CASE AUTH/3118/11/18 ***NO BREACH OF THE CODE***

DIRECTOR v TESARO

Clinical trial disclosure

A study published online in the British Medical Journal (12 September 2018) was entitled 'Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource' (Goldacre *et al* 2018).

The study objectives included assessing compliance rates with the European Commission's requirement that all trials on the EU Clinical Trials Register (EUCTR) posted results to the registry within 12 months of completion (final compliance date 21 December 2016). The study objectives also included identifying features associated with non-compliance, ranking sponsors by compliance and building a tool for live ongoing audit of compliance. The published paper listed the trial sponsors with the highest proportion of trials reported and the trial sponsors with the highest proportion of trials unreported. The results were that of 7,274 trials where results were due, 49.5% (95% confidence interval 48.4% to 50.7%) reported results.

Goldacre *et al* stated that the European Commission (EC) Guideline required the results of all trials to be reported in structured form on to the register itself. It was possible that some trials that did not report results to EUCTR reported results elsewhere eg in a conference presentation, an academic journal article, as part of a meta-analysis after data were requested by systematic reviewers, or in the grey literature. Such publications did not meet the reporting requirements of the EC Guideline and were therefore outside the scope of the study.

Goldacre *et al* listed sponsors with more than 50 trials on the EUCTR and did not mention products or specific clinical trials. Goldacre *et al* gave details of disclosure of clinical trial results for each sponsor.

The Director decided that the Goldacre *et al* article was such that she had received information from which it appeared that Merck Sharp & Dohme might have breached the Code and decided in accordance with Paragraph 5.1 of the Constitution and Procedure to take the matter up as a complaint (Case AUTH/3086/9/18). Following receipt of the response from Merck Sharp & Dohme the matter was taken up with Tesaro as the medicine was transferred to Tesaro.

The detailed response from Tesaro is given below.

General detailed comments from the Panel are given below.

The Panel noted Tesaro's submission that the clinical trial in question was about the use of SCH619734 in chronic idiopathic cough and was sponsored by Schering Plough Research Institute in the US, a division of Schering Corporation. The Panel noted Tesaro's submission that SCH619734 was now known as Varuby (Rolapitant) and was

first licensed for sale in the US on 1 September 2015 and was first made commercially available in the US in November 2015. In the UK, Varuby was currently licensed for the prevention of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults. Rolapitant was not authorised anywhere in the world for chronic idiopathic cough nor being developed for use in that indication. The Panel noted that the trial which was carried out at a single UK site, started on 18 January 2007 and completed on 22 October 2007.

The Panel noted Tesaro's submission that the summary report of the trial which was dated 23 September 2008 was made available on the EU Clinical Trials Register on 19 October 2018. The Panel noted that the results did not appear to be published on EUCTR within the required timeframe. The Panel therefore ruled a breach of the Code which was appealed by Tesaro. The Panel noted from the evidence before it that there did not appear to have been any formal finding by any judicial authority or appropriate body charged with determining matters in relation to the Commission Guidelines that the company had not complied with the relevant laws and regulations. The Panel therefore ruled no breach of the Code in relation to this trial. The Panel noted that the results were now disclosed on EUCTR and therefore it did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

The Appeal Board noted that Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 required that clinical trial data be published on EUCTR. European Commission (EC) Guideline 2012/c302/03 gave guidance as to when the clinical trial results data should be published. According to the guideline posting of results of clinical trials which ended one year or more prior to finalisation of the programming of the relevant database, should be done within 24 months of finalisation of that programming. According to the 'What's New' section of EudraCT public website (post-dated 13 January 2016) the deadline for submission of these results was 21 December 2016. This date was referred to in Goldacre *et al*. It appeared to the Appeal Board that whilst the regulation mandated disclosure of results on EUCTR, the EC Guideline and other material advised companies how to comply with the regulation including in relation to the timing of such disclosures. The Appeal Board considered that it was within the spirit of the Code and good practice to comply with the EC Guideline in question.

The Appeal Board noted Tesaro had results due for one trial (trial 2006-002164-26), but no results had been posted. The Appeal Board noted the data in Goldacre *et al* in that as the results for Tesaro's one due trial had not been reported on EUCTR; the disclosure percentage was therefore 0%.

The Appeal Board noted that the Panel had ruled a breach of the Code for Tesaro's failure to disclose results by 21 December 2016 or within the required timeframe in relation the trial (trial 2006-002164-26) and this was the subject of the appeal.

