainant complained about the promotion of Tresiba (insulin degludec) to the public through a posting on LinkedIn.**

**The communication mentioned a Novo Nordisk employee by name and gave contact details including his/her Novo Nordisk email address. The communication was a link entitled 'Tresiba® -¼ (insulin degludec) demonstrates significantly lower rates of hypoglycemia vs insulin…'.**

**Tresiba was a basal insulin for the treatment of diabetes mellitus in certain patients.**

**The complainant stated that he/she believed this communication on LinkedIn to be in breach of advertising regulations for advertising medicines to the public.**

**The detailed response from Novo Nordisk is given below.**

**The Panel noted that Novo Nordisk UK had issued a press release dated 13 June 2016 for UK medical media comparing Tresiba rates of hypoglycaemia with insulin glargine. The press release gave contact details for Novo Nordisk and agency staff who were all named in the LinkedIn communication at issue.**

**The Panel noted Novo Nordisk's submission that the LinkedIn communication appeared to be as a result of Novo Nordisk's press release and an app which brought news articles to users based on their interests and connections within LinkedIn and highlighted to users when people they were connected with were mentioned in the news. According to Novo Nordisk it was not something that the company or its staff had instigated or knew about until the complaint was received. The fact that the application relied on an algorithm did not absolve Novo Nordisk from responsibility. The Panel noted that LinkedIn was widely used in the pharmaceutical industry. It was not inconceivable that Novo Nordisk and/or its staff had been the subject of previous communications placed by the LinkedIn application. In the Panel's view companies should remain vigilant and needed to ensure that they took reasonable steps to prevent relevant secondary postings of their material.**

**Nevertheless the Panel did not consider that on the evidence before it Novo Nordisk had advertised a prescription only medicine to the public. The Panel also considered that the particular circumstances did not indicate a failure to maintain high standards nor did they bring discredit upon or reduce confidence in the pharmaceutical industry and thus no breaches of the Code were ruled including Clause 2.**

An anonymous, contactable complainant complained about the promotion of Tresiba (insulin degludec) to the public through a posting on LinkedIn.

The communication mentioned a Novo Nordisk employee by name and gave contact details including his/her Novo Nordisk email address. The communication was a link entitled 'Tresiba® -¼ (insulin degludec) demonstrates significantly lower rates of hypoglycemia vs insulin…'.

Tresiba was a basal insulin for the treatment of diabetes mellitus in certain patients.

**COMPLAINT**

The complainant stated that he/she believed this communication on LinkedIn to be in breach of advertising regulations for advertising medicines to the public.

When writing to Novo Nordisk the Authority asked it to respond in relation to the requirements of Clauses 2, 9.1 and 26.1 of the Code.

**RESPONSE**

Novo Nordisk submitted that it was very concerned to receive this complaint. It took these matters very seriously and had conducted a thorough investigation.

Novo Nordisk submitted that the appearance of the link referring to Tresiba on LinkedIn was not posted by the Novo Nordisk member of staff. The individual had many years' experience within the pharmaceutical industry at a variety of companies with extensive knowledge of the Code.

Novo Nordisk provided details of the employees' activity within LinkedIn. The last activity was to update his/her user profile. The employee had not posted any product related news or links to product related news items.

It appeared from the link within the email from the complainant that the linked headline came from a German news group. Novo Nordisk issued a certified press release regarding Tresiba to UK specialist/medical publications only and a copy of the press release which stated that it was for UK medical media only was provided.

During Novo Nordisk's investigations it also appeared that the individual was mentioned in the post rather than attributed to posting the link.

Novo Nordisk submitted that the posting had occurred via the LinkedIn Pulse app. Novo Nordisk had learned that this application automatically brought news articles to users based on their interests and connections within LinkedIn.

According to the LinkedIn help page, it was curated by LinkedIn's editorial team. This application also highlighted to users when people they were connected to were mentioned in the news. As the individual was listed as a contact on the original press release, he/she had been highlighted by this algorithm. Novo Nordisk therefore believed that this news link might have been sent to a small number of people who had downloaded this application and were also contacts of the individual within LinkedIn.

Novo Nordisk submitted that it had absolutely no intent to undertake any activity to promote Tresiba to the public. Following its investigation, Novo Nordisk submitted it was not in breach of Clauses 26.1 (advertising to the public), 9.1 (maintaining high standards) nor Clause 2 (discredit to the industry).

As a result of this complaint and Novo Nordisk's awareness of this feature on LinkedIn, the individual had changed relevant privacy settings to prevent being mentioned in a news related post in the future. Novo Nordisk was also recirculating its social media policy to all UK staff to ensure they remained fully compliant in this respect.

**PANEL RULING**

The Panel noted that Novo Nordisk UK had issued a press release dated 13 June 2016 for UK medical media comparing Tresiba rates of hypoglycaemia with insulin glargine. The press release included contact details for the individual Novo Nordisk and staff at the company's agency.

The Panel noted that Clause 26.1 which prohibited the advertising of prescription only medicines to the public reflected UK and EU law. The Panel could only make decisions regarding the Code.

The Panel noted Novo Nordisk's submission that the LinkedIn communication appeared to be as a result of Novo Nordisk's press release in which the individual was listed as a contact and an app which brought news articles to users based on their interests and connections within LinkedIn and highlighted to users when people they were connected with were mentioned in the news. According to Novo Nordisk it was not something that the company or its staff had instigated or knew about until the complaint was received. The Panel was very surprised that this issue had not come to light previously. It was unsure whether similar postings had been made to the contacts of the two agency staff named in the communication at issue. The fact that the application relied on an algorithm did not absolve Novo Nordisk from responsibility. The Panel noted that LinkedIn was widely used in the pharmaceutical industry. It was not inconceivable that Novo Nordisk and/or its staff had been the subject of previous communications placed by the LinkedIn application. In the Panel's view companies should remain vigilant and needed to ensure that they took reasonable steps to prevent relevant secondary postings of their material.

Nevertheless the Panel did not consider that on the evidence before it Novo Nordisk had advertised a prescription only medicine to the public and therefore ruled no breach of Clause 26.1. The Panel also considered that the particular circumstances did not indicate a failure to maintain high standards nor did they bring discredit upon or reduce confidence in the pharmaceutical industry and thus no breaches of Clauses 9.1 and 2 were ruled.

**Complaint received** **16 June 2016**

**Case completed** **18 August 2016**

**CASE AUTH/2852/6/16** *NO BREACH OF THE CODE*

# EX-EMPLOYEE v GRÜNENTHAL

## Medical science liaisons' working practices

**An anonymous, contactable ex-employee complained about the working arrangements for medical science liaisons (MSLs) at Grünenthal.**

**The complainant stated that he/she had always sought help and guidance from senior leadership and compliance to ensure that his/her day-to-day work was conducted according to Grünenthal's stance that compliance was at the core of its culture. Unfortunately as commercial pressures mounted in 2015, head office and field-based medical affairs colleagues were asked to take on tasks which were not within the scope of their respective roles.**

**The complainant decided to complain to protect future Grünenthal MSLs/scientific advisors or medical information scientists, from being used in a non-compliant manner, in the absence of clear briefing documents and guidance which was verbal rather than consistent, transparent and formally documented.**

**The complainant alleged that Grünenthal used a reactive, non-promotional, field-based MSL team in a 100% proactive manner to target an inappropriate group of health professionals who did not primarily treat pain (Grünenthal's main therapy area). The company set 100% customer-facing time targets, with the aim of facilitating discussions with oncologists and palliative care specialists, to disguise the promotion of Palexia Oral Solution (tapentadol).**

**At the end of the April 2015 the MSLs were informed that they would be expected to spend every day seeing customers in the field and could no longer work reactively. No exceptions were to be made and the line was 'every day is a field day'.**

**Despite disagreement from the MSLs, an email was sent to the team (copy provided) with a target list of palliative care and oncology health professionals. Some additional verbal instructions were also provided. The new way of working meant that MSLs had to proactively target an agreed list of 100 customers every day with a particular opportunity for Palexia Oral Solution which was not doing very well since launch. The MSLs protested that Grünenthal pain products were not licensed in palliative care so they would effectively be conducting disguised promotion of an off-licence indication.**

**The MSLs were dissatisfied with this new proactive, disguised promotion to an off-licence customer base, and so not all followed the instructions at first. The MSLs thus received another email asking them to keep their calendars up-to-date with where they would proactively be each day. This caused stress and resentment amongst the MSLs as they were approaching hospital oncology and palliative care departments to proactively speak to health professionals about a pain medicine not licensed in oncology and palliative care; the trials for Palexia were in osteoarthritis and lower back pain.**

**The complainant stated that Grünenthal demonstrated its seriousness with the 100% proactive approach by asking each MSL to record whom they had seen and the output of those interactions. Some MSLs stated that the approach was demoralising and that health professionals refused to see them. Additionally, at monthly team meetings, MSLs had to share what they had done each month which was disguised on the agenda under 'Any other business'.**

**The complainant alleged that Grünenthal wanted the salesforce and market access teams to focus on the main brands ie Palexia SR, Palexia tablets, and Versatis, and thought of an underhand way of disguising the promotion of the relatively new Palexia Oral Solution via the MSL team so the salesforce would not be distracted from the core brands.**

**The detailed response from Grünenthal is given below.**

**The Panel noted the complainant had provided copies of two short emails from his/her manager which provided the target list of health professionals, with instructions as to its use, and a reminder to update calendars respectively. The complainant subsequently provided two lists of health professionals which had been entitled by hand 'unlicensed customer group, palliative care and oncology' and 'target list' respectively. The Panel noted that the Constitution and Procedure clearly stated that a complainant had the burden of proving his/her complaint on the balance of probabilities.**

**The first email provided by the complainant was sent by the head of MSLs and was not dated. The MSLs were instructed to look at the top 100 people from their list, check with colleagues if they were already doing business with those individuals and determine whether seeing an individual would have a negative impact. Once satisfactory, the lists could be finalised and would form part of the end of year assessments. The second email headed 'Every day is a field day' was dated and sent by the head of MSLs who asked those MSLs who had not already done so to update their calendars with where they would be in the field given Grünenthal's new focus. The Panel noted that whilst neither email instructed MSLs to discuss products it appeared that the MSLs would be assessed on the percentage of health professionals seen on their 'proactive' target lists. This appeared to be contrary to the Medical Science Liaison Policy (effective from December 2015) which stated that remuneration for MSLs must not be linked to number of visits, meetings etc. but a bonus scheme linked to the percentage of enquiries or visit *requests* (emphasis added) completed might be acceptable.**

**In the Panel's view it was thus not necessarily unacceptable for MSLs to be in the field every**

**day. The Panel noted Grünenthal's submission that the role of the MSLs was non-promotional in action and intent. However, the Panel noted that the MSL job descriptions relevant at the time were identical and stated at the outset that the position provided support to the medical department in order to achieve the company's goals. The overall purpose of the role included, *inter alia*, to introduce and build new product awareness and facilitate formulary submissions. MSLs were required to identify and develop strong sustainable relationships with external customers to deliver the opportunity to execute product strategy. The Panel noted that the working instruction for the MSLs (which was in place over the first six months in question (June – November 2015) and the Medical Science Liaison Policy which succeeded it, both allowed MSLs to proactively introduce their role. In that regard the MSL introductory leavepiece listed a number of services available including, *inter alia*, 'information on effective and appropriate use of Grünenthal pain products'. The Panel queried whether requests for information received in response to the leavepiece/ introductory visit were, in effect, solicited and so responses to them would not be exempt from the definition of promotion. Overall, the Panel considered that, given the broad definition of promotion in the Code, elements of the MSL role were promotional. In that regard, the MSLs were thus covered by the requirements in the Code for representatives who were defined in the Code as calling on members of health professionals and other relevant decision makers in relation to the promotion of medicines.**

**The Panel noted Grünenthal's submission that before the target list was emailed there were verbal discussions with the MSL team in preparation of the release of the list (objectives, actions required, measures that would be used, inclusion in assessment priorities). The Panel was concerned that Grünenthal had not provided any written briefing document to accompany the target list particularly as this was a new way of working for the MSLs. The Panel noted that Grünenthal confirmed that there were never any instructions provided to 'steer conversation' towards any of its products. The Panel also noted that in the first 6 months of setting the MSLs a new way of working (June-December 2015), only two team meetings were held; one in June to discuss target lists and priorities and one in October for which there was no agenda. Meetings in 2016 (January – June) were held in every month but February. No minutes were available from any meeting. The Panel noted Grünenthal's submission that future meetings would be documented. The Panel considered that the lack of any record of the MSL team discussions was regrettable. It meant that the company had no evidence to support its submission that MSLs were not instructed to steer the conversation towards Palexia Oral Solution or any of Grünenthal's products or that they were not otherwise briefed in a way that would advocate, either directly or indirectly, a course of action which would be likely to lead to a breach of the Code. The Panel noted that the complainant bore the burden of proof to establish that, on the balance of probabilities, MSLs were so briefed. The Panel noted its comment above that the emails provided by the complainant did not instruct MSLs to discuss products. In the circumstances, no breach of the Code was ruled.**

**The Panel noted Grünenthal's submission that nothing was ever raised directly from any MSL or in association with this complaint to suggest that a health professional had been inconvenienced by an MSL, nor that arrangements at any particular establishment were not observed. On the basis of the evidence before it the Panel ruled no breach of the Code.**

**The Panel considered that there was no evidence before it to suggest that the MSLs had promoted any medicine, for off-licence use or otherwise, as alleged and therefore ruled no breach of the Code. There was thus no evidence to suggest that there had been disguised promotion. No breach of the Code was ruled.**

**The Panel noted Grünenthal's submission that it had prioritised the introduction of the MSL role to oncologists and palliative care specialists as the number of enquiries received from them demonstrated their need for information. A review of requests for information logged in the medical information system identified 200 queries from health professionals that flagged positive for the words 'oncology' 'palliative' 'cancer' between 17 May 2013 and 18 May 2015. The Panel considered that given these figures oncologists and palliative care health professionals' need for, or interest in information about Grünenthal's products could reasonably be assumed and no breach of the Code was ruled.**

**The Panel did not consider that the complainant had shown that on the balance of probabilities the MSLs or Grünenthal had failed to maintain high standards. No breaches of the Code were ruled. The Panel noted its rulings above and consequently ruled no breach of Clause 2.**

An anonymous, contactable ex-employee complained about the working arrangements for medical science liaisons (MSLs) at Grünenthal Ltd.

**COMPLAINT**

The complainant stated that he/she had always sought help and guidance from senior leadership and compliance to ensure that his/her day-to-day work was conducted in the spirit of the company's acclaimed slogan that compliance was at the core of its culture. Unfortunately as commercial pressures mounted in 2015, both head office and field-based medical affairs colleagues were asked to take on tasks which were not within the scope of their respective roles.

The complainant decided to complain to protect future members of Grünenthal medical, be it MSLs/ scientific advisors or medical information scientists, from being used in a non-compliant manner, in the absence of clear briefing documents and guidance which was verbal rather than consistent, transparent and formally documented.

The complainant alleged that Grünenthal used a reactive, non-promotional, field-based MSL team in a 100% proactive manner to target an inappropriate group of health professionals who did not primarily treat pain (the therapy area Grünenthal products fell within). The company set 100% customer-facing time targets, with the aim of getting the team to facilitate discussions with oncologists and palliative care health professionals, to disguise the promotion of Palexia Oral Solution (tapentadol).

The complainant explained that at the end of the April 2015 company conference the MSLs were informed by their manager that there would be a new way of working in that they would be expected to spend every day seeing customers in the field and could no longer work as a reactive function. No exceptions were to be made and the line was 'every day is a field day'. Even administrative days had to be requested and were granted at the manager's discretion. The new way of working meant that MSLs had to be out proactively targeting a list of customers every day.

Despite disagreement from the MSLs, it was made clear that there was no room for discussion, and that commercial pressures meant this had to happen. Soon after this announcement an email was sent to the MSL team with an attached target list of palliative care and oncology health professionals. Some additional verbal instructions were also provided.

The complainant stated that MSLs were to proactively pursue an agreed target list of 100 customers and discuss products, with a particular opportunity for Palexia Oral Solution which was not doing very well since launch. The team was not to disrupt existing customers ie those already prescribing Grünenthal's products, as this could be bad for business. In short, the MSLs were to introduce themselves to health professionals and try to steer the conversation to discuss product. The MSLs protested that Grünenthal pain products were not licensed in palliative care, so they would effectively be conducting disguised promotion of an off-licence indication.

The complainant stated that the MSLs considered this to be non-compliant for a reactive MSL function because:

1 All of the activity (100%) would become proactive with 100% field time in that manner, and they were meant to serve as a reactive function.

2 Steering the conversation to the Palexia Oral Solution was non-compliant, and they would be in breach of the Code under disguised promotion. The MSL team learnt very quickly with frowny looks from doctors that the focus of oncology/ haematology health professionals was on chemotherapy. Often colleagues were told by oncology health professionals that, as a pain specialist company, Grünenthal was seeing the wrong people.

3 Each MSL had to meet a target which would form part of the end of year assessments, which were all about bonus and a salary increase.

The MSL team was dissatisfied with this new proactive, disguised promotion to an off-licence customer base, and so not all followed the instructions in the first few days. The MSLs thus received another email from the MSL manager asking them to keep their calendars up-to-date with where they would proactively be each day. This caused stress and resentment amongst the MSLs as they were approaching hospital oncology and palliative care departments to proactively speak to health professionals about a pain medicine not licensed in oncology and palliative care; the trials for Palexia were in osteoarthritis and lower back pain.

The complainant stated that Grünenthal demonstrated its seriousness with the 100% proactive approach by asking each MSL to record whom they had seen on a spreadsheet and to explain what the output of those interactions were at monthly meetings. Some MSLs stated that the approach was demoralising and that oncologists and palliative care health professionals were shutting doors in their faces. Additionally at monthly team meetings, MSLs had to share what they had done each month which was disguised on the agenda under 'Any other business'.

The complainant alleged that Grünenthal wanted the salesforce and market access teams to focus on the main brands ie Palexia SR, Palexia tablets, and Versatis, and thought of an underhand way of disguising the promotion of the relatively new Palexia Oral Solution via the MSL team so the salesforce would not be distracted from the core brands.

The complainant subsequently provided two lists of health professionals which had been entitled by hand 'unlicensed customer group, palliative care and oncology' and 'target list' respectively.

When writing to Grünenthal, the Authority asked it to consider the requirements of Clauses 2, 3.2, 9.1, 11.1, 12.1, 15.2, 15.4 and 15.9 of the Code.

**RESPONSE**

Grünenthal explained that its team of field-based MSLs were all either PhD scientists, or pharmacists. Copies of the MSL job descriptions, effective August 2013 – June 2015 and June 2015 to date, were provided.

Grünenthal submitted that the MSL role was non-promotional in action and intent. Further to the MSL job description, this was supported by the Medical Science Liaison Policy (the current version effective from 1 December 2015 and the previous work instruction which it replaced (effective from 14 February 2013 – November 2015) were provided). The role provided a clinical/scientific service to health professionals to facilitate optimal healthcare provision for patients. This could be achieved through either reactive contact in response to unsolicited, specific, individual requests from health professionals or via proactive contact by the MSLs.

Reactive contact was in response to unsolicited specific enquiries or requests for information (RFIs)

that the company received from health professionals. RFIs might be about one of Grünenthal's products (within and outwith product licence) or a disease area in which it operated. The majority of RFIs were managed by the head office medical information department but if a face-to-face visit was requested, this was allocated to the local MSL.

The current Medical Science Liaison Policy described the following proactive activities in which MSLs might engage:

- 'MSL role introduction
- Matters relating to patient safety, for example to support a risk mitigation activity or further to a request from drug safety (ie to follow up adverse drug reaction reports)
- Identification of investigators for clinical trials, feasibility work of sites for clinical trials
- Legitimate exchange of medical and scientific information during the development of a medicine
- Medical education or clinical disease area discussions. NB There must be no reference either direct or indirect to specific medicines; however, general reference to Grünenthal's interest in the disease area is acceptable
- Training of internal staff.'

The Medical Science Liaison Policy specifically stated that 'Any proactive activity outside of those described above, particularly in relation to information about a specific medicine, could be deemed promotional and are not acceptable or appropriate activities for MSLs to perform'.

Other activities the MSL team engaged in included visits with health professionals that were requested return visits (where following a RFI the health professional requested a subsequent meeting with the MSL), training of external speakers, internal employee training, support of medical and educational goods and services (MEGs) and involvement in special projects. In addition, the MSL team was represented on numerous internal cross-functional groups, eg compliance champion team, field marketing group champion.