The Appeal Board noted from Tesaro's submission that trial 2006-002164-26, posting on EUCTR was delayed because the trial was related to asset SCH619734, now known as Varuby (rolapitant), which was originally developed by Schering Plough; as a consequence of Schering Plough's merger with Merck & Co in 2009, rolapitant was divested to OPKO Health Inc. in October 2009. In December 2010, OPKO Health Inc. granted Tesaro Inc. an exclusive licence of the worldwide rights to develop and

commercialise rolapitant. The Appeal Board noted that Tesaro understood that the trial in question was conducted and completed at a single UK site by its sponsor, the US based Schering Plough Research Institute, a division of Schering Corporation.

The Appeal Board considered that there would be a difference between action to deliberately hide clinical trial data or systematic failure resulting in non or late disclosure and late disclosure of results as part of a retrospective exercise contrary to non-mandatory timelines due to mitigating factors. The Appeal Board, nonetheless, noted its view above about good practice and disclosure in accordance with the EC Guideline.

The Appeal Board noted from Tesaro's submission that, on 19 October 2018 before Tesaro was notified of the complaint, the trial results (trial 2006-002164-26) were provided to EUCTR by Tesaro Inc following a request from Merck Sharp & Dohme, which no longer had a right to access the report. The Appeal Board noted Tesaro's submission about sponsorship of the trial and that it was not an affiliate of, nor did it acquire, the sponsor. Nonetheless, bearing in mind its comments above, the Appeal Board noted that Tesaro Inc had access to, and posted, the trial results.

The Appeal Board was concerned about the failure to disclose the summary results of one trial on EUCTR within the timelines advised by the EC Guideline and other relevant advice. In the exceptional circumstances of this case, the Appeal Board did not consider that the late posting of the results of this trial on the EUCTR as part of a retrospective exercise warranted a breach of the Code, particularly as the results of the trial had already been publicly disclosed and prior to receipt of the complaint. The Appeal Board ruled no breach of the Code. The appeal was successful.

Following its completion of the consideration of the appeal in this case and in Cases AUTH/3079/9/18 (Pfizer), AUTH/3087/9/18 (GlaxoSmithKline) and AUTH/3102/9/18 (Lilly) the Appeal Board noted that the respondent companies in Case AUTH/3084/9/18 (Boehringer Ingelheim), Case AUTH/3091/9/18 (UCB), Case AUTH/3097/9/18 (Teva), and Case AUTH/3099/9/18 (Allergan), accepted the Panel's rulings of breaches of the Code and had not appealed.

The Appeal Board agreed that Boehringer Ingelheim, UCB, Teva and Allergan should be contacted and informed of the outcome of the appeals in Cases AUTH/3079/9/18, AUTH/3087/9/18, AUTH/3118/11/18 and AUTH/3102/9/18. The PMCPA Constitution and Procedure did not cover this unusual situation where more than one company was involved in a similar set of circumstances and the Appeal Board had taken a different view to the Panel. Boehringer Ingelheim, UCB, Teva and Allergan should each be offered the opportunity to appeal out of time and the appeal process would operate in the usual way. The Appeal Board noted that each cases' circumstances might differ, and the result of any appeal could not be guaranteed. The reports for Case AUTH/3084/9/18 (Boehringer Ingelheim), Case AUTH/3091/9/18 (UCB), Case AUTH/3097/9/18 (Teva) and Case AUTH/3099/9/18 (Allergan), should be updated to reflect the situation and to cross refer to the cases which were successfully appealed. Allergan and UCB declined the opportunity to appeal. Boehringer Ingelheim and Teva successfully appealed the Panel's rulings of breaches of the Code.

A study published online in the British Medical Journal (12 September 2018) was entitled 'Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource' (Goldacre *et al* 2018).

The study objectives included assessing compliance rates with the European Commission's requirement that all trials on the EU Clinical Trials Register (EUCTR) posted results to the registry within 12 months of completion (final compliance date 21 December 2016). The study objectives also included identifying features associated with non-compliance, ranking sponsors by compliance and building a tool for live ongoing audit of compliance. The published paper listed the trial sponsors with the highest proportion of trials reported and the trial sponsors with the highest proportion of trials unreported. The results were that of 7,274 trials where results were due, 49.5% (95% confidence interval 48.4% to 50.7%) reported results. Results from trials with a commercial sponsor were substantially more likely to be posted than those from a non-commercial sponsor (68.1% v 11.0%, adjusted odds ratio 23.2, 95% confidence interval 19.2 to 28.2) as were trial results from a sponsor who conducted a large number of trials (77.9% v 18.4%, adjusted odds ratio 18.4, 15.3 to 22.1). More recent trials were more likely to report results (per year odds ratio 1.05, 95% confidence interval 1.03 to 1.07). Extensive evidence was found of errors, omissions, and contradictory entries in EUCTR data that prevented ascertainment of compliance for some trials.

The Director decided that the Goldacre *et al* article was such that she had received information from which it appeared that Merck Sharp & Dohme (Case AUTH/3086/11/18) might have breached the Code and decided in accordance with Paragraph 5.1 of the Constitution and Procedure to take the matter up as a complaint.

COMPLAINT

The study concluded that compliance with the European Commission requirement for all trials to post results on to the EUCTR within 12 months of completion had been poor, with half of all trials non-compliant. EU registry data commonly contained inconsistencies that might prevent even regulators assessing compliance. Accessible and timely information on the compliance status of each individual trial and sponsor might help to improve reporting rates.

Goldacre *et al* noted that any trial of any medicinal product conducted since 2004 in an EU country had already been required to register on the EUCTR, which was administered by the European Medicines Agency (EMA). Following the 2012 European Commission (EC) Guideline 2012/c302/03, sponsors must ensure that they disclosed their results of all trials registered on EUCTR since 2004 to the EMA within 12 months of trial completion; Phase I trials were exempt unless they were denoted as being part of a paediatric investigation plan. These trial reports were posted publicly on to the EUCTR within 15 working days of receipt by the EMA and were required to include salient features such as results for all pre-specified trial outcomes and statistical analyses, details of 'serious' and 'non-serious' adverse events, participants' baseline characteristics, and protocol deviations, as well as discussion of design limitations and caveats. Following various delays in the EMA's implementation of the software platform for results posting, the final date for sponsors' compliance was 21 December 2016.

Goldacre *et al* assessed compliance with the EU requirement to post results on to EUCTR for all trials on the registry, explored factors associated with non-compliance, identified the individual trial sponsors that were best at complying, and created a live online service, driven by regular

updates of the EUCTR data, to give ongoing and regularly updated performance statistics for compliance.

The publication listed a number of variables.

Goldacre *et al* stated that the EUCTR data underlying this study were updated regularly. An interactive online website presenting the overall reporting rate for all due trials, the reporting rates for each sponsor, ranks for these reporting rates, and details of each sponsor's individual reported and unreported trials was developed. The data underlying this site was updated regularly following each new download of the EUCTR database: the results and ranks for each individual sponsor were therefore always current and changed as performance changed. All software underlying this service was shared as open source and available for open code review or for adaptation and re-use.

Goldacre *et al* stated that the European Commission (EC) Guideline required the results of all trials to be reported in structured form on to the register itself. Ascertainment of the outcome – a results report on EUCTR – was therefore accurate and complete. It was possible that some trials that did not report results to EUCTR reported results elsewhere eg in a conference presentation, an academic journal article, as part of a meta-analysis after data were requested by systematic reviewers, or in the grey literature. Such publications did not meet the reporting requirements of the EC Guideline and were therefore outside the scope of the study. A manual search of academic journals and grey literature for a random sample of 100 trials unreported on EUCTR was conducted as requested as part of the peer review of the publication. Five were reported in the grey literature and 46 in a journal publication.

Goldacre *et al* listed sponsors with more than 50 trials on the EUCTR and did not mention products or specific clinical trials. The study publication listed the sponsors with the highest proportion of trials reported and those with the lowest proportion of trials reported.

The Director decided that Goldacre *et al* was such that she had received information from which it appeared that Merck Sharp & Dohme might have breached the Code and decided in accordance with Paragraph 5.1 of the Constitution and Procedure to take the matter up as a complaint (Case AUTH/3086/11/18).

Goldacre *et al* gave details of disclosure of clinical trial results for each sponsor.

The response received from Merck Sharp & Dohme (Case AUTH/3086/11/18) suggested that Tesaro UK Ltd might be responsible for disclosing results from trial 2006-002164-26. The authority understood that the medicine in question (SCH619734) was transferred out of Merck Sharp & Dohme Limited by Tesaro in January 2014.