The MSL team had a number of objectives, referred to internally as 'priorities'. These were set and reviewed annually as part of the individual appraisal process with each MSL. Achievement or failure of priorities influenced salary and bonus. Details of the five priorities that were set for the MSL team in 2015, all of which were equally weighted was provided and included a range of customer-facing and non customer-facing activities; promoting the MSL role to health professionals was one of them. The review of priorities was a frequent agenda item for the monthly face-to-face MSL team meetings (examples of six MSL team meeting agendas from 2015 and 2016 were provided).

The difference between proactive engagement of health professionals by MSLs and representatives was that representatives proactively sought to promote the use of Grünenthal's product portfolio, whereas MSLs were limited to the activities described and did not proactively contact health professionals in order to discuss medicines. Grünenthal confirmed that the email supplied by the complainant was sent to the MSL team in June 2015.

Since 2014 the MSLs had been required to proactively introduce their role to health professionals. Initially this activity focussed on pharmacists as they were not routinely targeted by other company staff. The management of pain was often polypharmacy and therefore pharmacists submitted a large proportion of RFIs. Approaching a group of health professionals not otherwise engaged by the business prevented any blurring between the objectives of promotional and non-promotional interactions with the same individuals so the differences between representatives and MSLs should have been obvious for the health professionals, in line with the PMCPA guidance on Clause 3.

A leavepiece which introduced the MSL role to health professionals was first used in April 2014 and had the objective of 'Leaflet to raise awareness and understanding of the MSL role, these will be given out by the MSL at congresses, or when meeting healthcare professionals, to introduce the role of the MSL'. A copy of the leavepiece was provided.

Following a company conference in May 2015 (not April 2015 as stated by the complainant), the MSLs widened the group of health professionals they introduced their role to, to include oncologists and palliative care clinicians. This decision was borne from the capacity for MSLs to increase their customer-facing activities, and focussed on oncologists and palliative care clinicians because both groups prescribed analgesics to patients in often clinically complicated scenarios, and the demand for RFIs received from both groups. The scope of the MSL role remained unchanged and they continued to operate with all health professionals in a strictly non-promotional manner.

Grünenthal noted the complainant's concern that 'every day is a field day'. The context behind this was that whilst the MSL team was non-promotional, it was field-based and therefore when diaries were empty, each team member should approach work proactively, including liaising with health professionals to introduce the MSL role. In reality, company commitments, eg internal meetings, training sessions, conferences, etc impacted on individuals' ability to be field-based for 100% of their time so this was never realistically achieved week on week; nevertheless, there was a drive to prioritise customer-facing time.

The MSL team was never instructed that 100% of its activities were to be proactive; the five equally weighted priorities across a range of different activities, included the proactive introduction of their role. If there was an expectation to spend 100% of their time proactively introducing their role, they would not have been able to meet their other priorities.

A report on medical information enquiries assigned to and closed by MSLs between Grünenthal's company conference in 2015 (22 May 2015), and

22 June 2016 (when the investigation into this complaint commenced) indicated that over 180 RFIs were assigned to the MSL team by the medical information service (this did not include enquiries that were assigned to an MSL but the health professional did not respond or no longer wanted a visit and the RFI was closed by medical information). If the MSLs had been expected to spend 100% of their time proactively engaging health professionals, they would not have been able to fulfil these RFIs.

The complainant alleged that oncologists and palliative care clinicians were inappropriate groups to work with because they did not primarily treat pain, however pain was a symptom common to many disease states, particularly cancer and terminal conditions, and therefore it was relevant to all clinicians; few clinicians primarily just managed pain. Furthermore, clinicians that managed cancer patients, even if they did not routinely initiate pain management themselves (eg oncologists), would treat patients who were suffering pain and/or being treated with analgesics. An awareness of analgesics that might be used in cancer patients, and which could be used concurrently with other medicines that were used in the treatment of cancer, was therefore important.

A review of RFIs logged between 17 May 2013 and 18 May 2015 (ie the two years preceding the 2015 company conference) identified over 200 that flagged positive for the words 'oncology' 'palliative' and 'cancer' (most were logged by physicians, or by pharmacists). Of the queries, nearly 50 were allocated to, responded to and closed down by MSLs. It could thus be reasonably assumed that oncologists and palliative care clinicians might have queries in relation to Grünenthal medicines and might be interested in the services provided by the MSL team. This was why it was decided that MSLs should widen the group of health professionals to whom the role was introduced to include oncologists and palliative care specialists.

Given the above, Grünenthal disputed the alleged a breach of Clause 11.1 as oncologists and palliative care specialists could reasonably be assumed to be interested in pain management.

Grünenthal stated that its list of oncologists and palliative care specialists was compiled based on clinical commissioning group (CCG) patient population size in each MSL's territory using data from an external data provider. The MSL team was sent the list as per the email provided by the complainant, and asked to liaise with cross-functional colleagues to ensure that for each individual there was no other engagement with Grünenthal eg an existing relationship with the company, an ongoing project, a known blockage to pharmaceutical companies or any other reasons why it would be inappropriate for the MSL to call. This ensured health professional interactions with cross-functional colleagues were kept separate. If there was an existing relationship or other challenge, the identified individuals were removed from the list and replaced with others from the master list. The final group of oncologists and palliative care specialists was therefore intentionally not also called upon by promotional teams to prevent clouding of promotional interactions with Grünenthal with non-promotional interactions – different activities were to be kept separate. Once the list was finalised, each MSL began to initiate proactive activities with the top 100, moving into the list of subsequent individuals as needed.

In engaging oncologists and palliative care specialists, the MSLs were instructed to approach them in the same manner as with their proactive engagements with pharmacists, ie to introduce the MSL role using the MSL introductory leavepiece as support.

Grünenthal confirmed that the team had never been instructed to 'steer conversation' towards any of Grünenthal's products. Whilst the wording of the email provided by the complainant implied prior conversations took place about the list, unfortunately no written briefings or supporting evidence (eg meeting minutes) could be provided. Grünenthal understood that there was a failing in the clarity in the email as a standalone briefing document, that this was not good business practice and it fell below the standards expected. It had also been made clear that minutes must be taken during future MSL team meetings and these must be centrally stored along with written agendas circulated in advance of meetings.

Before the email was sent there were verbal discussions with the MSL team in preparation of the release of the list (objectives, actions required, measures that would be used, inclusion in assessment priorities). Grünenthal understood that the wording of the email was ambiguous, and in the absence of other written briefing there might have been confusion as to some of the language used, however as the activity was limited to MSL activities, it did not believe Clause 15.9 was relevant as that clause related to the briefing of representatives. The head of MSLs acknowledged that there should have been a more detailed written briefing, and had committed to ensure more structured written MSL briefing documents and meeting minutes in future. Grünenthal was disappointed that it was unable to provide more substantive evidence, however it confirmed that the MSLs were currently guided in their behaviour by the Medical Science Liaison Policy and used the MSL leavepiece to proactively introduce their role to health professionals.

Grünenthal submitted that it had contacted all members of the MSL team in role in 2015, when the list was distributed but who had now left the company, to gauge from them their understanding of the objective of the activity at issue. Whilst all were willing to be contacted, none were available within the timelines stipulated for providing the response to this complaint.

Grünenthal stated the complainant's reference to 'frowny looks from doctors' was never raised directly with the manager by any MSL or at any MSL team meeting. No evidence had therefore been provided to Grünenthal either directly from any MSL or in association with this complaint to suggest that any health professional was ever inconvenienced by an MSL, nor that arrangements at any particular establishment were not observed. Further, as the

MSL role was non-promotional and did not meet the definition of 'representative' as stated in Clause 1.7, the company submitted that Clauses 15.2 and 15.4 were not applicable with regard to the MSLs and so Grünenthal denied any breach of these clauses.

The complainant alleged that the MSLs were told their focus when working with oncologists and palliative care specialists was for the disguised promotion of Palexia Oral Solution in response to commercial pressures ('introduce yourself and try to steer the conversation to discuss product'). Grünenthal strongly refuted any allegation that MSLs were instructed to steer conversations with health professionals to discuss any of Grünenthal's products.

Grünenthal noted that Palexia Oral Solution was added to the UK Palexia portfolio in April 2014. It was not a significant product for the UK as it was clinically equivalent to Palexia film coated tablets rather than Palexia SR (slow release); there had been no additional company investment or any commercial incentives for its promotion. The complainant did not accurately recall the key strategic messages from the company conference in May 2015 if he/she truly believed the focus for the UK business was Palexia Oral Solution at that time.

In response to this complaint, Grünenthal reviewed RFIs logged and confirmed that from 1 May 2014 to 7 July 2016, just over 100 requests were logged with the words 'oral solution' or 'os'. Nearly 30 requests were responded to by MSLs. The basic reporting and search functionalities of the logging system meant that some enquiries about Palexia Oral Solution might have been missed, and others included that were not about the product (eg if requesting Palexia formulary information, the requestor might request that information was not provided on Palexia Oral Solution). There was therefore not much interest in Palexia Oral Solution information and few MSL calls logged about the product.

Grünenthal submitted that a review of a sample of calls logged in the company's customer relationship management (CRM) system as 'Introduction of MSL role' revealed no recorded discussions of Palexia Oral Solution or any other Grünenthal product in a proactive MSL call, therefore no evidence existed that there was any disguised promotion. Copies of 6 call notes were provided.

Given the above, Grünenthal strongly refuted the alleged disguised promotion of Palexia Oral Solution (or any other Grünenthal product) (Clause 12.1).

Grünenthal noted the complainant's reference to 'a pain medicine not licensed in oncology or palliative care' and that 'MSLs protested that Grünenthal pain products were not licensed in palliative care … so they would effectively be conducting disguised promotion of an off-licence indication'. Grünenthal reiterated that product promotion was not part of the MSL role, however Palexia could be prescribed, within licence, to treat pain in cancer patients. Palexia tablets and Palexia Oral Solution were licensed for 'the relief of moderate to severe acute pain in adults, which can be adequately managed only with opioid analgesics'; Palexia SR was licensed for 'the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics'. Similarly, classical opioids such as morphine sulphate and oxycodone were indicated for 'severe pain' and not according to the underlying cause of the pain.

As stated above, the review of a sample of proactive call notes in the CRM system did not identify any proactive MSL calls during which product was discussed. Without any evidence to the contrary, Grünenthal therefore denied the off-licence promotion (Clause 3.2) of any product as alleged by the complainant.

Grünenthal stated that some of the MSLs themselves decided to modify the spreadsheet referred to by the complainant to create a tracker so they could monitor their own coverage of the list however, they were never asked to include any outputs of discussions as alleged.

There was no drive from the company to use this spreadsheet to record interactions, however attainment was measured on the basis of MSL self-reporting (by the spreadsheet when used by individuals, and other data sources). Details were provided of the coverage of the oncologist/palliative care list at the end of the year to be 100% achievement (internal priority rating = Performing). Grünenthal provided examples of the trackers used by two MSLs.

Although the priority was set with these measures during 2015 there was a high turnover within the MSL team which meant individuals had covered additional territories. In the end, this priority was not assessed according to the parameters set; examples were provided.

The use of a tracker did not replace entry of interactions with health professionals in the company CRM system and when responding to a RFI. No evidence was identified in the sample of call notes reviewed during the investigation that Grünenthal products were discussed during these introductory calls. Examples were seen of RFIs being submitted as RFI during the interaction and were logged as per the defined internal process.

Agendas for each of the MSL team meetings conducted in 2015 and 2016 were provided. The agendas were circulated in advance of meetings with input from the whole team. Grünenthal noted the following regarding MSL team meetings:

- June 2015: 'Target list and priorities' was an agenda item for the meeting which immediately followed the 2015 company conference.
- For the rest of the year, apart from October, there were no meetings for a variety of reasons. The agenda for the October meeting could not be found.
- January 2016: 'ED and MyView' ('ED' stands for Employee Dialogue, and MyView is the internal system priorities are logged within)
- February 2016: combined medical department meeting so no MSL team agenda

- March 2016: 'Change Pain and MSL Introductions'
- April 2016: 'Priorities 2016'
- May 2016: 'MSL introductions'
- June 2016: 'Priorities 2016'.

Minutes were not available for the meetings. As noted above, Grünenthal recognised that failing to take minutes was unfortunate and all future meetings would be appropriately documented.

A senior Grünenthal manager, who had recently left the company, had no recollection that any MSL expressed concern about proactive engagement with health professionals, the appropriateness of oncologists or palliative care specialists, or any fear of disguised promotion.

Grünenthal submitted that Compliance had led a group of cross-functional compliance champions who met every 6 to 8 weeks to discuss compliance-related topics and projects. There had always been an MSL team member in this group. A review of emails received from, and sent to the MSL team in 2015 and 2016 showed no queries that could be identified that were not responded to. No emails referred to the challenges described within the complaint and there was no recollection of verbal conversations related to these topics either. Compliance was consulted regarding proactive interactions with health professionals early in 2014, ahead of commencement of this activity; however this was led by two senior managers including the head of MSLs. Advice was provided that it was acceptable to proactively introduce the role of the MSL to health professionals provided that no product was discussed in such meetings.

A communication was written by a manager regarding the introduction of the MSL role to health professionals which was disseminated to commercial field managers. The wording of the communication was provided.

Grünenthal submitted that as it did not consider there were any breaches of the Code as above, the activity at issue did not fail to maintain high standards and thus was not in breach of Clause 9.1. The activity did not reduce confidence in the industry or bring the industry in to disrepute and was not in breach of Clause 2.

Grünenthal stated that its commitment to ensuring compliance was at the core of its culture was driven by the senior management team, the general manager, and by all line managers. This was clearly conveyed to all new employees when they commenced employment and continued during their employ. The tone with which the internal slogan was referred to by the complainant suggested that the company commitment to compliance was not genuine or sincere. Grünenthal wholly refuted this and wished to convey in the strongest terms that it took its commitment to the Code, in both the letter and the spirit, actively in all that it did, both internally and externally.

Employees could raise queries or concerns through a number of routes although their line manager should be their first point of contact, failing that they could contact their functional compliance champion, the head of compliance or any member of the senior management team – the company was of a size that there was not a great hierarchy therefore senior managers were well known within the business. In addition, there was a general UK compliance email to which they could send queries if they did not know which individual to contact. Employees could also raise concerns anonymously using the Grünenthal Global Ombuds Hotline. This directed concerns to global compliance in Germany, which managed the report. The hotline was made available in 2013 but as yet there had been no reports logged from the UK.

In summary Grünenthal was disappointed to have received this complaint, and queried why the complainant felt unable to raise his/her concerns internally if he/she genuinely felt there were compliance-related issues. The company could not identify any queries which had not been responded to and had no record of any concerns being flagged on the topics outlined above.

Grünenthal strongly refuted the complainant's allegations with regard to inappropriate proactive engagement with health professionals and disguised or off-licence promotion. It had no evidence that high standards had not been maintained, that health professionals were spoken to who would not reasonably be assumed to have an interest in the management of pain or that MSL interactions inconvenienced health professionals. The company believed that all its staff, including the MSLs, conducted themselves in an ethical manner upholding high standards, and therefore did not believe that there had been any action that could discredit or reduce confidence in the industry. The company acknowledged that there was a lack of written briefing documents for the MSLs about the proactive discussions they were to have with oncologists and palliative care specialists as per the email provided by the complainant, and that this was not good business practice. It confirmed that the MSL team was a non-promotional team, and its only proactive activity was to introduce its role to health professionals, as supported by the Medical Science Liaison Policy. The company could see why information in the email provided by the complainant might be seen to be unclear regarding expectations in the absence of a more formalised briefing, however the non-promotional nature of the MSL role was emphasised in many other documents including the job description, the Medical Science Liaison Policy, and the MSL introductory leavepiece.

**PANEL RULING**

The Panel noted the complainant's allegation that since the 2015 company conference MSLs had been required to proactively target oncologists and palliative care health professionals, introduce themselves and try to steer the conversation to discuss products, particularly Palexia Oral Solution. The Panel further noted the complainant's submission that Grünenthal pain products were not licensed in palliative care and so the MSLs' activity would be disguised promotion of an off-

licence indication. In support of his/her allegations, the complainant had provided copies of two short emails from his/her manager which provided the target list of health professionals, with instructions as to its use, and a reminder to update calendars respectively. The complainant subsequently provided two lists of health professionals which had been entitled by hand 'unlicensed customer group, palliative care and oncology' and 'target list' respectively. The Panel noted that the Constitution and Procedure clearly stated that a complainant had the burden of proving his/her complaint on the balance of probabilities.

The first email provided by the complainant was not dated, it was headed 'MSL Pall_Oncology List'; it was sent by the head of MSLs and described how each MSL should select their business unit to reveal their target list of customers. The MSLs were instructed to look at the top 100 people from their list, check with colleagues if they were already doing business with those individuals and determine whether seeing an individual would have a negative impact. Once satisfactory, the lists could be finalised and would form part of the end of year assessments. The second email headed 'Every day is a field day' was sent on 2 June 2015 and asked those MSLs who had not already done so to update their calendars with where they would be in the field given Grünenthal's new focus. The Panel noted that whilst neither email instructed MSLs to discuss products it appeared that the MSLs would be assessed on the percentage of health professionals seen on their 'proactive' target lists. This appeared to be contrary to the Medical Science Liaison Policy (effective from December 2015) which stated that remuneration for MSLs must not be linked to number of visits, meetings etc. but a bonus scheme linked to the percentage of enquiries or visit **requests** (emphasis added) completed might be acceptable.

The Panel noted Grünenthal's submission that the current (undated) MSL job description was effective from June 2015. The alleged activity referred to by the complainant occurred from the end of April 2015 so the previous (also undated) version of the job description was also relevant. The Panel noted, however, that both versions were identical. The Panel noted that the MSL job descriptions described the role as being field-based. In the Panel's view it was thus not necessarily unacceptable for MSLs to be in the field every day provided that the activities carried out whilst in the field complied with the Code. The Panel noted Grünenthal's submission that the role of the MSLs was non-promotional in action and intent. However the Panel noted that both MSL job descriptions stated at the outset that the position provided support to the medical department in order to achieve the company's goals. The overall purpose of the role included, *inter alia*, to introduce and build new product awareness and facilitate formulary submissions. MSLs were required to identify and develop strong sustainable relationships with external customers to deliver the opportunity to execute product strategy. The Panel noted that the Working Instruction for the MSLs (which was in place over the first six months in question (June-November 2015)) and the Medical Science Liaison Policy which succeeded it, both allowed MSLs to proactively introduce their role. In that regard the MSL introductory leavepiece listed a number of services available including, *inter alia*, 'information on effective and appropriate use of Grünenthal pain products'. The Panel queried whether requests for information received in response to the leavepiece/ introductory visit were, in effect, solicited and so responses to them would not be exempt from the definition of promotion. Overall, the Panel considered that, given the broad definition of promotion in Clause 1.2 of the Code, elements of the MSL role were promotional. In that regard, the MSLs were thus covered by the requirements in the Code for representatives including, *inter alia*, Clauses 15 and 16. Representatives were defined in Clause 1.7 as representatives calling on members of health professionals and other relevant decision makers in relation to the promotion of medicines.

The Panel noted Grünenthal's submission that before the target list was emailed there were verbal discussions with the MSL team in preparation of the release of the list (objectives, actions required, measures that would be used, inclusion in assessment priorities). The Panel was concerned that Grünenthal had not provided any written briefing document to accompany the target list particularly as this was a new way of working for the MSLs. The Panel noted that Grünenthal confirmed that there were never any instructions provided to 'steer conversation' towards any of Grünenthal's products. The Panel also noted that in the first 6 months of setting the MSLs a new way of working (June – December 2015), only two team meetings were held; one in June to discuss target lists and priorities and one in October for which there was no agenda. Meetings in 2016 (January – June) were held in every month but February. No minutes were available from any meeting. The Panel noted Grünenthal's submission that all future meetings would be documented. The Panel considered that the lack of any record of the MSL team discussions was regrettable. It meant that the company had no evidence to support its submission that MSLs were not instructed to steer the conversation towards Palexia Oral Solution or any of Grünenthal's products or that they were not otherwise briefed in a way that would advocate, either directly or indirectly, a course of action which would be likely to lead to a breach of the Code. The Panel noted that the complainant bore the burden of proof to establish that, on the balance of probabilities, MSLs were so briefed. The Panel noted its comment above that the emails provided by the complainant did not instruct MSLs to discuss products. In the circumstances, no breach of Clause 15.9 was ruled.

The Panel noted that Clause 15.4 required representatives to ensure that the frequency, timing and duration of calls on health professionals and other relevant decision makers in hospitals and NHS and other organisations, together with the manner in which they were made, did not cause inconvenience. The wishes of individuals on whom representatives wished to call and the arrangements in force at any particular establishment, must be observed. The Panel noted Grünenthal's submission

that nothing was ever raised directly from any MSL or in association with this complaint to suggest that a health professional had been inconvenienced by an MSL, nor that arrangements at any particular establishment were not observed. On the basis of the evidence before it the Panel ruled no breach of Clause 15.4.

The Panel noted that Clause 3.2 stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics. The Panel noted its comments above and Grünenthal's submission that in the sample of call notes reviewed during the investigation into this complaint, there were no recorded discussions of Palexia Oral Solution or any other Grünenthal medicine in a proactive MSL call. The Panel considered that there was no evidence before it to suggest that the MSLs had promoted any medicine, for off-licence use or otherwise, as alleged and therefore ruled no breach of Clause 3.2. There was thus no evidence to suggest that there had been disguised promotion. No breach of Clause 12.1 was ruled.

The Panel noted Grünenthal's submission that introduction of the MSL role to oncologists and palliative care health professionals was defined as a priority given that the number of RFIs received from these specialists demonstrated their need for information. A review of requests for information logged in the medical information system identified 200 queries from health professionals that flagged positive for the words 'oncology' 'palliative' 'cancer' between 17 May 2013 and 18 May 2015. The Panel considered that given these figures oncologists and palliative care health professionals' need for, or interest in information about Grünenthal's products could reasonably be assumed and no breach of Clause 11.1 was ruled.

The Panel did not consider that the complainant had provided evidence to show that on the balance of probabilities the MSLs or Grünenthal had failed to maintain high standards. No breach of Clauses 15.2 and 9.1 were ruled. The Panel noted its rulings above and consequently ruled no breach of Clause 2.

**Complaint received** **20 June 2016**

**Case completed** **14 September 2016**

# ANONYMOUS v GLAXOSMITHKLINE

## Alleged promotion of a vaccine to the public

**An anonymous complainant drew attention to an advertisement for GlaxoSmithKline on the Telegraph Online which appeared on 28 June 2016.**

**The complainant noted that the advertisement stated something like 'GlaxoSmithKline has been working on the world's first malaria vaccine, which if approved we intend to make available at a reduced cost'. The complainant alleged that this constituted the promotion of an unlicensed medicine direct to patients.**

**The detailed response from GlaxoSmithKline is given below.**

**The Panel noted that the complainant had been asked for more information including a download of the advertisement on The Telegraph website but had not responded. The Panel noted that GlaxoSmithKline had placed the video on YouTube and its corporate website and noted that it would also be picked up by individuals who searched for certain topics. It was not clear how the complainant had seen the video on the Telegraph Online. GlaxoSmithKline submitted that a targeting algorithm would have placed the material on that webpage if the user had previously searched for relevant items.**

**The Panel noted that GlaxoSmithKline had been working with partners on a vaccine for malaria for use in children of a specific age in certain areas of Africa. The vaccine had been considered by the European Medicines Agency (EMA) but would not be marketed in the EU. A positive Committee for Medicinal Products for Human Use (CHMP) opinion was adopted in July 2015 for use of the vaccine outside the EU. Further studies were being discussed as well as a pilot implementation programme. The collaboration would help determine in which Sub-Saharan African countries the first marketing authorisations should be submitted. The vaccine was intended to be for malaria and hepatitis B.**

**The Panel noted GlaxoSmithKline's submission that there was no mention in the video that the vaccine had received a positive approval by the CHMP under Schedule 58. However, screenshots of headlines were included in the video. One from The Daily Telegraph 'GSK Steps closer to making world's first malaria vaccine' and another 'GlaxoSmithKline malaria vaccine trials successful but drug will be not-for-profit'.**

**In the Panel's view it was relevant that the vaccine was for use in Sub-Saharan Africa in those countries where malaria was highly endemic and that GlaxoSmithKline had no intention at this point of making a licence submission in Europe (including the UK). It also noted the company's submission that use in the UK was precluded as there would be little, if any, therapeutic need.**

**The Panel considered that given the content of the video, the nature of the medicine and its potential intended geographical use, the video was a corporate advertisement. It was neither promotion of an unlicensed medicine nor promotion of a prescription only medicine to the public. The Panel thus ruled no breach of the Code in this regard. Further the advertisement would not encourage members of the public to ask their health professional to prescribe the vaccine which was for potential use in Sub-Saharan Africa in those countries where malaria was endemic. The Panel did not consider that GlaxoSmithKline had failed to maintain high standards nor did it consider that the company had brought discredit upon or reduced confidence in the pharmaceutical industry. No breaches of the Code were ruled including Clause 2.**

An anonymous complainant drew attention to an advertisement for GlaxoSmithKline on The Telegraph website, the Telegraph Online, which appeared on 28 June 2016.

### COMPLAINT

The complainant noted that the advertisement stated something like 'GlaxoSmithKline has been working on the world's first malaria vaccine, which if approved we intend to make available at a reduced cost'. The complainant alleged that this constituted the promotion of an unlicensed medicine direct to patients.

When writing to GlaxoSmithKline, the Authority asked it to consider the requirements of Clauses 2, 3.1, 9.1, 26.1 and 26.2 of the Code.

### RESPONSE

GlaxoSmithKline believed that the complaint might relate to a 30 second video entitled 'How we are tackling malaria on all fronts' which was available on The Telegraph Online on 28 June as it contained similar wording to that referred to by the complainant. The video was hosted on YouTube and also appeared on the GlaxoSmithKline corporate website.

The short transcript which accompanied the video was as follows:

> 'Malaria kills 1 child every two minutes in Africa.
> That's why GSK has been working with partners for the past 30 years to develop the world's first malaria vaccine.
> If approved, we're committed to making it available at a not-for-profit price.
> We're also joining forces with Comic Relief to help fight malaria in the worst affected countries.

Because it doesn't matter who solves the problem. Only that someone does.
TITLE: To challenge. To change. GSK Do more, feel better, live longer. Find out more at gsk.com/change.'

GlaxoSmithKline explained that the video was part of a campaign run by the corporate and government affairs, global brand team in GSK House, which was specifically designed to enhance the corporate image and reputation of the company with the 'informed' public (defined as 25 years or older, with at least a first degree, connected on social media, with interests such as current affairs, healthcare, charitable giving, science education and innovation). The need for such a campaign was based on the results of a market research initiative, conducted in 2014 and again in 2016 which sought to determine how the UK public perceived GlaxoSmithKline as a company amongst its industry peers and how its image and reputation could be further enhanced. One of the key findings of this research was that the company should be more transparent in its research activities as well as with the various stakeholders with whom it engaged.

The malaria video formed part of the campaign to highlight the role played by GlaxoSmithKline as a global healthcare company in a specific therapeutic area ie malaria which still placed a significant global healthcare burden in Sub-Saharan Africa. The film highlighted the commitment and longevity of research that GlaxoSmithKline had been engaged in over the last 30 years, as well as its collaboration with Comic Relief, which were aimed at implementing a variety of other initiatives related to the prevention and spread of malaria in these regions. The 30 second film was developed in collaboration with Comic Relief, which supplied the image of a named celebrity and approved its use. In addition, Comic Relief acknowledged GlaxoSmithKline as an international partner on its website and gave some information as how together, the two organisations planned to fight malaria in Africa. Comic Relief was not involved with the vaccine itself, the research which had been undertaken, nor the distribution of the vaccine when it eventually became available for use in Sub-Saharan Africa.

The video started with the World Health Organisation (WHO) facts about the number of childhood deaths in Africa directly attributable to malaria. Two sentences then referred to the GlaxoSmithKline vaccine 'That's why GSK has been working with partners for the past 30 years to develop the world's first malaria vaccine. If approved, we're committed to making it available at a not-for-profit price'. Finally, the partnership with Comic Relief was mentioned. The video showed African children and African health professionals and the opening footage referred to Africa, so it was quite clear that all these initiatives were and would take place in Africa.

GlaxoSmithKline explained that the film was targeted at the informed public (defined above) or someone who had specifically Googled topics like malaria etc. If someone had searched for an item on Google, eg shoes, Google retained the information and used cookies to serve him/her relevant and similar advertisements as it knew he/she had had an intention to purchase or view shoes. So the malaria film might have appeared on the complainant's screen as part of a targeting algorithm, which had identified him/her as someone who was interested in that sort of topic. There was no editorial control with this sort of advertisement placement by the media owner, so the film was not amended or changed by The Telegraph Online – it was solely bought advertising space. These advertisements were frequency capped to ensure a user would not see a specific advertisement more than was reasonable, subject to individual privacy settings and the tracking ability of the software serving the advertising.

GlaxoSmithKline submitted that the malaria vaccine featured in the video was Mosquirix (*Plasmodium falciparum* and hepatitis B vaccine) although it was not referred to as such in the video. The vaccine was intended for use in areas where malaria was regularly found, for the active immunisation of children aged 6 weeks to 17 months against malaria caused by the *Plasmodium falciparum* parasite, and against hepatitis B.

The vaccine was submitted to the European Medicines Agency (EMA) under a regulatory procedure (Article 58) that allowed the EMA to assess the quality, safety and efficacy of a medicine or vaccine and its benefit-risk balance, although it would not be marketed in the EU. This meant that the EMA could help facilitate access to new medicines for people living outside the EU.

As in all Article 58 procedures, the Committee for Medicinal Products for Human Use (CHMP) worked closely with other experts, including those from the WHO and regulatory authorities from the relevant countries. In its assessment, the CHMP applied the same rigorous standards as for medicines to be marketed within the EU. On 24 July 2015 the CHMP adopted a positive scientific opinion for Mosquirix for use outside the EU. From this press release it was clear that this vaccine would not be made available for use in Europe (including the UK).

GlaxoSmithKline stated that it was now working with the WHO with respect to what further clinical trials might be required to evaluate the vaccine in phase 4 studies, and a pilot implementation program as recommended by WHO's advisory bodies (Strategic Advisory Group of Experts on Immunisation and the Malaria Policy Advisory Committee). This collaboration would help to determine how best to implement a global vaccination policy for malaria and in which Sub-Saharan African countries the first marketing authorisations should be submitted. The malaria vaccine was currently a 'pipeline product' for GlaxoSmithKline as no submissions for marketing authorisation had yet been made.

The fact that marketing authorisations for the vaccine, which was intended for use in very young children aged 6 weeks to 17 months, would only be submitted in countries where malaria was highly endemic precluded its use in the UK, for which there would be

very little, if any, therapeutic need. Thus any mention of the vaccine to the UK public did not constitute promotion prior to the grant of a market authorisation as the vaccine would never be made available to UK patients. As Clause 3.1 stated that 'A medicine must not be promoted prior to the grant of the marketing authorisation which permits its sale or supply', GlaxoSmithKline denied a breach of Clause 3.1.

GlaxoSmithKline submitted that the video could not therefore be considered as being 'promotional' to patients within the UK as Clause 1.2 of the Code stated that 'The term 'promotion' is defined as any activity undertaken by a pharmaceutical company or with its authority which promotes the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines'. As stated above, the vaccine currently was not licensed anywhere in the world, and there was no intention at this point for a licence submission to be made in Europe (including the UK) as was shown by GlaxoSmithKline choosing the Article 58 Procedure in the European Regulatory Process. GlaxoSmithKline therefore denied any breach of Clause 26.1 which stated that 'Prescription only medicines must not be advertised to the public'.

The 30 second video only included a two sentence reference to the malaria vaccine as follows:

> 'That's why GSK have been working with partners for the past 30 years to develop the world's first malaria vaccine. If approved, we're committed to making available at a not-for-profit price.'

GlaxoSmithKline believed that information about the vaccine was presented in a fair and balanced way. The above statement simply reflected the longevity of this research and then placed a caveat with 'If approved' therefore signifying that the benefit:risk profile had yet to be determined by a national regulatory authority. Indeed, there was no mention in the video that the malaria vaccine had received a positive approval by the CHMP under Schedule 58 in July 2015. In not mentioning this, nor making any claims regarding the efficacy of the vaccine *per se*, GlaxoSmithKline did not consider that it had raised any unfounded hopes about the success that it might have in preventing malaria in very small children. There was also no references to the safety of the vaccine. Clause 26.2 stated that 'Information about prescription only medicines which is made available to the public either directly or indirectly must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product'. GlaxoSmithKline therefore denied any breach of Clause 26.2.

In view of the above, GlaxoSmithKline submitted that it had not breached the Code and thus was not in breach of Clauses 9.1 or 2.

**PANEL RULING**

The Panel noted that the complainant had been asked for more information including a download of the advertisement on The Telegraph website but had not responded. The Panel noted that GlaxoSmithKline had placed the video on YouTube and its corporate website and noted that it would also be picked up by individuals who searched for certain topics. The complainant had seen the video on the Telegraph Online. GlaxoSmithKline submitted that a targeting algorithm would have placed the material on that webpage if the user had previously searched for relevant items. It was not clear how the complainant had come to see the advertisement.

The Panel noted that GlaxoSmithKline had been working with partners on a vaccine for malaria for use in children of a specific age in certain areas of Africa. The vaccine had been considered by the EMA but would not be marketed in the EU. A positive CHMP opinion was adopted in July 2015 for use of the vaccine outside the EU. Further studies were being discussed as well as a pilot implementation programme. The collaboration would help determine in which Sub-Saharan African countries the first marketing authorisations should be submitted. The vaccine was intended to be for malaria and hepatitis B.

The Panel noted GlaxoSmithKline's submission that there was no mention in the video that the vaccine had received a positive approval by the CHMP under Schedule 58. However, screenshots of headlines were included in the video. One from The Daily Telegraph 'GSK Steps closer to making world's first malaria vaccine' and another 'GlaxoSmithKline malaria vaccine trials successful but drug will be not-for-profit'.

In the Panel's view it was relevant that the vaccine was for use in Sub-Saharan Africa in those countries where malaria was highly endemic and that GlaxoSmithKline had no intention at this point of making a licence submission in Europe (including the UK). It also noted the company's submission that use in the UK was precluded as there would be little, if any, therapeutic need.

The Panel noted the efficacy results of the data gathered so far which were described as 'modest protection' and 'limited' in the CHMP press release. It also noted the importance of continuing to use the established protective measures eg insecticide-treated bed nets. The WHO question and answer document included similar comments.

The Panel noted that the purpose of the advertisement was to increase awareness of GlaxoSmithKline as a global healthcare company and to be more transparent about its research activities and collaborations. The Panel noted that the vaccine was an interesting development and it was understandable that GlaxoSmithKline wanted to promote its role in the progress to date.

The Panel considered that given the content of the video, the nature of the medicine and its potential intended geographical use, the video was a corporate advertisement. It was neither promotion of an unlicensed medicine nor promotion of a prescription only medicine to the public. The Panel thus ruled no breach of Clauses 3.1 and 26.1. Further the advertisement would not encourage members

of the public to ask their health professional to prescribe the vaccine which was for potential use in Sub-Saharan Africa in those countries where malaria was endemic. No breach of Clause 26.2 was ruled. Given its rulings the Panel did not consider that GlaxoSmithKline had failed to maintain high standards nor did it consider that the company had brought discredit upon or reduced confidence in the pharmaceutical industry and no breaches of Clauses 9.1 and 2 were ruled.

**Complaint received** **28 June 2016**

**Case completed** **22 August 2016**

**CASE AUTH/2854/7/16**

# VOLUNTARY ADMISSION BY BOEHRINGER INGELHEIM

## Failure to certify the final form of promotional material

**Boehringer Ingelheim voluntarily admitted a breach of the Code in that a recent review of materials showed that a number of job bags had not received an extra signature to confirm that the certified electronic material matched the final printed hard copy.**

**In accordance with Paragraph 5.6 of the Constitution and Procedure, the Director treated the matter as a complaint.**

**The detailed response from Boehringer Ingelheim is given below.**

**The Panel noted that Boehringer Ingelheim, in its initial letter referred to 'a number' of promotional job bags which showed that the final printed copy of the material had not been checked to ensure that it matched the previously approved final electronic version. The Panel was disappointed that the company had not revealed the extent of the matter at the outset; just over 1 in 3 of a sample of nearly 275 job bags were affected (103). The problem appeared to be widespread. Nonetheless, Boehringer Ingelheim had subsequently checked the material and found that in all cases the final form matched that which had been electronically approved. However, the Code required the printed material to be checked against the electronic copy before use and this had not happened. Breaches of the Code were ruled including that high standards had not been maintained.**

Boehringer Ingelheim Limited voluntarily admitted a breach of the Code with regard to the certification of promotional material.

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 Boehringer Ingelheim.

### VOLUNTARY ADMISSION

Boehringer Ingelheim stated that a recent review of materials showed that a number of hard copy job bags had not received an extra signature to confirm that the electronic material, which had been viewed and certified in Zinc, matched the final printed hard copy of the material as required by the supplementary information to Clause 14.1 which stated that, 'When such material is printed the company must ensure that the printed material cannot be used until any one of the company's signatories has checked and signed the item in its final form. In such circumstances the material will have two certificates and both must be preserved'.

Boehringer Ingelheim submitted that it had since checked all the job bags and found that in all cases the final form matched that which was certified electronically. Boehringer Ingelheim voluntarily admitted a breach of Clause 14.1.

Boehringer Ingelheim submitted that following review of the job bags it changed its approval process and communicated this to staff to prevent a reoccurrence of this breach of the Code.

Boehringer Ingelheim was asked to provide the Authority with any further comments in relation to the requirements of Clauses 9.1 and 14.1.

### RESPONSE

Boehringer Ingelheim submitted that it had conducted a full review of a sample of approximately 275 hard copy job bags and found 103 which did not comply with the supplementary information to Clause 14.1. All of these job bags had been correctly certified in Zinc and in each case there was no difference between the final electronic copy and the physical item. However, Boehringer Ingelheim accepted that these job bags did not comply with the Code.

Boehringer Ingelheim stated that to correct the issue it had:

1 Immediately issued a deviation to the existing standard operating procedure (SOP) and now required a physical certificate to be attached to the printed material. The importance of correct certification had been communicated to the business.

2 Instituted a process for hard copy job bags to be checked before materials were used.

3 Instituted an interim secondary check by the healthcare compliance function before archiving hard copy job bags.

4 Instituted quarterly monitoring of a sample of job bags, including hard copy job bags.

With regard to Clause 9, Boehringer Ingelheim submitted that by not ensuring that this final action in the certification process took place, it acknowledged that it had not maintained high standards in this instance.

### PANEL RULING

The Panel noted that Boehringer Ingelheim, in its initial letter to the Authority, had referred to 'a number' of promotional job bags which showed that the final printed copy of the material had not been checked to ensure that it matched the previously approved final electronic version to which no subsequent amendments would be made. The Panel was disappointed that the company had not revealed

the extent of the matter at the outset; over 1 in 3 of a sample of nearly 275 job bags were affected (103). The problem appeared to be widespread. Nonetheless, Boehringer Ingelheim had subsequently checked the material and found that in all cases the final form matched that which had been electronically approved. However, the Code required the printed material to be checked against the electronic copy before use and this had not happened in a sizeable proportion of cases. A breach of Clause 14.1 was ruled. The Panel considered that the failure to certify the final printed form of the material meant that high standards had not been maintained; a robust certification procedure underpinned self-regulation. A breach of Clause 9.1 was ruled. The Panel noted that once it knew of the error, Boehringer Ingelheim had taken steps, including amending its SOP, to ensure that final printed copies of material were certified in future.

**Complaint received** **6 July 2016**

**Case completed** **8 August 2016**

**CASES AUTH/2855/7/16 and AUTH/2856/7/16**

# PHARMACIST v BOEHRINGER-INGELHEIM AND LILLY

## Promotion of Abasaglar

**A pharmacist submitted a complaint about an email which was sent to a nurse in the clinical commissioning group (CCG) and stated that following an update to the NHS Sunderland CCG formulary, Abasaglar (insulin glargine), Europe's first biosimilar insulin glargine was now available to prescribe. The complainant stated that Abasaglar was not on the Sunderland Joint Formulary. The email was issued by Boehringer Ingelheim and Eli Lilly and Company.**

**The detailed response from Boehringer Ingelheim and Lilly is given below.**

**The Panel noted that the email with the subject heading 'Biosimilar insulin glargine is approved for use in NHS Sunderland CCG' was sent to primary care prescribers and referred to an update to the NHS Sunderland CCG formulary. There did not appear to be an NHS Sunderland CCG formulary as stated in the email. Given that Abasaglar was on the Sunderland CCG guideline but not on the Sunderland Joint Formulary it considered that irrespective of which took precedence it was misleading to state that the product was on the Sunderland CCG formulary. The Panel thus ruled a breach of the Code as acknowledged by the companies.**

A pharmacist submitted a complaint about an email (Ref UK/GLA/00177) advertising Abasaglar (insulin glargine) issued by Boehringer Ingelheim and Eli Lilly and Company Limited.

The email (dated 5 July 2016) was sent to a nurse in the clinical commissioning group (CCG) and stated that following an update to the NHS Sunderland CCG formulary, Abasaglar, Europe's first biosimilar insulin glargine was now available to prescribe.

### COMPLAINT

The complainant stated that Abasaglar was not on the Sunderland Joint Formulary.