When writing to Tesaro the Authority asked it to bear in mind the requirements of Clauses 2, 9.1, 1.11 and 13.1 of the Code. The Authority noted that previous editions of the Code might be relevant and provided details.

RESPONSE

Tesaro explained that the clinical trial in question was about the use of SCH619734 in chronic idiopathic cough; it was sponsored by Schering Plough Research Institute in the US, a division of Schering Corporation. The trial started on 18 January 2007 and completed on 22 October

2007. From the information available in the EU Clinical Trials Register (EUCTR), Tesaro understood that the trial was carried out at a single UK site. A report of the results of the trial, dated 23 September 2008, was available on the EU Clinical Trials Register.

SCH619734 was now known as Varuby (rolapitant) and was originally developed by Schering Plough; as a consequence of Schering Plough's merger with Merck & Co. in 2009, rolapitant was divested to OPKO Health Inc. in October 2009.

In December 2010, OPKO Health Inc. granted Tesaro Inc. an exclusive licence of the worldwide rights to develop and commercialise rolapitant. Tesaro Inc. was not part of the same corporate group as OPKO Health Inc., Schering Plough or Merck & Co. The clinical development of rolapitant for use in chronic idiopathic cough was discontinued after the trial in question, a number of years before Tesaro Inc. licensed the rights to rolapitant from OPKO Health Inc. In the UK, Varuby was currently licensed for the prevention of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults ('CINV'). Rolapitant was not authorised anywhere in the world for chronic idiopathic cough nor being developed for use in that indication.

Rolapitant was first licensed for sale in the US on 1 September 2015 and was first made commercially available in the US in November 2015.

Tesaro stated that it was not responsible for disclosing the trial in question under the Code because:

- The trial was not conducted by or on behalf of Tesaro UK or an affiliate of Tesaro UK, either directly or via a third party. The trial was run in the UK by a non-UK company which had no link to Tesaro. The sponsor had not been acquired by Tesaro.

- The trial related to an unlicensed indication for which development ceased a number of years before Tesaro Inc. licensed the rights to develop rolapitant.

- Tesaro noted that the disclosure obligation under the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases applied to products that were approved for marketing and commercially available, and 'if trial results for an investigational product that has failed in development have significant medical importance, study sponsors are encouraged to post the results if possible'. The Joint Position did not address trials for unlicensed indications specifically, but by analogy Tesaro considered that trials for indications that had failed in development should only need to be disclosed if they had significant medical importance. The results of the trial in question were not of significant medical importance, and therefore did not need to be disclosed. Similarly, the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature stated that, as a minimum, results from all Phase 3 trials and any clinical trial results of significant medical importance should be submitted for publication; the trial in question was a Phase 2 trial.

Tesaro noted from a previous case that the Panel's position on which Code and which Joint Position applied was based on the date the product was first approved and commercially available anywhere in the world. For a product first licensed and commercially available

anywhere in the world after 1 May 2011, the applicable Joint Positions required relevant clinical trial results to be posted within a year of the product being first approved and commercially available or within a year of trial completion for trials completed after the medicine was first available. Based on this position and following the questions set out in the Authority's Decision Tree:

- the product was licensed and commercially available;
- no UK company was involved in the trial - the sponsor of the trial was a non-UK company and the product was subsequently acquired from the original sponsor by a US company, OPKO Health Inc;
- the trial involved a UK site;
- the product was first licensed and available in November 2015, so the 2015 Code and the 2009 Joint Position were relevant;
- under the 2009 Joint Position, all clinical trials in patients from Phase 1 onwards should be disclosed (but as stated above, Tesaro considered that trials for indications that failed in development only needed to be disclosed if they had significant medical importance);
- the trial was completed before the product was first licensed and commercially available;
- therefore, if there was an obligation to disclose the trial, it would need to have been be disclosed within one year of being commercially available, ie by November 2016.

Tesaro noted that the summary report of the trial had been published on the EU Clinical Trials Register. The summary report, written by Schering Plough, was dated 23 September 2008 and was listed on the Register as having been made available on 19 October 2018 ie before Tesaro was notified of the complaint. The summary report was provided to the Register by Tesaro Inc following a request from Merck Sharp & Dohme, which no longer had a right to access the report. While Tesaro UK considered that it was not responsible under the Code for disclosing the results of the trial, the Tesaro group was committed to supporting transparency of clinical trial results wherever possible and so in response to the request located and provided a copy of the report to the Register for publication.