When writing to Boehringer Ingelheim and Lilly the Authority asked them to consider the requirements of Clause 7.2 of the Code.

### RESPONSE

Boehringer Ingelheim and Lilly each submitted identical responses on behalf of the Boehringer Ingelheim and Eli Lilly Diabetes Alliance (the Alliance).

The Alliance stated that the email at issue was part of an email campaign to inform primary care health professional's within CCGs (where Abasaglar was approved on the local formulary) that Abasaglar was now approved by the local formulary and available to prescribe. The health professionals from these CCGs were selected for the email campaign in collaboration with a third party which held an up-to-date database of health professionals agreeing to receive emails in this way. A list of the CCGs to whom the email was sent was provided.

The objectives were to raise the awareness of health professionals who were practising in CCGs where Abasaglar was available on formulary, of the efficacy of Abasaglar and its cost compared to Lantus (insulin glargine, Sanofi). Each area's email was localised by showing the name of the CCG, the formulary status of Abasaglar and the annual Lantus sales in that CCG.

The email was certified in the final form as a template with another CCG as an example. The additional instructions on and the information for the email campaign flow for individual CCGs where Abasaglar was on the formulary were provided.

The Alliance stated that its investigation found that in December 2015, NHS Sunderland CCG published guidelines on prescribing hypoglycaemic agents for adult patients with type 2 diabetes. These guidelines included, and as of 20 July 2016 still included, Abasaglar as a treatment option for type 2 diabetes patients. The Alliance pointed out that the Sunderland CCG guidelines were issued by Sunderland CCG and were different from the Sunderland Joint Formulary although the joint formulary website's home page had a link to the guidelines recommending Abasaglar but Abasaglar was not on the Sunderland Joint Formulary.

The email campaign in Sunderland started on 5 July 2016. On 6 July the Alliance was notified by a pharmacist in Sunderland CCG that Abasaglar was not on the Sunderland Joint Formulary. The Alliance stated that an immediate investigation was launched.

The Alliance accepted that the information in the email describing Abasaglar being on the NHS Sunderland CCG formulary was wrong as it did not reflect the actual status of Abasaglar in Sunderland CCG. The Alliance therefore accepted this was in breach of Clause 7.2 of the Code.

The Alliance submitted that it had taken immediate corrective measures. The Abasaglar campaign was halted until the full investigation was completed and a corrective email was issued to all those emailed in Sunderland which included an apology for any confusion caused.

### PANEL RULING

The Panel noted that the NHS Sunderland guideline ('Prescribing of Hypoglycaemic Agents for Adult Patients with Type 2 Diabetes: Sunderland') stated that Abasaglar was now available, it was biologically similar in action to Lantus and that other biosimilar preparations would follow. Biosimilar insulin was

only to be used in new patients and patients with suboptimal control where a review of therapy was being considered. Patients should not be rountinely switched between brands.

The Panel noted that according to a presentation about the email campaign Lilly key account managers were responsible for providing information about the status of Abasaglar on CCGs' formularies.

The Sunderland Joint Formulary website stated that this consisted of medicines recommended by the Joint Formulary Committee in consultation with consultants, GPs and other prescribers. This formularly was supported by Sunderland CCG, City Hospital Sunderland and Northumberland Tyne and Wear NHS Foundation Trust. The Alliance stated that Abasaglar was not listed on the Sunderland Joint Formulary.

The Panel noted that the email with the subject heading 'Biosimilar insulin glargine is approved for use in NHS Sunderland CCG' was sent to primary care prescribers and referred to an update to the NHS Sunderland CCG formulary. The Panel was unsure which took precedence, the Sunderland Joint Formulary or the Sunderland CCG guideline. There did not appear to be an NHS Sunderland CCG formulary as stated in the email. Given that Abasaglar was on the Sunderland CCG guideline but not on the Sunderland Joint Formulary it considered that irrespective of which took precedence it was misleading to state that the product was on the Sunderland CCG formulary. The Panel thus ruled a breach of Clause 7.2 as acknowledged by The Alliance.

**Complaint received** **8 July 2016**

**Cases completed** **11 and 12 August 2016**

CASE AUTH/2857/7/16

# ANONYMOUS, NON CONTACTABLE v DAIICHI-SANKYO

## Promotional activities and call rates

**An anonymous non-contactable complainant raised four issues about the promotional activities and call rates by Daiichi-Sankyo UK.**

**The complainant alleged that market access consultants at Daiichi-Sankyo were sending emails to customers without prescribing information.**

**The complainant provided email correspondence between a market access consultant and a pharmacist from an NHS foundation trust in which a regional patient information leaflet was discussed.**

**The first email from the market access consultant referred to a change of role and his/her new role working on edoxaban (Daiichi-Sankyo's product Lixiana) and an error in a new oral anti-coagulant (NOAC) patient information regarding the need to take rivaroxaban (Bayer's product Xarelto) with food. The pharmacist's reply stated that the document had been updated. The next email from the market access consultant asked for a revised copy and confirmation that a new drug chart in the hospital contained three NOACs but not edoxaban (Daiichi- Sankyo's product Lixiana). The pharmacist sent the updated leaflet and stated that drug charts were outside his/her remit but that there was ongoing work on a unified chart for the region and that it would be best to liaise with pharmacists on a trust-by-trust basis.**

**The detailed response from Daiichi-Sankyo is given below.**

**The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure stated that anonymous complaints would be accepted, but that like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant could not be contacted for more information.**

**The Panel examined the emails provided by the complainant. The Panel noted the market access consultant's concern that the guidance stated 'This document doesn't cover the need to take rivaroxaban with food as has generalised for all NOACs as below… The medication can be taken with or without food and should be swallowed whole with water'. A link to the rivaroxaban SPC was provided and the relevant section which stated 'The tablets are to be taken with food' was included in the email.**

**The Panel noted that it was not clear from the emails which doses were being referred to, it appeared from the summary of product characteristics (SPC) that rivaroxaban 10mg and 2.5mg could be taken with or without food whereas rivaroxaban 15mg and 20mg had to be taken with food. Although the Panel was concerned about the provision of the information, particularly due to the lack of clarity about the dose, it did not consider that the lack of prescribing information was a breach of the Code as alleged. The email did not require certification. The Panel did not consider that there had been a failure to maintain high standards on the points alleged. No breaches of the Code were ruled.**

**The Panel noted the generality of the allegations. Daiichi-Sankyo had provided a selection of emails from its staff. The Panel did not consider that the complainant had demonstrated on the balance of probabilities that promotional emails were being sent by Daiichi-Sankyo market access consultants without the requisite prescribing information. No breaches of the Code were ruled.**

**The complainant alleged that new staff members were doing validation examinations before any product training. A hospital sales manager was referred to by name.**

**The Panel noted Daiichi-Sankyo's submission that the named individual, had passed the ABPI Medical Representatives Examination. The hospital manager was, according to Daiichi-Sankyo, trained on the Lixiana SPC and not required or expected to promote to customers.**

**The Panel did not consider that the complainant had established on the balance of probabilities that the training of the named individual was in breach of the Code. It thus ruled no breaches of the Code.**

**The complainant alleged that the market access staff were insisting on doing promotional calls alongside medical liaison scientist (MLS) appointments. Medical liaison scientists refused to do this, an example of a named individual refusing to do so was given.**

**The Panel noted Daiichi-Sankyo's submission that joint calls had not been made by market access consultants and medical liaison scientists. One market access consultant had requested such a meeting but it appeared from an email to a customer that '…MSLs can't do joint calls with market access because of compliance'. The market access consultant had suggested to the customer that he/she and the MSL came to the pharmacy at the same time. The MSL would '…spend some time on his own with you answering the questions you have around the data and leave'. The market access consultant would then 'see you all to finish in a separate call at the end just to sense check next steps for our support, which shouldn't take long. This is good in a way because I can show you the patient material available and discuss what else you may need'.**

**The Panel considered that the arrangements as set out in the email might be seen as similar to the market access staff doing promotional calls alongside MSL appointments as alleged. In this regard the Panel noted that the market access consultant would arrive with the MSL. The MSL would see the health professional separately and then leave. The Panel was concerned about the arrangements but did not consider that the complainant had proven his/her complaint on the balance of probabilities. No breaches of the Code including Clause 2 were ruled.**

**The complainant explained that Daiichi-Sankyo had reduced geographical areas and therefore reduced the target list. The company had introduced healthcare outcomes manager's call rate of three per day/contact rate four per day, hospital call rate four per day/contact six per day. The company had threatened performance improvement plans and disciplinaries if staff did not achieve those rates. In some areas this would mean calling on target customers in excess of six times in one year and sometimes as many as ten.**

**The Panel noted there was no definition of call or contact rates in the materials provided by Daiichi-Sankyo nor were the relevant requirement of the Code clearly referred to. It could, of course, be perfectly possible for Daiichi-Sankyo staff to meet the expected call and contact rates depending on the total number of prescribers on the territory. These had recently been reduced due to the reduced geographical areas. There was no evidence that representatives had over-called but the expected rates had not been clearly defined and thus were not clearly distinguished nor had they been placed in the context of the limitations in the relevant supplementary information. The Panel ruled a breach of the Code. In the Panel's view such omissions meant that on the balance of probabilities the briefing materials indirectly advocated a course of action which would be likely to breach the Code. A breach of the Code was ruled.**

An anonymous non-contactable complainant submitted a complaint about the promotional activities and call rates by Daiichi-Sankyo UK Limited. The complainant raised four issues.

Daiichi-Sankyo was disappointed that one of its employees had reported an issue to the PMCPA. Daiichi-Sankyo encouraged employees to report issues to their line manager and operated a confidential whistle blowing line. Daiichi-Sankyo submitted that even with two recent restructures, it had introduced processes to ensure continuous compliant conduct of its business without compromising on safety and training of staff.

**1 Emails to customers**

**COMPLAINT**

The complainant alleged that market access consultants at Daiichi-Sankyo were sending emails to customers, including emails in which competitor information was referred to without prescribing information attached.

The complainant provided email correspondence between a market access consultant and a pharmacist at an NHS foundation trust, in which a regional patient information leaflet was discussed.

The first email from the market access consultant referred to a change of role and her new role working on edoxaban (Daiichi-Sankyo's product Lixiana) and an error in a new oral anti-coagulant (NOAC) patient information regarding the need to take rivaroxaban (Bayer's product Xarelto) with food. The pharmacist replied stating that the document had been updated. The next email from the market access consultant asked for a revised copy and confirmation that there was a new drug chart in the hospital containing three NOACs but not edoxaban (Daiichi-Sankyo's product Lixiana). The pharmacist sent the updated leaflet and stated that drug charts were outside his/her remit but that he/she thought there was ongoing work on a unified chart for use in the region. It would be best to liaise with pharmacists on a trust-by-trust basis.

When writing to Daiichi-Sankyo in relation to this allegation, the Authority asked it to consider the requirements of Clauses 4.1, 9.1 and 14.1.

**RESPONSE**

Daiichi-Sankyo submitted that its policy was that all promotional material sent to customers had to be certified in line with the Code and its standard operating procedure (SOP). This included emails. Emails to customers were only transactional in nature. Daiichi-Sankyo had a specific scheme for customers that opted in to promotional emails, the content of these emails were certified and centrally managed. Daiichi-Sankyo submitted that the email exchange mentioned in the complaint was a specific exchange regarding a NOAC patient information leaflet developed by the regional NHS foundation trust. There was also a question asked about the drug charts and their inaccuracy. Neither of these emails were promotional and related to documents that would otherwise be inconsistent with the most up-to-date information. The market access consultant had been working with internal colleagues on this project but was the contact with the lead pharmacist.

Daiichi-Sankyo submitted that the market access consultant initially contacted the pharmacist in June 2016 to highlight inaccuracies within the NOAC patient information leaflet relating to rivaroxaban and advice that was inconsistent with the summary of product characteristics (SPC). As no response was received, a director followed up by email. A response was received. The pharmacist confirmed that the document had been updated and thanked the market access consultant for his/her input. The market access consultant followed up the outstanding issue relating to drug charts and his/her final communication was to the internal team as the regional documents were considered of national importance. The email exchange was project specific and consistent with the Code, not promotional.

Daiichi-Sankyo submitted that it reviewed emails sent from the market access consultants to

customers and provided copies. It denied breaches of Clauses 4.1, 9.1 and 14.1.

**PANEL RULING**

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure stated that anonymous complaints would be accepted, but that like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant could not be contacted for more information.

The Panel examined the emails provided by the complainant. The Panel noted that the market access consultant had raised a concern about the content of the NOAC guidance with regard to rivaroxaban stating 'This document doesn't cover the need to take rivaroxaban with food as has generalised for all NOACs as below … The medication can be taken with or without food and should be swallowed whole with water'. A link to the rivaroxaban SPC was provided and the relevant section which stated 'The tablets are to be taken with food' was included in the email.

The Panel noted the definition of promotion at Clause 1.2 and did not consider that this exchange amounted to promotion of any Daiichi-Sankyo medicine and thus did not require prescribing information. Companies should be careful if staff were commenting on competitor products such references should comply with the Code, particularly Clause 7. It was not clear from the emails which doses were being referred to, it appeared from the SPC that rivaroxaban 10mg and 2.5mg could be taken with or without food whereas rivaroxaban 15mg and 20mg had to be taken with food. Although the Panel was concerned about the provision of the information, particularly due to the lack of clarity about the dose, it did not consider that the lack of prescribing information was a breach of Clause 4.1 as alleged. The Panel ruled no breach of Clause 4.1. The email did not require certification and no breach of Clause 14.1 was also ruled. The Panel did not consider that there had been a failure to maintain high standards on the points alleged and no breach of Clause 9.1 was ruled.

The Panel noted the generality of the allegations. Daiichi-Sankyo had provided a selection of emails from its staff. The Panel did not consider that the complainant had demonstrated on the balance of probabilities that promotional emails were being sent by Daiichi-Sankyo market access consultants without the requisite prescribing information. No breach of Clauses 4.1, 14.1 and consequently 9.1 was ruled.

**2 Training**

**COMPLAINT**

The complainant alleged that there was an issue with new staff members doing their validation examinations before having had any product training. A hospital sales manager was referred to by name.

When writing to Daiichi-Sankyo in relation to this allegation, the Authority asked it to consider the requirements of Clauses 9.1 and 15.1.

**RESPONSE**

Daiichi-Sankyo submitted that the specific training schedule for market access consultants was put in place whereby basic training would be delivered to all newcomers as befitted their role with comprehensive training courses to be held roughly four times a year. Daiichi-Sankyo noted that it was undergoing another restructure and two dedicated training heads were being introduced.

Daiichi-Sankyo submitted that the arrival of market access consultants corresponded to the former period, all were trained on the disease area, products and were validated. With regard to the named individual, Daiichi-Sankyo submitted that he/she recently joined the organisation (a copy of the ABPI Medical Representative Examination certificate was provided). The role was a hospital manager and therefore he/she was not required or expected to promote to customers (a copy of the job profile was provided).

The training record for the hospital sales manager was provided, training on company policies and procedures and on the product SPC had been provided. Given the scope of the role he/she would not be expected to participate in a full validation examination as per a hospital sales representative.

Daiichi-Sankyo denied breaches of Clauses 9.1 and 15.1.

**PANEL RULING**

The Panel noted its general comments above about the status of the complainant and burden of proof.

The Panel noted Daiichi-Sankyo's submission that the named individual had passed the ABPI Medical Representatives Examination. The individual was a hospital manager and, according to Daiichi-Sankyo, was trained on the Lixiana SPC and was not required or expected to promote to customers.

The Panel noted that the general requirements in Clause 16.1 of the Code that staff concerned in any way with the preparation or approval of materials or activities covered by the Code must be fully conversant with the Code and the relevant laws and regulations.

The Panel did not consider that the complainant had established, on the balance of probabilities, that the training of the named individual was in breach of the Code. It thus ruled no breach of Clause 15.1 and consequently no breach of Clause 9.1 of the Code.

**3 Market access consultants'/medical liaison scientists' calls**

**COMPLAINT**

According to the complainant the market access staff were insisting on doing promotional calls alongside

medical liaison scientist (MLS) appointments. Medical liaison scientists refused to do this, an example of a named individual refusing to do so was given but market access said it would happen.

When writing to Daiichi-Sankyo in relation to this allegation, the Authority asked it to consider the requirements of Clauses 2, 3.1, 3.2 and 9.1.

**RESPONSE**

Daiichi-Sankyo noted that the complainant made it clear that joint calls by the market access consultants and the medical liaison scientists had not happened. Daiichi-Sankyo reassured the Panel that there was no plan for it to occur even in its new restructured organisation. Daiichi-Sankyo reiterated that medical access consultants were new to the organisation and in the case of the market access consultant, he/she had requested such a meeting which was turned down by the named medical liaison scientists. The company submitted that there was evidence to support its position.

In addition to training upon arrival, the medical department regularly conducted training to show how best to interact with medical liaison scientists and details were provided.

Daiichi-Sankyo denied breaches of Clauses 3.1, 3.2, 9.1 and 2.

**PANEL RULING**

The Panel noted its general comments on point 1 about the status of the complainant and the burden of proof.

The Panel noted Daiichi-Sankyo's submission that joint calls had not been made by market access consultants and medical liaison scientists. One market access consultant had requested such a meeting but it appeared from an email to a customer that '…MSLs can't do joint calls with market access because of compliance'. The market access consultant had suggested to the customer that she and the MSL came to the pharmacy at 2pm. The MSL would '…spend some time on his own with you answering the questions you have around the data and leave'. The market access consultant would then 'see you all to finish in a separate call at the end just to sense check next steps for our support, which shouldn't take long. This is good in a way because I can show you the patient material available and discuss what else you may need'.

The Panel considered that the arrangements as set out in the email might be seen as similar to the market access staff doing promotional calls alongside MSL appointments as alleged. In this regard the Panel noted that the market access consultant would arrive with the MSL. The MSL would see the health professional separately and then leave. The Panel was concerned about the arrangements but did not consider that the complainant had proven his/her complaint on the balance of probabilities. No breach of Clauses 3.1, 3.2, 9.1 and 2 were ruled.

**4 Call rates and targets**

**COMPLAINT**

The complainant explained that Daiichi-Sankyo had reduced geographical areas for the healthcare outcomes managers and hospital representatives and therefore the target list was reduced. The company had introduced healthcare outcomes manager's call rate of three per day/contact rate four per day, hospital call rate four per day/contact six per day. The company had threatened performance improvement plans and disciplinaries if staff did not achieve those rates. In some areas this would mean calling on target customers in excess of six times in one year and sometimes as many as ten.

When writing to Daiichi-Sankyo in relation to this allegation, the Authority asked it to consider the requirements of Clauses 15.4 and 15.9.

**RESPONSE**

Daiichi-Sankyo submitted that it operated a key account management model, specifically meaning that representatives were to see whichever health professionals in the key account that were involved in the decision on the use of the product be they prescriber or non-prescriber. There was therefore no limit on the number of customers within the account that could be seen. There was no bonus payment linked to activity.

With regard to allegations made by the complainant that Daiichi-Sankyo had been performance managing individuals that had not been meeting required overall performance standards, Daiichi-Sankyo noted that the complainant specifically cited activity and although not a primary consideration with respect to performance for the purpose of refuting the allegation it provided the following information.

Daiichi-Sankyo stated that the historic activity levels within the company (the average per day was provided) were considered suboptimal. As a consequence a verbal briefing was given to the entire sales team in June 2016 that that level of activity along with other performance measures was unacceptable. At no time was there any direction to breach the guidance in relation to the Code or that there would be a reduced target list of customers. Daiichi-Sankyo acknowledged that geographies had changed but was not consistent with a reduction in the target list of customers seeing as the group of customers that were appropriate to be informed about the product spread across multiple specialities ie cardiology, stroke, care of the elderly, general medicine, GP, pharmacy medicines management etc.

As a follow-up to the briefing, each representative also had a one to one discussion with his/her manager to address specific performance issues and where expectations were set. Daiichi-Sankyo accepted that performance improvement plans had been put in place prior to further action where overall individual performance had not been acceptable. That was not linked specifically to achievement of activity rates as alleged.

**PANEL RULING**

The Panel noted its general comment above at point 1 about the status of the complainant and the burden of proof.

The Panel noted that Clause 15.4 of the Code required representatives to ensure that the frequency, timing and duration of calls on, *inter alia*, health professionals, together with the manner in which they were made, did not cause inconvenience. The supplementary information to that clause stated, *inter alia*, that companies should arrange that intervals between visits did not cause inconvenience. The number of calls made on a doctor or other prescriber by a representative each year should normally not exceed three on average excluding attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up a report of an adverse reaction. Thus although a representative might speculatively call upon or proactively make an appointment to see a doctor or other prescriber three times on average in a year, the annual number of contacts with that health professional might be more than that. The supplementary information to Clause 15.4 also advised that when briefing representatives companies should distinguish clearly between expected call rates and expected contact rates. Targets must be realistic and not such that representatives breached the Code in order to meet them. Clause 15.9 stated that briefing material must not advocate directly or indirectly any course of action which would be likely to lead to a breach of the Code.

The Panel noted Daiichi-Sankyo's expectations regarding activity standards. Hospital representatives were expected to do four face-to-face calls and six contacts per day. Market access staff were expected to do three face-to-face calls and four contacts per day. There was no definition of call or contact rates in the materials provided by Daiichi-Sankyo nor were the relevant requirement of the Code clearly referred to. It could, of course, be perfectly possible for Daiichi-Sankyo staff to meet the expected call and contact rates depending on the total number of prescribers on the territory. These had recently been reduced due to the reduced geographical areas. There was no evidence that representatives had over-called but the expected rates had not been clearly defined and thus were not clearly distinguished nor had they been placed in the context of the limitations in the relevant supplementary information. The Panel ruled a breach of Clause 15.4. In the Panel's view such omissions meant that on the balance of probabilities the briefing materials indirectly advocated a course of action which would be likely to breach the Code. A breach of Clause 15.9 was ruled.

**Complaint received** **1 July 2016**

**Case completed** **30 September 2016**

# HEALTH PROFESSIONAL v ASTRAZENECA

## Alleged promotion to the public

**A complainant who described him/herself as a health professional with a named clinical commissioning group (CCG) stated that he/she was amazed that at a meeting which took place in May 2016 at a named restaurant, the pharmaceutical companies' exhibitions were in full view of the public. The restaurant was open to the public and the area where the stands were was visible from outside.**

**The detailed response from AstraZeneca appears below.**

**The Panel noted AstraZeneca's submission that the doors to the private room, which was signposted for the meeting, were closed and there was a manned registration desk inside. From photographs provided by AstraZeneca, the doors to the private room appeared to be frosted glass with a small band of unfrosted glass in the middle. The Panel noted AstraZeneca's submission that the lower sections of the windows between the restaurant and the private room were also frosted as was the lower section of the windows in the private room to the outside of the restaurant and there were net curtains on the full length of these windows. From the room plan provided by AstraZeneca the exhibition stands were positioned by the windows at the far end of the meeting room, facing into it; even if the door was open, it appeared that the stands would not be visible without stepping into the room and turning to the right.**

**The Panel noted that the complainant, as set out in the introduction to the Constitution and Procedure, had the burden of proving his/her complaint on the balance of probabilities. The complainant had provided little information and no evidence to support his/her position.**

**The Panel considered that the fact that a restaurant was open to the public at the same time that a meeting was held in a private room was not, in itself, unacceptable. Appropriate precautions needed to be taken particularly if the public was able to see into a room where prescription-only medicines were being advertised. The Panel considered that there was no evidence that prescription-only medicines had been promoted to the public. Further, there was no evidence to support the allegation that AstraZeneca's stand was in full view of the public and visible from the outside. The Panel did not consider that a prescription only medicine had been promoted to the public. No breaches of the Code were ruled including Clause 2.**

A complainant who described him/herself as a health professional with a named clinical commissioning group (CCG) complained about a meeting which took place in May 2016 at a named restaurant.

**COMPLAINT**

The complainant attended the meeting and stated that he/she was amazed that the pharmaceutical companies' exhibitions were in full view of the public. The complainant explained that there were a number of companies present including AstraZeneca. The restaurant was open to the public and the area where the stands were was visible from outside.

When writing to AstraZeneca the Authority asked it to respond in relation to the requirements of Clauses 2, 9.1 and 26.1.

**RESPONSE**

AstraZeneca submitted that the meeting described by the complainant was a local health professional group meeting held two months prior to the complaint. Approximately twenty-four health professionals attended.

AstraZeneca had a stand and two representatives present at the meeting, representative A and representative B. AstraZeneca interviewed both representatives. AstraZeneca also reviewed the information contained within its customer relationship management system regarding the meeting. AstraZeneca stated that it had made several unsuccessful attempts to speak to the health professional responsible for organising the meeting.

The group was a newly established group of general practitioners and secondary care doctors. The meeting in May was its first meeting. The person organising the meeting contacted representative A to discuss AstraZeneca supporting the meeting. This communication was mainly by telephone but emails between the meeting organiser and representative A were provided. The agenda consisted of a fifteen minute introduction to the association, a forty-five minute presentation on 'Chronic obstructive pulmonary disease (COPD) - updates and new management techniques' and thirty minutes for a practical group session, case studies and questions and answers. The agenda also contained the statement 'This is a medical educational meeting and open to health care professionals only'.

Representative A was familiar with the venue and he/she considered that the restaurant was suitable to hold the meeting as it was centrally located, had car parking facilities and a private function room. Representative B was not involved in arranging AstraZeneca's attendance at the meeting but was invited by representative A. Representative A knew that the restaurant would be open to the public on the evening of the meeting but was informed that the event would take place in the private room.

AstraZeneca had a Duaklir Genuair (aclidinium/formoterol) promotional stand at the meeting

and the representatives used the Duaklir Genuair interactive detail aid and leavepiece with health professionals. Before the presentations at the meeting commenced, the stand was taken down.

AstraZeneca stated that its stand was located in the private room, along with the stands of the other pharmaceutical companies supporting the meeting. The meeting organisers decided where the stands were placed inside the private room but the exact location of the AstraZeneca stand in relation to the other pharmaceutical company stands was decided by the AstraZeneca representatives. Both representatives were comfortable that the location of the stand meant that it was not visible to members of the public.

Restaurant staff directed anyone entering the restaurant to the meeting room or to the public area of the restaurant, as appropriate. Outside the room was a sign that it was for the meeting; the doors to the room were closed and there was a registration desk inside, next to the door, manned by the meeting organisers. The doors to the private room were frosted glass with a small band of unfrosted glass in the middle. The lower section of the windows between the restaurant area and the private room were also frosted so people in the restaurant could not see into the meeting room from the general dining area. Both representatives stated that the restaurant was very quiet when they passed through it to access the private room. The windows in the private room to the outside of the restaurant were also frosted on their lower section and they also had full length net curtains. As the venue was on a roundabout there was no public pathway outside that area.

AstraZeneca provided an approximate plan of the venue, photographs of the private room and submitted as the stand and material were located in the private room, they were not visible to the public as alleged.

Both representatives at the meeting knew that promotion to the public constituted a breach of the Code. This was detailed in AstraZeneca's Ethical Interactions Standard Operating Procedure. Furthermore, AstraZeneca's salesforce meetings compliance guide stated that exhibition stands and AstraZeneca material must not be displayed where they might be viewed by the public, non-health professionals, or people who did not attend the meeting.

AstraZeneca stated that it took its compliance with the pharmaceutical industry codes of practice very seriously; its stand and material were displayed to health professionals in a private room and not in full view of the public as alleged. AstraZeneca thus denied breaches of Clauses 26.1, 9.1 and 2 of the Code.

**PANEL RULING**

The Panel examined the agenda provided to AstraZeneca by the meeting organiser. This version of the agenda named three pharmaceutical companies in addition to AstraZeneca and another company named by the complainant. The case preparation manager had taken the matter up with each company named by the complainant.

The Panel noted that Clause 26.1 stated, *inter alia*, that prescription only medicines must not be advertised to the public. The Panel noted AstraZeneca's submission that the doors to the private room, which was signposted for the meeting, were closed and there was a manned registration desk inside the room next to the door. From the photographs provided by AstraZeneca, and seemingly taken when the restaurant and room were empty, the doors to the private room appeared to be frosted glass with a small band of unfrosted glass in the middle. The Panel noted AstraZeneca's submission that the lower section of the windows between the restaurant and the private room were also frosted. The Panel estimated from the photographs supplied that the frosting went to about head height; above the frosting the glass was clear. The Panel further noted AstraZeneca's submission that the lower sections of the windows in the private room to the outside of the restaurant were also frosted and there were net curtains on the full length of these windows. From the room plan provided by AstraZeneca the exhibition stands were positioned by the windows at the far end of the meeting room, facing into it; even if the door was open, it appeared that the stands would not be visible without stepping into the room and turning to the right.

The Panel noted that the complainant, as set out in the introduction to the Constitution and Procedure, had the burden of proving his/her complaint on the balance of probabilities. The complainant had provided little information and no evidence to support his/her position.

The Panel considered that the fact that a restaurant was open to the public at the same time that a meeting was held in a private room was not, in itself, unacceptable. Appropriate precautions needed to be taken particularly if the public was able to see into a room where prescription-only medicines were being advertised. In the circumstances, the Panel considered that there was no evidence that prescription-only medicines had been promoted to the public. Further, there was no evidence to support the complainant's allegation that AstraZeneca's stand was in full view of the public and visible from the outside. The Panel did not consider that a prescription only medicine had been promoted to the public. No breach of Clauses 26.1, 9.1 and 2 was ruled.

**Complaint received** **25 July 2016**

**Case completed** **8 September 2016**

**CASE AUTH/2860/7/16** ***NO BREACH OF THE CODE***

# HEALTH PROFESSIONAL v CHIESI

## Alleged promotion to the public

**A complainant who described him/herself as a health professional with a named clinical commissioning group (CCG) stated that he/she was amazed that at a meeting which took place in May 2016 at a named restaurant, the pharmaceutical companies' exhibitions were in full view of the public. The restaurant was open to the public and the area where the stands were was visible from outside.**

**The detailed response from Chiesi appears below.**

**The Panel noted Chiesi's submission that there was signage for the meeting immediately outside the entrance and upon entering the meeting room there was a manned registration desk. Frosting and drapes on the external windows restricted any view from the outside and there was limited pedestrian footfall given the restaurant's location on a main road. The Panel noted Chiesi's submission that the internal windows and doors were covered by the same opaque film which covered the external window. The exhibition stands were positioned on the far right hand side of the room with the back panels facing the external windows and the promotional panels facing inwards. The room plan provided by Chiesi showed the exhibition stands positioned by the windows at the far end of the meeting room; even if the door was open, it appeared that the stands would not be visible without stepping into the room and turning to the right.**

**The Panel noted that the complainant, as set out in the introduction to the Constitution and Procedure, had the burden of proving his/her complaint on the balance of probabilities. The complainant had provided little information and no evidence to support his/her position.**

**The Panel considered that the fact that a restaurant was open to the public at the same time that a meeting was held in a private room was not, in itself, unacceptable. Appropriate precautions needed to be taken particularly if the public was able to see into a room where prescription-only medicines were being advertised. The Panel considered that there was no evidence that prescription-only medicines had been promoted to the public. Further, there was no evidence to support the allegation that Chiesi's stand was in full view of the public and visible from the outside. The Panel did not consider that a prescription only medicine had been promoted to the public. No breaches of the Code were ruled including Clause 2.**

A complainant who described him/herself as a health professional with a named clinical commissioning group (CCG) complained about a meeting which took place in May 2016 at a named restaurant.

**COMPLAINT**

The complainant attended the meeting and stated that he/she was amazed that the pharmaceutical companies' exhibitions were in full view of the public. The complainant explained that there were a number of companies present including Chiesi. The restaurant was open to the public and the area where the stands were was visible from outside.

When writing to Chiesi the Authority asked it to respond in relation to the requirements of Clauses 2, 9.1 and 26.1.

**RESPONSE**

Chiesi explained that the meeting was an independent, third party meeting which it supported through the purchase of stand exhibition space only. Based on the last available agenda sent to Chiesi, the meeting was also supported by three other named pharmaceutical companies. The Chiesi representative at the meeting confirmed that those three companies also exhibited at the meeting.

The meeting was organised and run by a local group of health professionals which held regular meetings for its members. Chiesi was initially made aware of the meeting verbally and received a follow up email providing further information and an outline agenda. The cost of exhibition space was detailed in the outline agenda.

As stated on the agenda the meeting started with arrival and registration at 18:30 and closed at 20:30 with refreshments. The meeting was held at the restaurant, an events venue which provided private meeting and function rooms. The Chiesi representative confirmed that the venue was commonly used due to location, cost and facilities. The venue was recognised locally for holding such business functions and was widely used by other sectors such as the local council and fire service.

Chiesi submitted that its local representative, the only Chiesi attendee, had previously visited the venue in a personal capacity. The representative was familiar with the layout and the ability to hold a meeting in a private function room away from the public. The organising health professional, via an events support person, had a conversation regarding where the meeting was to be held and the representative, with his/her local knowledge, was satisfied that the meeting complied with the relevant Chiesi standard operating procedure.

The representative originally entered the meeting into the customer relationship management (CRM) system in April and completed a meeting qualification form along with other material associated with the meeting ie agenda, as the first

stage of compliance due diligence. The meeting qualification form and any other relevant material associated with the meeting were sent electronically via the CRM to the regional business manager (RBM) for approval. The RBM had to review the meeting and all attachments in the CRM and either approve, reject or reject with further amends needed. That was the second compliance due diligence check. The meeting qualification form specifically required the representative to check that the meeting was away from the public. It specifically asked 'Will the stand be in a private area that is not open to the general public?' and the representative responded 'yes'. When asked for any additional venue information, the representative responded 'the venue is regularly used by pharma companies; only invited visitors have access to the exhibition room, no public access'.

The RBM on checking the associated documents with the entry in the CRM system noticed that the agenda was incomplete as Chiesi's name was omitted from the declaration of involvement at the foot of the agenda. The Chiesi representative then contacted the events support person to ask for the correction to be made. The events support person sent a revised agenda. The representative then forwarded the final agenda to the RBM and uploaded it into the CRM system for approval. A summary of the CRM history in relation to the meeting was provided as were copies of all material on display at the meeting.

Chiesi submitted that as part of the investigation, it visited the venue unannounced, in July, in order to verify the representative's account and to photograph the venue and room used for the meeting.

The venue was on a main road next to a busy roundabout, limiting pedestrian footfall; there were two floors with private function/meeting rooms available on both. The meeting was held on the ground floor and a sketch of the ground floor layout (not to scale) was provided.

Chiesi submitted that it would be extremely difficult for anyone to see into the meeting room through the external windows. The windows had a plastic opaque film covering the bottom half (frosting) and also had drapes restricting any view from the outside. A series of photographs taken in July showing the external and internal views of the meeting room and venue were provided.

Chiesi explained that on entering the building, the meeting room was on the far right. It could only be accessed by double doors which opened inwards into the room. There were windows visible internally to the restaurant. The internal windows and doors were covered by the same opaque film which covered the external windows. Whilst the doors to the meeting room were visible from the main public restaurant, they were in the far corner, not in mainstream view.

On the evening of the meeting the representative arrived at around 18:00, approximately thirty minutes before the start of the meeting. Prior to erecting the stand, he/she ensured that the door was closed and that both the meeting organiser and restaurant staff were positioned to ensure that the public could not enter the room. To help matters there was signage for the meeting immediately outside the entrance and on entering the meeting room there was a registration desk which was staffed by a member of the group. All delegates were asked to sign an attendance register. A photograph of the attendance register was provided to the representative after the meeting.

Chiesi submitted that its representative, together with the other pharmaceutical representatives, erected his/her promotional stand for the start of the meeting (18:30). All representatives collapsed their stands, boxed away any promotional material and left the meeting room before the formal presentations started.

Chiesi submitted that the exhibition stands were positioned side by side and on the far right hand side of the room with the back panels facing the external windows. The promotional panels faced into the room. Given the position of the stands it would be impossible to see them from either inside or outside the restaurant. After completing its investigation, Chiesi did not believe the exhibition stands were visible to the public.

Chiesi submitted that its representative knew that the restaurant would be open to the public on the evening, however the restaurant had limited footfall/ customers with the main purpose of the business being hosting events. The meeting took place in a private room away from the public.

Having fully investigated the complaint, Chiesi submitted that the meeting was held in accordance with the company's standard operating procedure and the Code. The meeting room was conducive to host a third party educational meeting and the due diligence carried out before the meeting ensured compliance. No evidence was found that the meeting was visible to the public at any stage.

In conclusion, Chiesi strongly denied that there had been any promotion to the public, that it had failed to maintain high standards and that it had reduced confidence in the industry or had brought the industry into disrepute. Chiesi thus denied any breach of Clauses 26.1, 9.1 and 2.

**PANEL RULING**

The Panel examined the latest agenda provided to Chiesi by the meeting organiser. This version of the agenda named three pharmaceutical companies in addition to Chiesi. The case preparation manager had taken the matter up with each company named by the complainant.

The Panel noted that Clause 26.1 stated, *inter alia*, that prescription only medicines must not be advertised to the public. The Panel noted Chiesi's submission that there was signage for the meeting immediately outside the entrance and upon entering the meeting room there was a registration desk manned by a member of the medical group. The Panel further noted Chiesi's submissions that frosting and drapes

on the external windows restricted any view from the outside and that there was limited pedestrian footfall given the restaurant's location on a main road next to a busy roundabout. From the photographs provided by Chiesi, and seemingly taken when the restaurant and room were empty, the doors to the private room appeared to be frosted glass with a small band of unfrosted glass in the middle. The Panel noted Chiesi's submission that the internal windows and doors were covered by the same opaque film which covered the external window. The Panel estimated from the photographs supplied that the frosting went to about head height; above the frosting the glass was clear. The Panel noted Chiesi's submission that the exhibition stands were positioned on the far right hand side of the room with the back panels facing the external windows and the promotional panels facing inwards. The room plan provided by Chiesi showed the exhibition stands positioned by the windows at the far end of the meeting room; even if the door was open, it appeared that the stands would not be visible without stepping into the room and turning to the right.

The Panel noted that the complainant, as set out in the introduction to the Constitution and Procedure, had the burden of proving his/her complaint on the balance of probabilities. The complainant had provided little information and no evidence to support his/her position.

The Panel considered that the fact that a restaurant was open to the public at the same time that a meeting was held in a private room was not, in itself, unacceptable. Appropriate precautions needed to be taken particularly if the public was able to see into a room where prescription-only medicines were being advertised. In the circumstances, the Panel considered that there was no evidence that prescription-only medicines had been promoted to the public. Further, there was no evidence to support the complainant's allegation that Chiesi's stand was in full view of the public and visible from the outside. The Panel did not consider that a prescription only medicine had been promoted to the public. No breach of Clauses 26.1, 9.1 and 2 was ruled.

**Complaint received** **26 July 2016**

**Case completed** **8 September 2016**

# ANONYMOUS, NON CONTACTABLE v BRISTOL-MYERS SQUIBB

## Promotion of Daklinza

**An anonymous, non-contactable complainant complained about the promotion of Daklinza (daclatasvir dihydrochloride) by Bristol-Myers Squibb Pharmaceuticals at a conference in June 2016. Daklinza was indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.**

**The complainant explained that the event covered all aspects of care including not only clinicians but also non-clinical and non-NHS delegates from many parts of the care community including the public providing volunteer care work.**

**The complainant attended a presentation in the keynote lecture theatre on day 1 that was open to all delegates including non-medical attendees and the public. A promotional piece for Daklinza, a prescription only medicine was put on every seat in the room. The complainant stated that such behaviour brought the industry into discredit as the meeting room was for education and not promotion. The complainant alleged that a prescription only medicine had been promoted to the public. This was a very serious breach.**

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

**The Panel noted that the Code applied to the promotion of medicines to members of the United Kingdom health professions and to other relevant decision makers. 'Other relevant decision makers' was defined as particularly those with an NHS role who could influence in any way the administration, consumption, prescription, purchase, recommendation, sale, supply or use of any medicine but who were not health professionals.**

**The Panel noted that the conference was a specialist meeting not aimed at the public. It was described as an integrated care conference that enabled health and social care professionals to forge new partnerships and productive ways of working. It brought the NHS and local authorities together and represented the largest annual gathering of commissioners, providers and their suppliers. Delegates were described as senior managers or higher although this was not necessarily clear from examination of the delegate list. It was made up of four events and was described as a trade-only event targeting health professionals and more specifically NHS payors and commissioners. The Panel noted that the show also targeted those involved in home and residential care. The marketing to potential delegates was stated to be via professional trade publications and websites. Consumers and direct patients were refused entry.**

**The leavepiece at issue was put on the seats for the attendees of five non sponsored sessions. The sessions were identified in advance and agreed verbally between Bristol-Myers Squibb and the organisers where it was considered that stakeholders would find the information regarding the National Institute for Health and Clinical Excellence (NICE) approval relevant.**

**The Panel noted that the complainant was concerned about the distribution of the leavepiece at a presentation on day 1 in the keynote lecture theatre. The presentation was not identified by the complainant. The Panel noted that the leavepiece was circulated at three presentations on that day, one in the keynote debate theatre 'Integrated care, what does it actually mean?' and the others in the Future of Clinical Commissioning Theatre and Medicines Optimisation Congress. The Panel noted the status of the audience on day 1 as set out in the delegate list. Although the Panel queried some of those listed, the majority were either health professionals or had a professional interest in healthcare such that, on the balance of probabilities, they appeared to meet the definition of other relevant decision makers. The nature of the identified sessions on day 1 would be clearly aimed at health professionals and/or other relevant decision makers. The Panel noted that the complainant had to establish that the attendees of the presentation that he/she referred to were other than health professionals and other relevant decision makers. The complainant had submitted no evidence in this regard. The Panel did not consider that providing the leavepiece to the attendees at the sessions on day 1 constituted advertising a prescription only medicine to the public as alleged. The Panel therefore ruled no breach of the Code.**

**The Panel was concerned that the relevant sessions for distribution of the material were agreed verbally; there were no written details about the arrangement or confirmation of any compliance assessment. Nonetheless, given its ruling of no breach, the Panel did not consider that Bristol-Myers Squibb had failed to maintain high standards nor had it brought discredit upon the pharmaceutical industry and ruled no breach of the Code including Clause 2.**

An anonymous, non-contactable complainant complained about the promotion of Daklinza (daclatasvir dihydrochloride) by Bristol-Myers Squibb Pharmaceuticals Limited at a 2-day conference in June 2016.