In relation to the relevant clauses of the Code, Tesaro:

- had complied with all applicable codes, laws and regulations to which it was subject and therefore was not in breach of Clause 1.11.
- was not responsible under the Code or the Joint Positions for publishing the results of the trial in question and therefore was not in breach of Clause 13.1.
- was not in breach of any undertaking in relation to a ruling under the Code and therefore was not in breach of Clause 29.

- was not in breach of Clauses 1.11, 13.1 or 29 of the Code and thus was not in breach of Clauses 2 or 9.1.

PANEL RULING

The Panel noted that Goldacre *et al* was not the subject of external complaint but was taken up under Paragraph 5.1 of the Constitution and Procedure.

General comments

The Panel noted that Goldacre *et al* was the basis of the complaint in relation to the allegation that sponsors with less than 100% reported trials were not meeting the requirements of the EC Guideline.

The Panel noted that all the cases would be considered under the Constitution and Procedure in the 2016 Code as this was in operation when Goldacre *et al* was published and the complaint proceedings commenced.

The Panel noted that there had been three previous studies looking at the disclosure of clinical trial data all published in Current Medical Research and Opinion (CMRO). The first study was the subject of an external complaint which gave rise to 27 cases in 2013 and 2014. The second study (Rawal and Deane 2015) was not the subject of external complaint but was taken up under Paragraph 5.1 of the Constitution and Procedure in 2015 and led to 15 cases. The third study (Deane and Sivarajah 2016) was not the subject of external complaint but was also taken up under Paragraph 5.1 in 2016 and led to 17 cases. Most of these cases were not in breach of the Code because they were not within the scope of the Code as there was no UK involvement and therefore only limited details were published on the PMCPA website.

The previous studies surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between specific dates covering medicines (except vaccines) that were approved by the European Medicines Agency (EMA) in a particular year or years. The Panel noted that the previous cases had established a number of principles including deciding which Code applied.

Goldacre *et al* was different to the previous three studies which assessed compliance with the Joint Positions; it only assessed compliance with the EU requirement to post results on to the European Union Clinical Trial Register (EUCTR) for all trials listed on the registry. In that regard, trials involving investigational products that were not licensed for use anywhere in the world might be included. Companies had not made a detailed submission on this point.

The Panel noted that the European Clinical Trials Database (EudraCT) was a database hosted by the EMA in which clinical trial sponsors would upload summary results. These results would then be published on the EUCTR.

The Panel considered that in these circumstances the trial completion date would be the trigger for results disclosure on EUCTR. The Panel noted that the publicly available EudraCT and EUCTR Q&A document stated in response to the question ‘if the trial is prematurely ended/early terminated due to lack of subjects or lack of data to analyse, do I have to provide results?’, that in the case that no subjects were recruited, it was not appropriate to complete the full dataset.

However, there was currently no functionality for sponsors to inform that recruitment never started or that the trial was prematurely ended in the results data model. In this specific case sponsors had to liaise directly with the National Competent Authority confirming that no results would be available for a specific trial due to 'lack of subjects' or that the trial was 'prematurely ended' so a statistical analysis could not be provided. The Panel noted that according to the Commission Guideline 'Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) and Regulation No 726/2001 and Article 41(2) of Regulation No 1901/2006', if the clinical trial ends prematurely, that date should be considered the end of trial date.

The Panel noted that according to Goldacre *et al* any trial of any medicinal product conducted since 2004 in an EU country had already been required to register on the EUCTR, which was administered by the European Medicines Agency (EMA). Following the 2012 European Commission (EC) Guideline 2012/c302/03, sponsors must ensure that they disclosed the results of all trials registered on EUCTR since 2004 to the EMA within 12 months of trial completion; Phase I trials were exempt unless they were denoted as being part of a paediatric investigation plan. These trial reports were posted publicly on to the EUCTR within 15 working days of receipt by the EMA and were required to include salient features. Goldacre *et al* noted that following delays in the EMA's implementation of the software platform for results posting, the final date for sponsors' compliance was 21 December 2016.

The Panel considered that the subject matter of the complaint was failure to publish results on EUCTR. It appeared to the Panel that under EUCTR for non-paediatric trials, at least one investigator site of the clinical trial should be located in Europe or in a contracting state of the European Economic Area (EEA). The Panel noted that it could only consider the matter with regard to the Code. In the Panel's view, only those with a UK nexus would be considered to be within the scope of the Code.