Daklinza was indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

**COMPLAINT**

The complainant explained that the event which he/she attended both days covered all aspects of care including not only clinicians but also non-clinical

and non-NHS delegates from many parts of the care community including the public providing volunteer care work.

The complainant explained the format was a large exhibition hall with a variety of lecture theatres strategically located to provide health education in different formats. These educational sessions were non promotional.

The complainant attended a presentation in the keynote lecture theatre on day 1 that was open to all delegates including non-medical attendees and the public. Bristol Myers Squibb representatives deposited a promotional piece for Daklinza which was a prescription only medicine on every seat in the room.

The complainant stated that such behaviour brought the industry into discredit as the meeting room was for education and not promotion. The complainant alleged that not all of the delegates attending lectures were medical and therefore a prescription only medicine had been promoted to the public. The complainant stated that it was clear that all promotion should take place away from the delivery of education and that promotion to the public was not permitted under the Code and as a result it was a very serious breach.

When writing to Bristol-Myers Squibb the Authority asked it to respond to Clauses 2, 9.1 and 26.1 of the Code.

**RESPONSE**

Bristol-Myers Squibb disputed the notion that it promoted to members of the public and denied a breach of Clause 26.1 and also refuted the alleged breaches of Clauses 9.1 and 2.

Bristol-Myers Squibb submitted that the event referred to by the complainant was the largest national integrated care conference in the UK, with nearly 9000 attendees and over 350 sponsors/ exhibitors present. Promotion of the event by the organisers was limited to communication channels targeted at health professionals and other relevant decision makers as follows:

- BMJ
- Guidelines in Practice (a primary care journal that contained numerous advertisements for prescription medicines)
- Doctors.net (an online platform exclusively for doctors)
- Primary Care Today
- National Association of Primary Care
- NHS Clinical Commissioners
- Practice Index.

Bristol-Myers Squibb stated that its sponsorship included stand space and a symposium slot. However, after the contract was entered into, Bristol-Myers Squibb decided not to progress with the symposium due to company prioritisation, and instead was offered the opportunity to have the leavepiece distributed to the presentations mentioned below.

Bristol-Myers Squibb sponsored this event with the strategic objective to continue to maintain engagement directly with healthcare policy makers and budget holders. Prior to committing to sponsoring the event, Bristol-Myers Squibb referred to the guidance on the organisers' website, and verbal communication between the Virology Access and Partnership lead with the organisers. It was this information, upon which the company relied in order to make an informed judgement that the conference was indeed targeted at NHS commissioners, health professionals and other relevant decision makers. This was recently re-confirmed by the organisers.

As detailed above, the intended audience for the conference was health professionals and other relevant decision makers. The delegate lists provided by the organisers upon request for each session confirmed that. There were several other pharmaceutical companies that also exhibited at this conference. A list was provided. Attendance attracted twelve self-accredited CPD points.

Daklinza was a prescription only treatment regimen for chronic hepatitis C (HCV), more specifically Genotype 3 (GT 3) patients. The National Institute for Health and Care Excellence (NICE) recently granted approval for Daklinza in November 2015, and the decision was implemented in February 2016. This was significant news for NHS budget holders, as HCV treatment would have a considerable impact on their budgets which would be funded centrally by NHS England rather than local budgets. In this context, it was customary for Bristol-Myers Squibb to appropriately communicate the recent NICE approval to health professionals and other relevant decision makers.

The Daklinza leavepiece was certified for promotional use in February 2016. It was a 4-sided flyer that focused on the recent NICE approval (in the public domain via the NICE website) with the appropriate associated clinical information:

- Page 1 clearly stated the fact of the NICE approval.
- Page 2 showed the NICE guidance for each patient type in a tabulated form.
- Page 3 contained three simple messages indicating the key features of the product to understand the context of the NICE guidance.
- Page 4 was the prescribing information.

In that context, Bristol-Myers Squibb submitted that the leavepiece was appropriate for prescribers and other relevant decision makers.

Bristol-Myers Squibb recognised that the specific presentations might not be directly associated with hepatitis C, however, all attendees were expected to be health professionals and other relevant decision makers, who typically had multiple therapy area responsibilities.

Six Bristol-Myers Squibb employees attended the conference and details were provided.

1200 copies of the leavepiece were delivered to the conference organisers, and as instructed verbally by the Bristol-Myers Squibb Virology

Access and Partnership team. The leavepiece was distributed by organisers onto seats in five lecture theatres, as follows:

- Keynote debate theatre at noon on day 1 – Integrated care, what does it actually mean
- Keynote debate theatre at noon on day 2 – Reshaping hospital care for the 21st century: moving from institutions to networks and chains
- Future of clinical Commissioning at noon on day 1 – Commissioning for improved mental health
- Future of clinical Commissioning at noon on day 2 – Countdown to accountable care in East Sussex
- Medicines Optimisation theatre at noon on day 1 – Pharmacy in care homes, a model for implementation and system change.

The audience for each of these sessions consisted of health professionals and other relevant decision makers. In collaboration with the organisers, Bristol-Myers Squibb selected sessions where the two jointly believed stakeholders would find the information contained in the leavepiece regarding NICE approval relevant.

Bristol-Myers Squibb submitted that it was extremely concerned to hear of the very serious allegations which had been levied against it. Bristol-Myers Squibb was a company that did all that it could to comply with the spirit and letter of the Code. Bristol-Myers Squibb submitted that it made comprehensive checks to ensure that the audience at the conference and in particular the presentations at which the leavepiece was distributed consisted of health professionals and other relevant decision makers, and it was given the assurances it was looking for. Bristol-Myers Squibb therefore refuted the allegation of a breach of Clause 26.1.

Further, Bristol-Myers Squibb submitted that it was diligent in its checks, and conducted itself in a manner which constituted the highest standards, which it expected of itself and in line with expected industry standards and the Code. Bristol-Myers Squibb therefore failed to see how it could be found to be in breach of Clauses 9.1, or 2.

**PANEL RULING**

The Panel noted that Clause 1.1 stated that the Code applied to the promotion of medicines to members of the United Kingdom health professions and to other relevant decision makers.

'Other relevant decision makers' was defined in Clause 1.5 as particularly those with an NHS role who could influence in any way the administration, consumption, prescription, purchase, recommendation, sale, supply or use of any medicine but who were not health professionals.

The Panel noted that the conference was a specialist meeting not aimed at the public. It was described as an integrated care conference that enabled health and social care professionals to forge new partnerships and productive ways of working. It was the only show to bring NHS and local authorities together and represented the largest annual gathering of commissioners, providers and their suppliers. Every delegate was described as a senior manager or higher although this was not necessarily clear from examination of the delegate list. It was made up of four events; details were provided. It was described by the media agency which organised the event as a trade only event targeting health professionals and more specifically NHS payors and commissioners. The Panel noted that the show also targeted those involved in home and residential care. The marketing to potential delegates was stated to be via professional trade publications and websites. Consumers and direct patients were refused entry.

The leavepiece at issue was put on the seats for the attendees of five non sponsored sessions. The sessions were identified in advance and agreed verbally between Bristol-Myers Squibb and the organisers where it was considered that stakeholders would find the information regarding NICE approval relevant.

The Panel noted that the complainant was concerned about the distribution of the leavepiece at a presentation on day 1 in the keynote lecture theatre. The presentation was not identified by the complainant. The Panel noted that the leavepiece was circulated at three presentations on 29 June one in the keynote debate theatre 'Integrated care, what does it actually mean?' and the others in the Future of Clinical Commissioning Theatre and Medicines Optimisation Congress. The Panel noted the status of the audience on day 1 as set out in the delegate list. Although the Panel queried some of those listed, the majority were either health professionals or had a professional interest in healthcare such that, on the balance of probabilities, they appeared to meet the definition of other relevant decision makers as set out in Clause 1.5. The nature of the identified sessions on day 1 would be clearly aimed at health professionals and/or other relevant decision makers. The Panel noted that the complainant, who was anonymous and non-contactable, bore the burden of proof and thus had to establish that the attendees of the presentation that he/she referred to were other than health professionals and other relevant decision makers. The complainant had submitted no evidence in this regard. The Panel did not consider that providing the leavepiece to the attendees at the sessions on day 1 constituted advertising a prescription only medicine to the public as alleged. The Panel therefore ruled no breach of Clause 26.1.

The Panel was concerned that the relevant sessions for distribution of the material were agreed verbally; there were no written details about the arrangement or confirmation of any compliance assessment. Nonetheless, given its ruling of no breach of Clause 26.1, the Panel did not consider that Bristol-Myers Squibb had failed to maintain high standards nor had it brought discredit upon the pharmaceutical industry. Thus the Panel ruled no breach of Clauses 9.1 and 2.

**Complaint received** **29 July 2016**

**Case completed** **2 September 2016**

**CASE AUTH/2867/8/16**

# ANONYMOUS, NON-CONTACTABLE EX-EMPLOYEE V UCB

## Representatives' call rates

**An anonymous, non-contactable ex-employee complained about UCB's representatives' call rates and stated that he/she had left the company because of constant pressure to carry out an excessive number of calls. The complainant understood that the Code allowed only three unsolicited calls on a doctor or other prescriber per year. However, representatives were told by their managers to get around that by either not recording calls or by recording them incorrectly. The complainant was sure that records for the last three years would confirm that representatives were asked to only report calls as solicited. The complainant asked the Authority to request the briefing material that distinguished between expected call rates and contact rates as well as a copy of the call recording and reporting procedure because whilst at UCB he/she never received written instructions on the application of the Code as required.**

**The complainant alleged that by asking representatives to pursue a course of action that was contrary to the Code, UCB had failed to maintain high standards and if not checked, such practices could potentially bring disrepute to the pharmaceutical industry.**

**The detailed response from UCB is given below.**

**The Panel noted that the complainant was anonymous and non-contactable. Like all complaints, anonymous complaints were judged on the evidence provided. The complainant bore the burden of proving his/her complaint on the balance of probabilities.**

**The Panel noted that an email dated 29 April 2016 from a regional sales manager instructed recipients to 'As a "rule of thumb" consider an average of 2 face to face calls with these [target] customers in [tertial two] ie May' (tertial two was a four month period starting in May). The email referred to planning to see some target customers more than that, and others less but that the author would envisage recipients seeing 10-20% of customers with only one call in that time and would expect to see a percentage that the recipient would plan to see more than twice. A supplementary email exchange clarified that the field force needed to plan at least two calls per tertial (4 month period) and that for most target customers that would mean there would be four calls planned for the remainder (8 months) of the year.**

**The Panel disagreed with UCB's submission that 'calls' referred to in the email correspondence encompassed solicited and unsolicited calls; calls solicited by a health professional could not be planned by a representative. In the Panel's view, planned face-to-face calls implied unsolicited 1:1 calls initiated by the representative. The Panel further noted that representatives were asked to 'think of the emphasis of the detailing around each indication' for each planned call. In that regard the Panel thus did not consider that 'calls' in the emails referred to group meetings and the like; in the Panel's view 'detailing' implied 1:1 interactions. The Panel considered that as the email correspondence encouraged representatives to plan to call on some customers at least four times over the next 8 months, it advocated a course of action which was likely to lead to a breach of the Code. A breach of the Code was ruled.**

**The Panel noted UCB's submission that mandatory induction training for representatives covered call rates and that frequent and regular briefings on call rates were unnecessary as call rates did not feature on the UCB UK agenda. A pre-results awareness campaign briefing for Exxelerate, approved in March 2016, referred to iKAMs delivering a slide deck in 60 customer calls by the end of April (35 working days). A footnote on the same slide stated that call frequency must comply with the Code but gave no further indication that if a health professional had only recently been called upon, another call within a short time period might not be appropriate. The training slides provided did not refer to call frequency. The Panel further noted that one representative per region would be rewarded with a generous amount to spend on a meal if they, *inter alia*, recorded 60 customer calls associated with this campaign. In the Panel's view this might encourage representatives to book calls with health professionals, even if those individuals had only been seen recently, just so they could reach the target of 60 calls.**

**The Panel noted UCB's submission that a recent internal report identified that individuals had called more than three times on a particular customer over a given period (unspecified). The Panel noted UCB submitted that in most cases there was a misunderstanding and lack of clarity on interpreting the definitions of unsolicited calls. The Panel queried this noting UCB's submission that for those that chose to classify the calls a definition of 'solicited' and 'unsolicited' calls appeared on the screen. The Panel considered that there was evidence to show that, on the balance of probabilities, some representatives had called on some customers more than three times in a year. The Panel ruled a breach of the Code.**

**The Panel noted its comments and rulings above and considered that UCB had failed to maintain high standards. A breach of the Code was ruled. The Panel did not consider that in the circumstances a breach of Clause 2, which was a sign of particular censure and reserved for such, was warranted and no breach of that clause was ruled.**

An anonymous, non-contactable complainant who described him/herself as a former UCB

representative, complained about UCB's representatives' call rates.

**COMPLAINT**

The complainant stated that he/she had left UCB because he/she and other colleagues were always under pressure to carry out an excessive number of calls. The complainant understood that the Code allowed only three unsolicited calls on a doctor or other prescriber per year. However, representatives were told by their managers to get around that by either not recording calls or by incorrectly recording calls. The complainant asked the Authority to request call records for all representatives, including those that had left the company, for the last three years with a breakdown of solicited vs unsolicited calls per doctor or prescriber per year; the complainant was sure that there would be a higher number of unsolicited calls per year and the ratio of solicited to unsolicited calls for the same representative for a particular health professional would be high in many cases confirming his/her allegation that representatives were asked to only report calls as solicited. The complainant asked the Authority to also request the briefing material that distinguished between expected call rates and contact rates as stated in the Code as well as a copy of the call recording and reporting procedure because whilst at UCB he/she never received written instructions on the application of the Code as required.

The complainant alleged that by asking representatives to pursue a course of action that was contrary to the Code, UCB had failed to maintain high standards and if not checked, such practices could potentially bring disrepute to the pharmaceutical industry.

When writing to UCB, the Authority asked it to consider the requirements of Clauses 2, 9, 15.4 and 15.9 of the Code.

**RESPONSE**

UCB stated that its strategy was underpinned by providing and demonstrating patient benefits and value. Call rates for representatives formed no part of that strategy or its execution.

UCB submitted that throughout its organisation the component units, operations, functions and practices were all configured around the patient value objectives. The UK sales teams fell under one of the patient value units.

UCB submitted screenshots from its intranet which detailed its organisations, vision and priorities and patient values strategy that illustrated that underlying theme, its 'top down' endorsement and the permeation into all activities. As a further illustration, an internal document on 2015 objectives demonstrated that both strategically and operationally there was no component of call rates.

With respect to representatives' call rates, the emphasis was firmly on quality, content and prioritisation. UCB submitted that in the 2015 objectives document, although achieving target sales was well represented, there was a well-documented objective of 'delivery of value to patients'. Additionally, under one of the objectives the ingredients of call/event monitoring (using the in-house customer relationship management (CRM) system implemented globally across UCB), ABPI compliance in all activities and training, were all in place. The elements of quality and content were specifically represented in another objective.

Another 2016 incentive plan in a different therapy area did not refer to call rates. It referred to alignment to patient value principles and had no eligibility related to call rates.

The approach for sales calls was defined periodically according to the prevailing campaign. Briefings to the sales team gave guidance on the feature above. An example was EXXELERATE: Pre-results Awareness Briefings for key account managers (iKAMs) and healthcare partnership managers (HPMs) a copy of which was provided. Objectives and contents for calls were set with a clear statement to comply with Clause 15.4.

UCB stated that given the above, it was implicit and actually the case that call rates were not part of representatives' incentives (both qualification and payment).

Achieving set objectives defined performance and formed a large part of the incentive payments. The 2015 objectives had no mention of call rates and in that regard UCB provided details of one representative's 2015 performance objectives. Moreover, the redacted 2016 performance objectives documents for a representative, his/her regional manager and business head consistently showed no inclusion of call rates. This consistency was continued across another therapy unit.

UCB submitted that there was no downward pressure or instruction from managers to achieve high call rates that would exceed limits set by the Code.

Briefing documents were generally produced by the sales managers or business heads alongside marketing. The lack of any manager or senior level endorsement of breaching the call rate limits set by the Code was generally supported by clear corporate strategy that was very visible for all employees.

Specific support for the same was from documents that were always endorsed by senior managers. Each territory produced a cycle plan to cover a four month period. Such plans were viewed, reviewed and approved by managers (screenshot of redacted cycle plan provided).

UCB submitted copies of the supporting documents.

UCB submitted that all representatives had mandatory, face-to-face Code training including on call rates, during the early induction period on joining UCB. There was additional mandatory training on modules provided by a third party. The training was tracked and training records were available for each representative.

When there were Code updates, the mandatory training was again implemented. The most recent of these was 'ABPI Code of Practice 2016: what's different?' In addition, all representatives were supplied with a printed copy of the latest version of the Code.

UCB stated that it was mandatory to record calls and events in the CRM system which had functionality to collect call information and generate reports. Pertinent features related to call and contact rates were:

- All representatives were trained on the system during their induction. The user manual was online with no distribution of paper copies.
- Although a globally used system, there was a dedicated UK 'user champion' who representatives could call with any problems. The same dedicated resource was well versed with generating reports and metrics, alongside specific individuals who were able to train others.
- Logging of calls, contacts and events was mandatory. This was supported in the individual's objectives and the accompanying evaluation of performance
- In logging a call there was an optional field of classifying it as solicited, unsolicited or none. This field was not mandatory as the tool was global and not all UCB territories required that information.
- For those that chose to classify the calls a definition of solicited and unsolicited calls appeared on the screen. An unsolicited call was defined as 'one without any request from the customer and initiated by the representative'
- The system had functionality to highlight any customers who had more than 3 calls over a given period. This facility was routinely performed by a UCB employee who left the organisation. A report was generated recently and representatives were interviewed by a senior manager where there had been more than three calls on any particular customer. UCB submitted that in most cases there was a misunderstanding and lack of clarity on interpreting the definitions of unsolicited calls. Such a conclusion was derived only after discussing all calls individually and the associated background to each.

Alongside the CRM system, each sales territory had a cycle plan logged on the system that focused on the overall objectives for the territory. The planned calls for a customer to deliver on objectives were defined and viewed and approved by the manager. Any alarming call rates would precipitate necessary correction of plans.

In conclusion UCB stated that mandatory training at the outset once a representative joined UCB clearly covered call rates. However, call rates were not a feature in strategy or tactics throughout the organisation from a corporate standpoint down to a local level territory plan. Indeed, the overwhelming themes were patient value, call quality, content and prioritisation. Sales representatives' incentives had no reference to call rates. With those points taken both individually and collectively it would be entirely disingenuous for managers to drive call rates. The documentation cited wholly supported this view.

UCB submitted that, within the above context, frequent and regular briefings on call rates were unnecessary as call rates did not feature on the UCB UK agenda.

UCB therefore submitted that appropriately focussed high standards had been set and maintained, briefings and support provided as necessary and there had been no breaches of Clauses 9.1, 15.4 and 15.9. The organisation had developed and clearly communicated the strategy and implemented it in compliance of the Code without a breach of Clause 2.

**FURTHER INFORMATION FROM UCB**

UCB stated that the very comprehensive response above was compiled using information and documentation collated from across relevant UCB departments in the British Isles and Ireland. However, an email came to UCB's attention in preparing for an internal meeting in August. UCB submitted that the human resources department was reviewing material and documentation reviewed during the matter including the internal email communications (copies provided) which given the similarity to the subject of this case, UCB submitted for completeness and for consideration alongside the response above.