The Panel noted that the Code did not explicitly refer to publication on the EUCTR. Clause 13.1 referred, *inter alia*, to disclosure of clinical trials in accordance with the Joint Positions on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Publication of Clinical Trial Results in the Scientific Literature. According to the 2009 Joint Position, publication of clinical trial results in any free, publicly accessible internet-based clinical trials database should achieve the intended objectives.

The Panel noted the differences between the Joint Positions and the requirement to publish clinical trial results on the EUCTR; it was possible that results might not need to be published under the Joint Positions (for instance because the medicine was not licensed for use or commercially available) but might nonetheless be required to be published on the EUCTR. The Panel considered that companies would be well advised to ensure that all the clinical trial results were disclosed as required by the law, codes and Joint Positions. The Panel noted that Goldacre *et al* had not commented on whether the results disclosed met the requirements of the Joint Positions so this was not considered; in the Panel's view, the only matter for consideration was whether or not trial results had been disclosed within the required timeframe as required by the Commission Guideline 2012/C302/03 which came into operation in 2012, and by 21 December 2016 which was referred to by Goldacre *et al* as the final data for sponsor's compliance. The Panel considered, therefore, that in this particular case it would make its rulings under the Code in operation on 21 December 2016, the 2016 Code. The Panel considered that its approach was a fair one.

The Panel noted that the companies had been asked to respond, *inter alia*, to Clause 13.1. Given that Goldacre *et al* did not refer to the Joint Positions and noting the differences between the requirements to disclose under the Joint Positions and under the Commission Guidelines the Panel considered, taking a pragmatic approach, that the matters raised by Goldacre *et al* would be considered under Clause 9.1, rather than Clause 13.1. The companies had been asked to respond to, *inter alia*, Clauses 9.1 and 1.11 at the outset and had been provided with a copy of Goldacre *et al*. The Panel noted that the publicly available EudraCT and EUCTR Q&A document referred to sponsors who were not fulfilling the legal requirements in providing results in EudraCT.

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

The Panel noted that the Authority was not an investigative body as such and its consideration of these cases relied upon the information provided by the parties. The quantitative data published by Goldacre *et al* formed the basis of the complaint. The Panel noted that in that regard the case preparation manager had not used the live data web resource to identify the trials at issue.

Panel ruling in Case AUTH/3118/11/18

The Panel noted its general comments above about the subject matter of the complaint as set out in Goldacre *et al.* The Panel had decided that the alleged failure to publish results in accordance with the Commission Guidelines was more appropriately covered by Clause 9.1 and potentially Clause 1.11. The Panel made no ruling in relation to Clause 13.1.

The Panel noted Tesaro's submission that the clinical trial in question was about the use of SCH619734 in chronic idiopathic cough and was sponsored by Schering Plough Research Institute in the US, a division of Schering Corporation. The Panel noted Tesaro's submission that SCH619734 was now known as Varuby (Rolapitant) and was first licensed for sale in the US on 1 September 2015 and was first made commercially available in the US in November 2015. In the UK, Varuby was currently licensed for the prevention of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults. Rolapitant was not authorised anywhere in the world for chronic idiopathic cough nor being developed for use in that indication. The Panel noted that the trial which was carried out at a single UK site, started on 18 January 2007 and completed on 22 October 2007.

The Panel noted Tesaro's submission that the summary report of the trial which was dated 23 September 2008 was made available on the EU Clinical Trials Register on 19 October 2018. The Panel noted that the results did not appear to be published on EUCTR within the required timeframe. The Panel therefore ruled a breach of Clause 9.1. The Panel noted from the evidence before it that there did not appear to have been any formal finding by any judicial

authority or appropriate body charged with determining matters in relation to the Commission Guidelines that the company had not complied with the relevant laws and regulations. The Panel therefore ruled no breach of Clause 1.11 in relation to this trial. The Panel noted that the results were now disclosed on EUCTR and therefore it did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

APPEAL BY TESARO

Tesaro noted that the trial at issue took place in 2007, a number of years before Tesaro UK Limited was incorporated and Tesaro Inc. licensed the rights to develop the compound. The trial was sponsored by Schering Plough, a company with which Tesaro and its group of companies were not and had not been affiliated. The Panel had ruled that Tesaro had failed to maintain high standards, in breach of Clause 9.1 of the Code, on the basis that the summary report of the results of the trial was not posted on the EUCTR within the timeframe of 21 December 2016 set out in the 2012 EC Guideline.