The email was between a regional sales manager (RSM) and the sales team reporting to him/her between April and June 2016. The RSM had sent an email including the team's target lists and asked the team to consider an average of 2 face-to-face calls per customers in T2 ie May which he/she stated would work out to 2 per tertial or once every two months. The RSM stated that he/she expected that there were some customers that the team would plan to see more and expected to see a percentage that the team planned to see more than twice. When a sales team member queried if the expectation was that they would have 4 calls planned for the majority of their target customers for the remainder of the year, the RSM replied 'Correct'.

UCB summarised the context and provided appropriate clarification as follows:

- Cycle plans (captured in the CRM system) were planning tools used by the field force to think ahead and document forthcoming territory activity.
- UCB used a term to describe a priority group of customers identified in terms of a perceived positioning on an adoption ladder priority for UCB products, in a particular therapy area. The term therefore defined a list of priority customers with whom the sales team should seek to have interactions; the representatives were directed to see both this priority group of customers and those not in the priority group. However, they should ensure that they saw a higher proportion of the priority customers than the non–priority ones.
- The term 'calls' in this email chain referred to all type of contact; solicited and unsolicited entered into cycle plans within the CRM system.
- For further clarity UCB submitted that 'calls' recorded in the CRM system were completed and could be categorised as solicited, unsolicited or none. 'Calls' planned in cycle plans (captured also

in the CRM system) were the numbers inserted for the total contacts planned/envisaged, taking into account the forthcoming activities in totality eg face-to-face calls, group meetings and speaker meetings
- After inserting the planned numbers of calls/ contacts, the next step was for the manager to review individual plans submitted by each representative in the territory.

Given the email communication combined with the above explanatory notes, UCB acknowledged that the clarity in communication between the RSM and representative could have been better, but that the overall context was not intended to breach the Code. UCB therefore maintained its position from its original response.

**PANEL RULING**

The Panel noted that the complainant was anonymous and non-contactable. Like all complaints, anonymous complaints were judged on the evidence provided. The complainant bore the burden of proving his/her complaint on the balance of probabilities.

The complainant referred to call record details over the past three years. Clause 15.4 of the 2016, 2015, 2014 and 2012 Codes required representatives to ensure that the frequency, timing and duration of calls on, *inter alia*, health professionals, together with the manner in which they were made, did not cause inconvenience. The supplementary information stated, *inter alia*, that companies should arrange that intervals between visits did not cause inconvenience. The number of calls made on a doctor or other prescriber by a representative each year should normally not exceed three on average excluding attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up a report of an adverse reaction. The supplementary information also advised that when briefing representatives companies should distinguish clearly between expected call rates and expected contact rates. Targets must be realistic and not such that representatives breached the Code in order to meet them. Clause 15.9 in the above Codes stated that briefing material must not advocate directly or indirectly any course of action which would be likely to lead to a breach of the Code.

The Panel noted that an email dated 29 April 2016 from a senior employee instructed recipients to 'As a "rule of thumb" consider an average of 2 face to face calls with these [target] customers in [tertial two] ie May' (tertial two was a four month period starting in May). The email referred to planning to see some target customers more than that, and others less but that the author would envisage recipients seeing 10-20% of customers with only one call in that time and would expect to see a percentage that the recipient would plan to see more than twice. A supplementary email exchange clarified that the field force needed to plan at least two calls per tertial (4 month period) and that for most target customers that would mean there would be four calls planned for the remainder (8 months) of the year.

The Panel disagreed with UCB's submission that 'calls' referred to in the email correspondence encompassed solicited and unsolicited calls; calls solicited by a health professional could not be planned by a representative. In the Panel's view, planned face-to- face calls implied unsolicited 1:1 calls 'without any request from the customer and initiated by the representative' as defined in the CRM system. The Panel further noted that representatives were asked to 'think of the emphasis of the detailing around each indication' for each planned call. In that regard the Panel thus did not consider that 'calls' in the emails referred to group meetings and the like; in the Panel's view 'detailing' implied 1:1 interactions. The Panel considered that as the email correspondence encouraged representatives to plan to call on some customers at least four times over the next 8 months, it advocated a course of action which was likely to lead to a breach of the Code. A breach of Clause 15.9 was ruled.

The Panel noted UCB's submission that mandatory induction training for representatives covered call rates and that frequent and regular briefings on call rates were unnecessary as call rates did not feature on the UCB UK agenda. A pre-results awareness campaign briefing for Exxelerate (ref UK/16CI0037), approved 3 March 2016, referred to iKAMs delivering the slide deck in 60 customer calls by the end of April (35 working days). A footnote on the same slide stated that call frequency must comply with Clause 15.4 but gave no further indication that if a health professional had only recently been called upon, another call within a short time period might not be appropriate. The training slides provided did not refer to call frequency. The Panel further noted that one representative per region would be rewarded with a generous amount to spend on a meal if they, *inter alia*, recorded 60 customer calls in the CRM system. In the Panel's view this might encourage representatives to book calls with health professionals, even if those individuals had only been seen recently, just so they could reach the target of 60 calls.

The Panel noted UCB's submission that a recent CRM system report identified instances where individuals had called more than three times on a particular customer over a given period (unspecified). The Panel noted that UCB had interviewed those representatives involved and submitted that in most cases there was a misunderstanding and lack of clarity on interpreting the definitions of unsolicited calls. The Panel queried this noting UCB's submission that for those that chose to classify the calls a definition of 'solicited' and 'unsolicited' calls appeared on the screen. The Panel considered that there was evidence to show that, on the balance of probabilities, some representatives had called on some customers more than three times in a year. The Panel ruled a breach of Clause 15.4.

The Panel noted its comments and rulings above and considered that UCB had failed to maintain high standards. A breach of Clause 9.1 was ruled. The Panel did not consider that in the circumstances a breach of Clause 2, which was a sign of particular censure and reserved for such, was warranted and no breach of that clause was ruled.

During the consideration of this case, the Panel was very concerned to note that, although recording calls in the CRM system was mandatory, UK representatives could choose whether they recorded those calls as 'solicited', 'unsolicited' or 'none'. The Panel queried why, given the importance of complying with the relevant requirements of the Code, UCB did not make recording the call type mandatory. In the absence of such recording it was unclear how UCB could be confident that its representatives complied with the relevant requirements of the Code. The Panel was also concerned to note that UCB considered that frequent and regular briefings on call rates were unnecessary because call rates did not feature on the UCB UK agenda. Irrespective of the UK agenda it was important for representatives to have clear instructions so as not to breach the Code. The Panel requested that UCB be advised of its concerns.

**Complaint received** **8 August 2016**

**Case completed** **11 October 2016**

**CASE AUTH/2870/8/16**

# VOLUNTARY ADMISSION BY JANSSEN

## Trevicta advertisements

**Janssen-Cilag voluntarily admitted breaches of the Code in relation to a number of Trevicta (paliperidone palmitate 3 monthly) journal advertisements placed during July and August 2016. Trevicta, a 3-monthly injection, was indicated for the maintenance treatment of schizophrenia in adults who were clinically stable on 1-monthly paliperidone palmitate injectable product.**

**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 Janssen.**

**Janssen explained that the advertisements were two page advertisements in which the prescribing information appeared overleaf, however the reference to where it could be found was missing, which was a breach of the Code. This was not picked up in the certification process.**

**Janssen submitted that the job bags had erroneously been uploaded into Zinc as digital job bags whereas the advertisements were in fact both digital and hard copy. This error meant that the journal advertisements were only electronically certified and not also certified in their final hardcopy form and so Janssen did not pick up on the missing prescribing information location reference. Janssen considered that the failure to certify the final form of the hardcopy advertisements also amounted to a breach of the Code.**

**The details submitted by Janssen are given below.**

**The Panel noted that the two page advertisements in question had prescribing information overleaf on the second page but the reference to where to find it was missing from the first page. A breach of the Code was ruled as acknowledged by Janssen.**

**The Panel noted Janssen's admission that the journal advertisements were only electronically certified and not also certified in their final hardcopy form. The Panel thus ruled a breach of the Code as acknowledged by Janssen.**

Janssen-Cilag Ltd voluntarily admitted breaches of the Code in relation to four Trevicta (paliperidone palmitate 3 monthly) advertisements (ref PHGB/XEP/0516/0022, PHGB/XEP/0516/0022a, PHGB/XEP/0516/0022b, and PHGB/XEP/0616/0015) which it placed during July and August 2016. Trevicta, a 3-monthly injection, was indicated for the maintenance treatment of schizophrenia in adult patients who were clinically stable on 1-monthly paliperidone palmitate injectable product.

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 Janssen.

**VOLUNTARY ADMISSION**

Janssen stated that the advertisements were all two page advertisements in which the prescribing information appeared overleaf; in July they were published in The Commissioning Review, the BMJ, Nurse Prescribing, Prescriber and the British Journal of Mental Health Nursing, in August they appeared in the British Journal of Psychiatry and Progress in Psychiatry.

Janssen stated that on 1 August its media buyer alerted the healthcare digital agency, which in turn alerted Janssen, that the reference to where the prescribing information could be found was missing from the journal advertisements listed above. The absence of the prescribing information location reference had unfortunately not been picked up in Janssen's copy approval and certification process. The prescribing information appeared overleaf in the four printed advertisements and Janssen admitted a breach of Clause 4.7. Janssen stated that it had elected to contact the PMCPA proactively about this incident and to date had not received any complaints from recipients of the journals nor fellow ABPI members.

After performing an internal review, Janssen found that the job type field was incorrect; the job bags had erroneously been uploaded into Zinc as digital job bags. The advertisements were in fact both digital and hard copy, rather than just digital as per the job bags submitted. Unfortunately, due to this error at the Zinc upload stage, the journal advertisements were only electronically certified and not also certified in their final hardcopy form. Although no changes were made to the advertisements from the electronic certification stage to the hardcopy stage, unfortunately it meant that Janssen also missed the opportunity to pick up on the missing prescribing information location reference at final hardcopy certification stage. Janssen considered that the failure to certify the final form of the hardcopy advertisements amounted to a breach of Clause 14.1.

Janssen stated that it had a clear copy approval process in place but during this process, steps were completed incorrectly. Following its review, Janssen was satisfied that it was an isolated incident of human error that occurred during the copy approval initiation stage, due to an incorrect job bag item field being selected in Zinc.

**Timelines**

1 August – Janssen was first made aware of the absence of a reference to the location of prescribing information on the advertisements in question by teleconference outside of working hours by its digital healthcare agency

Confirmation received in writing from its digital healthcare agency and proposed actions. Although an internal Janssen error, additional checks were agreed with the agency for implementation - moving forward the printers would schedule a colour proof for each advertisement that was printed so that both the digital healthcare agency and printers could see the positioning of the artwork and do a final check on the colour quality and content in final output format.

2 August –The job bags listed above were withdrawn from Zinc and cancelled.

New artwork was created under a successor job bag for the advertisements with a reference to the prescribing information location included

3 August – Copy of deletion reports received: Janssen's media buyer provided a copy of deletion reports from each of the journals that had received an advertisement without a reference to the prescribing information location, ensuring that it did not run the advertisements again without receiving new files first.

Janssen confirmed that the prescribing information included with the advertisements was correct and up-to-date therefore patient safety had not been compromised. Janssen had reminded all individuals involved of their responsibilities in the copy procedure process and the Code requirements related to two page advertisements when the prescribing information was located overleaf.

Janssen submitted that it took its responsibilities under the Code very seriously and deeply regretted the errors described above.

**RESPONSE**

Janssen submitted that it had no further comments in relation to the requirements of Clauses 4.7 and 14.1.

**PANEL RULING**

The Panel noted that Clause 4.7 stated that in the case of a printed journal advertisement where the prescribing information appeared overleaf, at either the beginning or the end of the advertisement, a reference to where it could be found must appear on the outer page of the other page of the advertisement in a type size such that a lower case 'x' was no less than 2mm in height. The Panel noted that the four advertisements in question placed in seven journals during July and August 2016 were two page advertisements in which the prescribing information appeared overleaf on the second page. The reference to where the prescribing information could be found as required by Clause 4.7 was missing from the first page and a breach of that Clause was ruled as acknowledged by Janssen.

The Panel noted that the supplementary information to Clause 14.1 stated that when certifying material where the final form was to be printed companies could certify the final electronic version of the item to which no subsequent amendments would be made. When such material was printed the company must ensure that the printed material could not be used until any one of the company's signatories had checked and signed the item in its final form. In such circumstances the material would have two certificates and both must be preserved. The Panel noted Janssen's admission that the journal advertisements were only electronically certified and not also certified in their final hardcopy form. The Panel thus ruled a breach of Clause 14.1 as acknowledged by Janssen.

**Complaint received** **10 August 2016**

**Case completed** **23 August 2016**

CASE AUTH/2871/8/16

# VOLUNTARY ADMISSION BY JANSSEN

## Pre-licence promotion

**Janssen-Cilag voluntarily admitted breaches of the Code as a Crohn's disease awareness campaign initiated and approved by the Janssen European team was used in the UK and amounted to pre-licence promotion.**

**The campaign consisted of an email sent on 2 June and images and news headline links made available to Gastroenterology members 29 June – 29 July.**

**The email was headed 'Developed under the direction and sponsorship of Janssen Pharmaceutical Companies' followed by 'Crohn's. Let's re-write their story'. The next heading was 'Relapse' where 'lapse' had been crossed out and 'mission' added ie 'Relapse' had been amended to 'Remission' followed by 'A disease with many unknowns, has many treatment challenges'. The email stated that there was no known cause or cure for Crohn's disease but with better understanding of the pathophysiology the ambition of treatment was to move from short-term symptom control to more targeted long term disease modification. There were high treatment failure rates with existing biological therapies (40% of patients did not respond to anti-tumour necrosis factor (TNF)). Patients needed more effective treatment options to improve overall disease management and optimise outcomes. The email then referred to the need to understand the disease pathway at the molecular level followed by 'Janssen has been working tirelessly to improve the way Crohn's is managed' and that the company was 'committed to discovering pioneering treatments for Crohn's disease'. Janssen introduced the first anti TNF in 1998 and continued to lead the way. It had expanded its research focus to include other targets now known to drive inflammation and autoimmune processes. Working with others Janssen was committed to developing new tailored therapeutic options 'in order to provide the right treatment for the right person in every part of the world'.**

**The email concluded with a box headed 'Learn more about Janssen's commitment to Crohn's management' with three links to the results of studies of ustekinumab in Crohn's Disease.**

**The last sentence below the references was 'This promotional communication is provided by [named third party]'.**

**The images and news headline links were made available to Gastroenterology members accessing the Medscape website; the alerts appeared adjacent to other news headlines at that time. During that period, the headline 'Remission: the goal for all patients with Crohn's disease ' followed by 'information from industry' were shown in three forms, desktop, news section and home page versions, to UK gastroenterologists. A link from the news headline took readers to the same email content 'Remission: Mapping new pathways for Crohn's disease treatment'.**

**Stelara (ustekinumab) was currently indicated for the treatment of moderate to severe plaque psoriasis and for the treatment of adult patients with psoriatic arthritis. Stelara did not yet have a licensed indication for the treatment of Crohn's disease. In November 2015 Janssen sought approval from the European Medicines Agency for this indication.**

**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 Janssen.**

**The detailed response from Janssen is given below.**

**The Panel noted that Janssen in Europe had emailed UK health professionals without the involvement of Janssen UK which had therefore not certified the materials. The email could also be accessed from advertisements which read 'Remission: the goal for all patients with Crohn's disease. Information from industry'. These advertisements were accessible to members of Medscape who were gastroenterologists.**

**The Panel noted that there appeared to be a serious error in that the relevant Janssen EMEA standard operating procedure (SOP) required materials to be sent to the local company for approval prior to use and this had not happened. Janssen UK submitted that this was due to human error. This appeared to the Panel to be conduct that fell short of competent care.**

**The Panel considered that the email was clearly promotional. It discussed the treatment of disease pathways of Crohn's disease and provided links to results of studies using Stelara for Crohn's Disease. It mentioned that Janssen was committed to discovering pioneering treatments for Crohn's disease and the need for more effective treatment options. Stelara was not indicated for Crohn's Disease. The advertisements were linked to the email and thus were also promotional. The Panel ruled a breach of the Code as the material was inconsistent with the Stelara summary of product characteristics (SPC) as acknowledged by Janssen UK. The material had not been certified and a breach of the Code was ruled as acknowledged by Janssen.**

**The Panel ruled that high standards had not been maintained in breach of the Code as acknowledged by Janssen UK. It considered that by promoting an unlicensed indication and failing to certify the material it brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2.**

Janssen-Cilag Ltd voluntarily admitted breaches of the Code as a Crohn's disease awareness campaign initiated and approved by the Janssen European team amounted to pre-licence promotion. The regional campaign in question was delivered to health professionals, including the UK and therefore Janssen-Cilag believed it might fall within the scope of the ABPI Code.

The campaign consisted of an email (Ref PHEM/STE/0116/0002d) sent on 2 June and images and news headline links made available to Gastroenterology members 29 June – 29 July.

The email was headed 'Developed under the direction and sponsorship of Janssen Pharmaceutical Companies' followed by 'Crohn's. Let's re-write their story'. The next heading was 'Relapse' where 'lapse' had been crossed out and 'mission' added ie 'Relapse' had been amended to 'Remission' followed by 'A disease with many unknowns, has many treatment challenges'. The email stated that there was no known cause or cure for Crohn's disease but with better understanding of the pathophysiology the ambition of treatment was to move from short-term symptom control to more targeted long term disease modification. There were high treatment failure rates with existing biological therapies (40% of patients did not respond to anti-tumour necrosis factor (TNF)). Patients needed more effective treatment options to improve overall disease management and optimise outcomes. The email then referred to the need to understand the disease pathway at the molecular level with details of cytokine activity including proinflammatory effector cytokines such as IFN, TNF and IL6. This was followed by 'Janssen has been working tirelessly to improve the way Crohn's is managed' and that the company was 'committed to discovering pioneering treatments for Crohn's disease'. Janssen introduced the first anti TNF in 1998 and continued to lead the way. It had expanded its research focus to include other targets now known to drive inflammation and autoimmune processes. Working with others Janssen was committed to developing new tailored therapeutic options 'in order to provide the right treatment for the right person in every part of the world'.

The email concluded with a box headed 'Learn more about Janssen's commitment to Crohn's management' with three links to the results of studies of ustekinumab in Crohn's Disease.

The last sentence below the references was 'This promotional communication is provided by [… named third party service].

The images and news headline links were made available to Gastroenterology members accessing the Medscape website; the alerts appeared adjacent to other news headlines at that time. During that period, the headline 'Remission: the goal for all patients with Crohn's disease ' followed by 'information from industry' were shown in three forms, desktop, news section and home page versions, to UK gastroenterologists. Clicking on the news headline took readers to the same email content 'Remission: Mapping new pathways for Crohn's disease treatment'.

Stelara (ustekinumab) was currently indicated for the treatment of moderate to severe plaque psoriasis and for the treatment of adult patients with psoriatic arthritis. Stelara did not yet have a licensed indication for the treatment of Crohn's disease. In November 2015 Janssen sought approval from the European Medicines Agency for this indication.

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 Janssen.

**VOLUNTARY ADMISSION**

Janssen stated that the Janssen European business was affiliated to Belgium-based Janssen Pharmaceuticals NV, not part of the Janssen UK legal entity. One of the European approvers for the campaign material resided in the UK, although he/she was neither employed by Janssen in the UK, nor based at Janssen UK headquarters.

While the primary focus of the campaign was on the role of the disease pathway in the progression and management of the condition, it incorporated click-through functionality which included links to on-line publications of previous legitimate scientific exchange relating to Stelara in Crohn's Disease, namely:

a) United European Gastroenterology Week (UEGW) congress summary report, featuring a brief summary of the Stelara Crohn's Disease phase 3 induction study, UNITI-2.

b) European Crohn's and Colitis Organisation (ECCO) congress abstract relating to a retrospective observation study of Stelara in Crohn's Disease patients in French tertiary centres.

c) Gastroenterology.org abstract of the Stelara Crohn's Disease phase 3 maintenance study, IM-UNITI.

During the course of regular monthly teleconferences with Janssen European colleagues in April and May 2016, a UK manager was informed that a disease awareness campaign was among a range of materials being developed in preparation for launch in the fourth quarter of 2016. However, in keeping with usual practice, the expectation was that these campaign materials would be rolled out to the local operating companies for amendments and copy approval to be completed prior to any local implementation. There was no further communication detailing the intended extent or time line for European roll-out of the campaign or that UK clinicians were to be included, nor were materials and references supplied to the UK team to enable local approval and certification prior to use.

On the evening of 15 August, the UK marketing team received an email from a European manager reporting that the disease awareness campaign had been deployed and it was then evident that the campaign had been sent to gastroenterologists practising in the UK. On further investigation Janssen-Cilag identified the following:

- An email (subject header 'Remission: Mapping new pathways for Crohn's disease treatment') was sent on 2 June 2016 by the third party, to its registered members. These included gastroenterologists in the UK, who had all opted-in to receive promotional email communications. 2,303 emails were sent to UK health professionals, of which 414 were opened. There were only 4 occasions on which health professionals followed the links to the additional information which pertained to Stelara specifically.

- During a 30-day period from 29 June to 29 July 2016 the three 'news headline' images were available to Gastroenterology members accessing the Medscape environment, adjacent to other news headlines at the time. Customers clicking on this news headline were taken to the same email content outlined above. During that period, the following headlines were shown to 1,042 UK gastroenterologists, of whom 345 accessed the email content. There were only 10 occasions on which health professionals followed the links to the additional information which pertained to Stelara specifically.

The number of click throughs from the email and alert to one of the three studies was provided and were 4 or fewer.

Janssen submitted that the above activities represented promotion outside the particulars listed in the Stelara summary of product characteristics (SPC) (Clause 3.2) failure to maintain high standards at all times (Clause 9.1) and failure to obtain UK certification of promotional materials distributed to UK health professionals (Clause 14.1 – albeit the European team had completed its regional certification process), with the potential to bring discredit to, and reduction of confidence in, the industry (Clause 2).

Janssen recognised the serious nature of these breaches and had already liaised with European colleagues to ensure that the above campaign had ceased and that no further activities relating to it were deployed. This was confirmed in writing by the third party provider.

Furthermore, Janssen was completing a local review of communications relating to this activity and had begun a dialogue with the senior European Stelara leadership team to identify what lessons could be learned and changes made following this specific incident.

Janssen concluded that the Crohn's Disease awareness campaign initiated by the European marketing team, but distributed to UK health professionals, amounted to pre-licence promotion. It was taking immediate steps to ensure that this could not be repeated. Janssen stressed that it was outside the usual process for the regional European team to initiate a campaign to UK clinicians without the prior approval of the UK team.

Given the nature and content of the material, Janssen was of the view that it had breached Clauses 3.2 (promotion outside the marketing authorization), 9.1 (failure to maintain high standards), 14.1 (failure to secure local certification) and that consideration should be given as to whether this may amount to a breach of Clause 2.

**RESPONSE**

Janssen provided a copy of the email (15 August) in which the UK marketing team was notified by the European team that the disease awareness campaign had been deployed and that it included UK gastroenterologists.

Janssen was unfortunately unable to provide electronic copies of the images available to Gastroenterology members accessing the Medscape website; the alerts appeared adjacent to other news headlines at that time. Customers clicking on the news headline were taken to the same email content 'Remission: Mapping new pathways for Crohn's disease treatment'. During that period, the headline 'Remission: the goal for all patients with Crohn's disease' followed by 'information from industry' were shown in three forms, desktop, news section and home page versions, to UK gastroenterologists.

According to the Janssen EMEA standard operating procedure (SOP), any European generated material had to be approved for use in local operating companies. A copy of the relevant SOP was provided.

Janssen UK submitted that the SOP was clear with regard to its scope and requirement for EMEA generated content to be sent to the countries for review and approval. Unfortunately, on this occasion that step was missed, due to human error. To avoid a repeat of this mistake the company would re-train all of its approvers on this SOP and re-emphasise specifically the need for local country approval in UNITAS (powered by Zinc) the electronic approval system for all such materials.

Janssen-Cilag submitted that although the Crohn's Disease awareness campaign initiated by the Janssen European team, but distributed to UK health professionals, was intended to be a disease awareness campaign, due to the inclusion of the links to information on Stelara (ustekinumab) this campaign qualified as pre-licence promotion; Stelara did not yet have a licensed indication for the treatment of Crohn's disease. This email campaign was a one-time event, it had ceased and no further activities relating to the campaign were being deployed.

Janssen recognised that the inclusion of links in the disease awareness campaign referring to product related information was not in line with the provided guidance on which the organisation was trained. This should not have happened and was certainly not the way Janssen wanted to do business.

Given the nature and content of the material, Janssen was of the view that it had breached Clauses 3.2 (promotion outside the marketing authorization), 9.1 (failure to maintain high standards) and 14.1 (failure to secure local certification). Janssen recognised that promotion outside of the marketing

authorisation was a particularly serious offence with the potential to bring discredit to, and reduction of confidence in the industry and therefore believed that consideration should be given as to whether this might also amount to a breach of Clause 2.

Janssen submitted that it took its responsibilities under the Code very seriously and deeply regretted this unfortunate error. It was completing an assessment of all activities leading up to this incident and also taking steps to identifying what lessons could be learned and changes made to avoid this situation in the future.

**PANEL RULING**

The Panel noted that the Code permitted certain activities prior to the grant of the marketing authorization. The supplementary information to Clause 3, Marketing Authorisation, stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited providing that any such information or activity did not constitute promotion prohibited by Clause 3 or any other clause. Clause 3.2 required that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC.

In the Panel's view it was not necessarily unacceptable for companies to conduct a disease awareness campaign and to use materials with health professionals that generated discussion prior to the grant of a relevant marketing authorization. The arrangements had to comply with the Code, particularly the requirements of Clause 3.

The Panel noted the Janssen in Europe had emailed UK health professionals without the involvement of Janssen UK which had therefore not certified the materials. This was not in line with the relevant SOP which, *inter alia*, required local approval of materials. The email could also be accessed from advertisements which read 'Remission: the goal for all patients with Crohn's disease. Information from industry'. These advertisements were accessible to members of Medscape who were gastroenterologists. Janssen submitted that these advertisements were seen by 1,042 UK gastroenterologists, 345 of whom accessed the email content.

The Panel was extremely concerned that advertisements and an email had been created and sent to UK health professionals by Janssen Europe without local approval of the materials. The supplementary information to Clause 1.11 Applicability of Codes required that activities carried out and material used by a pharmaceutical company located in a European country must comply with the national code of the European country as well as the national code of the country in which the activities took place or the materials were used. The Panel therefore considered that the advertisements and email came within the scope of the Code. Janssen UK was thus responsible for the use of the material in the UK.

The Panel noted that there appeared to be a serious error in that the relevant Janssen EMEA SOP required materials to be sent to the local company for approval prior to use and this had not happened. Janssen UK submitted that this was due to human error. This appeared to the Panel to be conduct that fell short of competent care.

The Panel examined the email in detail and considered that it was clearly promotional. It discussed the treatment of disease pathways of Crohn's disease and provided links to results of studies using Stelara for Crohn's Disease. It mentioned that Janssen was committed to discovering pioneering treatments for Crohn's disease and the need for more effective treatment options. Stelara was not indicated for Crohn's Disease. The advertisements were linked to the email and thus were also promotional. The Panel ruled a breach of Clause 3.2 of the Code as the material was inconsistent with the Stelara SPC as acknowledged by Janssen UK. The material had not been certified and a breach of Clause 14.1 was ruled as acknowledged by Janssen.

The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled as acknowledged by Janssen UK. It considered that by promoting an unlicensed indication and failing to certify the material it brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2.

During its consideration of this case the Panel was also concerned that the material might be disguised and thus might not meet the requirements of Clauses 12.1. It appeared from the heading to the email that the material was somewhat removed from Janssen. The very first piece of information being 'a communication from [named third party]'. The Panel queried whether this was so given that Janssen had in effect paid for the email. This misleading impression was reinforced by the heading 'Developed under the direction and sponsorship of Janssen Pharmaceutical Companies'. The Panel was also concerned that the email gave the impression that the new medicine from Janssen would provide 'the right treatment for the right person in every part of the world'. The claim in the advertisements 'Remission: the goal for all patients with Crohn's disease' might give the impression that the new product provided remission for all patients with Crohn's disease. These could be considered all-embracing and contrary to the requirements of Clause 7.10. The Panel requested that its concerns were drawn to Janssen's attention.

**Complaint received** **22 August 2016**

**Case completed** **6 October 2016**

**CASE AUTH/2873/9/16**

# ANONYMOUS v ACTELION

## Hospitality at an exhibition stand

**An anonymous, non-contactable complainant, who described him/herself as a physician, complained that Actelion had offered frozen yoghurt from its exhibition stand at a European congress held in London in September 2016 despite another named company being previously ruled in breach of the Code for doing so (Case AUTH/2812/12/15).**

**The detailed response from Actelion is given below.**

**The PMCPA's guidance on items at conferences and exhibition stands stated that the Code allowed the provision of hospitality at scientific meetings including from an exhibition stand; hospitality provided from an exhibition stand must be subsistence only and not such as to induce a delegate to visit the stand eg no more than non-alcoholic beverages, such as tea, coffee and water, and very limited quantities of sweets, biscuits or fruit. In the Authority's view hot dogs, ice-cream, waffles, etc should not be provided at exhibition stands.**

**The Panel noted Actelion's submission that the ruling in Case AUTH/2812/12/15 had been missed. In the Panel's view that ruling had been published soon enough for Actelion to have cancelled the frozen yoghurt offering at its stand in September 2016.**

**The Panel considered that it was important for a company to be mindful of the impression created by its activities; perception and cost were important factors when deciding whether subsistence was appropriate. In the Panel's view, the availability of frozen yoghurt from Actelion's stand went beyond the provision of subsistence and was contrary to the requirements of the Code and a breach was ruled. High standards had not been maintained and a further breach was ruled.**

An anonymous, non-contactable complainant, who described him/herself as a physician, complained that at the European Respiratory Society (ERS) Congress, Actelion Pharmaceuticals UK had offered frozen yoghurt from its exhibition stand. The congress was held in London, 3-7 September 2016.

**COMPLAINT**

The complainant stated that he/she was somewhat dismayed that despite Case AUTH/2812/12/15 in which a named pharmaceutical company was ruled in breach of the Code for serving frozen yoghurt, Actelion had offered a selection of frozen yoghurts that could be ordered via iPads to be delivered to the customer at their position on the booth to eat on or off the stand. The complainant stated that this was clearly unacceptable, particularly given the recent ruling.

When writing to Actelion the Authority asked it to respond in relation to the requirements of Clauses 9.1 and 22.1.

**RESPONSE**

Actelion stated that it took the Code and any complaints very seriously; it was the first time it had received a complaint about the provision of hospitality at a scientific congress. Actelion submitted that it had supplied naturally flavoured frozen yoghurt, tea, barista made coffee, and bottled water. Actelion provided details of the cost and number of servings of frozen yoghurt dispensed during the congress.

Actelion explained that visitors to its stand could order frozen yoghurt either via iPad stations located at the designated visitor seating areas or directly from the refreshment counter serviced by contracted staff. The provision of frozen yoghurt was not advertised and the frozen yoghurt dispensing stand was not obvious from the exhibition floor such as to induce passing delegates; there was no intention to induce attendees to the stand by offering frozen yoghurt. It was intended purely as a healthy form of subsistence and was secondary to the scientific exchange at the booth.

The decision to provide the choice and options of refreshments, including frozen yoghurt, was made in April 2016 when Actelion was not aware of the ruling in Case AUTH/2812/12/15 as published in May 2016. The decision was made by the joint Actelion UK affiliate and Actelion global ERS 2016 senior project team, convened by the UK affiliate to ensure adherence to the Code in all ERS activities sponsored by Actelion.

Code of Practice Reviews published by the PMCPA were a helpful resource for companies to keep abreast of recent trends in governance undertakings, in particular, to take note of any sanction that might be relevant to activities sponsored by Actelion. However, and it was unfortunate that, for a variety of extenuating circumstances which was not an excuse, the review and ruling of Case AUTH/2812/12/15 was missed by Actelion.

Actelion noted that PMCPA guidance about hospitality listed types of subsistence allowed but did not give a definitive list of subsistence that was strictly forbidden, including frozen yoghurt. The guidance stated that 'the provision of subsistence allowed includes – non-alcoholic beverages, such as tea, coffee and water and very limited quantities of sweets, chocolates or fruit. In the Authority's view, hot dogs, ice-cream, waffles etc should not be provided at exhibition stands'.

As a confounding factor, in April when Actelion decided to provide, *inter alia*, frozen yoghurt on its booth, it did not know about Case AUTH/2813/12/15 in which an anonymous complainant stated that the level of hospitality provided at an international

congress (the same congress as that in Case AUTH/2812/12/15) was contrary to the Code. However, although the named company supplied tea, coffee, hot chocolate, flavoured iced drinks, chai latte, iced coffee as well as some small chocolates, and in contrast, a richer array of refreshments than that offered by Actelion, no breaches of Clauses 22.1 and 9.1 were ruled.

Actelion noted that whilst 'flavoured iced drinks' together with the impression of an extensive refreshments options provided by the company in Case AUTH/2813/12/15 was appropriate and allowable subsistence, frozen yoghurt was not. One could reasonably argue that the perception of frozen yoghurt (itself an iced/frozen based milk refreshment) was subjective and no different to the supply of 'flavoured iced drinks', which could be, by way of impression, similar to a 'flavoured slush puppy-like drink'.

Nevertheless, Actelion accepted that since it had decided to provide frozen yoghurt, a potential precedent was published in the May 2016 Code of Practice Review. In that case, the Panel ruled that frozen yoghurt provision was an unacceptable form of subsistence.

**PANEL RULING**

The Panel noted that Clause 22.1 stated that hospitality must be strictly limited to the main purpose of the event and must be secondary to the purpose of the meeting ie subsistence only. The level of subsistence offered must be appropriate and not out of proportion to the occasion. Clause 22.1 applied to scientific meetings, promotional meetings, scientific congresses and other such meetings and training. The supplementary information to Clause 22.1 also stated that a useful criterion in determining whether the arrangements for any meeting were acceptable was to apply the question 'Would you and your company be willing to have these arrangements generally known?' The impression that was created by the arrangements for any meeting must always be kept in mind.

The PMCPA's guidance on items at conferences and exhibition stands stated that the Code allowed the provision of hospitality at scientific meetings and the like and there was no reason why it should not be offered from an exhibition stand. Companies would have to be certain that the hospitality overall complied with the Code and that any hospitality provided from an exhibition stand was subsistence only and not at a level as to induce a delegate to visit the stand. In the Authority's view companies should provide no more than non-alcoholic beverages, such as tea, coffee and water, and very limited quantities of sweets, biscuits or fruit. The Authority advised that it did not consider that hot dogs, ice-cream, waffles, etc should be provided at exhibition stands.

The Panel noted Actelion's submission that the ruling in Case AUTH/2812/12/15, published in the May 2016 Code of Practice Review, had been missed. In the Panel's view that ruling had been published soon enough for Actelion to have cancelled the frozen yoghurt offering at its stand in September 2016.

The Panel further noted Actelion's submission that its supply of frozen yoghurt was not advertised and nor was the frozen yoghurt dispensing stand obvious from the exhibition floor such as to induce passing delegates. The Panel considered, however, that word of mouth would play at least some part in informing delegates about the provision of frozen yoghurt and it was possible that delegates would see others eating the yoghurt on Actelion's stand. Actelion had stated that the frozen yoghurt was not used to attract delegates to visit its stand; it was offered only as a healthy form of subsistence and was secondary to the scientific exchange at the booth. The Panel noted the cost per serving and the number of servings over the duration of the congress.

The Panel considered that it was important for a company to be mindful of the impression created by its activities; perception and cost were important factors when deciding whether subsistence was appropriate. In the Panel's view, the availability of frozen yoghurt from Actelion's stand went beyond the provision of subsistence and was contrary to the requirements of the Code and a breach of Clause 22.1 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

**Complaint received** **15 September 2016**

**Case completed** **2 November 2016**

# CODE OF PRACTICE REVIEW – November 2016

Cases in which a breach of the Code was ruled are indexed in **bold type.**

| | | | | | |
|---|---|---|---|---|---|
| **AUTH/2823/2/16** | **Anonymous, contactable v Grünenthal** | **Conduct of representatives** | **Breach Clause 2**<br>**Two breaches Clause 9.1**<br>**Breaches Clauses 15.4, 15.9, 20.1, 23.1 and 29** | **Appeal by the respondent** | **Page 3** |
| **AUTH/2836/4/16** | **AstraZeneca v Janssen** | **Promotion of Invokana** | **Breaches Clauses 3.2, 7.2 and 7.4** | **Appeal by the complainant** | **Page 20** |
| **AUTH/2840/4/16 and AUTH/2847/5/16** | **Anonymous, non contactable v Novartis and Pfizer** | **Promotion of Ultibro Breezhaler and Seebri Breezhaler** | **Three breaches Clauses 3.2 and 7.2**<br>**Four breaches Clause 9.1**<br>**Two breaches Clause 15.9** | **No appeal** | **Page 33** |
| **AUTH/2841/4/16** | **Anonymous, non contactable v GlaxoSmithKline** | **Promotion of Anoro Ellipta** | **Breach Clause 3.2**<br>**Two breaches Clause 7.2**<br>**Breach Clause 9.1** | **Appeal by the respondent** | **Page 41** |
| **AUTH/2842/4/16** | **Anonymous, non contactable v AstraZeneca** | **Promotion of Duaklir Genuair** | **Breach Clause 2**<br>**Three breaches Clause 3.2**<br>**Four breaches Clauses 7.2 and 9.1** | **No appeal** | **Page 52** |
| **AUTH/2843/4/16** | **Anonymous, non contactable v Boehringer Ingelheim** | **Promotion of Spiriva** | **Two breaches Clauses 3.2, 7.2 and 9.1**<br>**Breach Clause 15.9** | **No appeal** | **Page 60** |
| **AUTH/2844/5/16** | **Voluntary admission by Amdipharm Mercury** | **Email sent by a representative** | **Breaches Clauses 7.2, 7.4 and 9.1 and 14.1** | **No appeal** | **Page 65** |
| AUTH/2845/5/16 | CSL Behring v Swedish Orphan Biovitrum | Charity ball | No Breach | No appeal | Page 67 |
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| **AUTH/2849/6/16** | **A consultant oncologist and a pharmacist v Lilly** | **Oncology handbook** | **Breaches Clauses 2, 7.2, 7.4 and 9.1** | **Appeal by respondent** | **Page 76** |
| **AUTH/2850/6/16** | **Anonymous, non contactable v Sunovion** | **Disparagement at a meeting** | **Breaches Clauses 8.2 and 9.1** | **No appeal** | **Page 84** |
| AUTH/2851/6/16 | Anonymous, contactable v Novo Nordisk | Alleged promotion of Tresiba to the public | No Breach | No appeal | Page 87 |
| AUTH/2852/6/16 | Ex-employee v Grünenthal | Medical science liaison working practices | No Breach | No appeal | Page 89 |
| AUTH/2853/6/16 | Anonymous, contactable v GlaxoSmithKline | Alleged promotion of a vaccine to the public | No Breach | No appeal | Page 98 |

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| **AUTH/2854/7/16** | **Voluntary admission by Boehringer Ingelheim** | **Failure to certify the final form of promotional material** | **Breaches Clauses 14.1 and 9.1** | **No appeal** | **Page 102** |
| **AUTH/2855/7/16 and AUTH/2856/7/16** | **Pharmacist v Boehringer Ingelheim and Lilly** | **Promotion of Abasaglar** | **Breach Clause 7.2** | **No Breach** | **Page 104** |
| **AUTH/2857/7/16** | **Anonymous, non contactable v Daiichi- Sankyo** | **Promotional activities and call rates** | **Breaches Clauses 15.4 and 15.9** | **No appeal** | **Page 106** |
| AUTH/2859/7/16 | Health professional v AstraZeneca | Alleged promotion to the public | No Breach | No appeal | Page 111 |
| AUTH/2860/7/16 | Health professional v Chiesi | Alleged promotion to the public | No Breach | No appeal | Page 113 |
| AUTH/2861/7/16 | Anonymous, non contactable v Bristol-Myers Squibb | Promotion of Daklinza | No Breach | No appeal | Page 116 |
| **AUTH/2867/8/16** | **Anonymous, non contactable ex-employee v UCB** | **Conduct of representatives** | **Breaches Clauses 9.1, 15.4 and 15.9** | **No appeal** | **Page 119** |
| **AUTH/2870/8/16** | **Voluntary admission by Janssen** | **Trevicta advertisements** | **Breaches Clauses 4.7 and 14.1** | **No appeal** | **Page 124** |
| **AUTH/2871/8/16** | **Voluntary admission by Janssen** | **Pre-licence promotion** | **Breaches Clauses 2, 3.2, 9.1, and 14.1** | **No appeal** | **Page 126** |
| **AUTH/2873/9/16** | **Anonymous v Actelion** | **Hospitality at an exhibition stand** | **Breaches Clauses 9.1 and 22.1** | **No appeal** | **Page 130** |

# PMCPA | Prescription Medicines Code of Practice Authority

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 other relevant decision makers 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 any printed or electronic material used by them
- the supply of samples
- the provision of inducements in connection with the promotion of medicines and 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, social media 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
- disclosure of tranfers of value to health professionals and organisations
- joint working between the NHS and pharmaceutical companies
- 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, donations and benefits in kind 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

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.