Tesaro appealed the ruling of a breach of Clause 9.1 for the following reasons:

1 The Panel had not provided clear reasoning for its ruling, as was required to be given to the respondent company under the Constitution and Procedure.

2 The posting of the summary report of the results of the trial on the EUCTR outside the timeframe in the EC Guideline did not warrant a finding of a breach of Clause 9.1 as:

   i) the Panel had not ruled a breach of Clauses 13.1, 1.11 or any other provision of the Code by Tesaro;
   ii) the timelines in the EC Guideline were advisory rather than legally binding and there had been no determination by a regulatory authority of a breach of the EC Guideline in relation to the trial by Tesaro, its affiliate or the sponsor of the trial; and
   iii) the EC Guideline applied to the sponsor of a trial and neither Tesaro nor its affiliate were the sponsor of the trial.

Detailed response

Tesaro submitted that the Panel had not provided clear reasoning for its ruling under Paragraph 7.1 of the Constitution and Procedure, where the Panel ruled that there was a breach of the Code. The Panel's ruling did not set out a full and clear explanation of the reasons why it had concluded that not posting the summary report of the results of the trial on the EUCTR within the required timeframe in the EC Guidance was a failure to 'maintain high standards' and therefore warranted a breach of Clause 9.1. In addition, the ruling set out the principle that pharmaceutical companies were responsible for the activities of their 'overseas affiliates' but did not explain why the Panel regarded Tesaro as being either the party responsible for the breach of Clause 9.1 or the 'overseas affiliate' of the party responsible for such breach. Without full and clear reasoning, it was difficult for Tesaro to respond adequately to the Panel's ruling. Nonetheless, Tesaro had tried to respond to the Panel's ruling below as fully as possible. Tesaro reserved the right to respond further if such reasoning was given.

Tesaro submitted that the Code contained a specific provision relating to the disclosure of clinical trial results in the form of Clause 13.1. Under Clause 13.1 of the Code, companies were required to disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. While the original complaint asked Tesaro to respond, *inter alia*, with reference to Clause 13.1, the Panel had made no finding of a breach of Clause 13.1 which specifically addresses clinical trial disclosure and has instead considered the matters raised under the more general provision of Clause 9.1.

Tesaro submitted that the Panel's ruling stated that in the Panel's view, the only matter for consideration was whether or not trial results were disclosed within the required timeframe as required by the EC Guideline 2012/C302/03 which came into operation in 2012, and by 21 December 2016. However, the Panel also noted in the ruling that the Code did not explicitly refer to publication on the EUCTR, so the basis on which the Panel had considered the disclosure of trial results under the EC Guideline as being within the scope of the Code was not made clear. The Panel's ruling also did not set out clearly the basis on which, in the absence of a ruling of a breach of Clause 13.1, the Panel regarded Tesaro as having failed to maintain high standards under Clause 9.1 in relation to the disclosure of the summary report of the results of the trial in question. In previous Panel rulings relating to clinical trial transparency, a breach of Clause 9.1 had only been ruled in circumstances where a breach of Clause 13.1 was also ruled.

Tesaro submitted that the Panel's ruling referred to a potential breach of Clause 1.11, which was the requirement for pharmaceutical companies to comply with all applicable codes, laws and regulations to which they were subject, though this did not appear from the ruling to be the basis for the finding of a breach of Clause 9.1. Nonetheless, the Panel's ruling specifically stated that 'The Panel noted from the evidence before it that there did not appear to have been any formal finding by any judicial authority or appropriate body determining matters in relation to the Commission Guidelines that the company had not complied with the relevant laws and regulations'. The Panel had also not identified any code, law or regulation as having been breached by Tesaro.

Tesaro submitted that the EC Guideline was not a mandatory legal requirement. The EC Guideline applied to the sponsor of the trial in question, consistent with the obligations placed on the sponsor under Regulation (EC) No. 726/2004. The Panel's ruling acknowledged that the EC Guideline applied to the sponsor (but did not acknowledge the non-mandatory status of the guideline): 'Following the 2012 European Commission (EC) Guideline 2012/c302/03, sponsors must ensure that they disclosed the results of all trials registered on EUCTR since 2004 to the EMA within 12 months of trial completion … the final date for sponsors' compliance was 21 December 2016'. Tesaro UK was not, nor was any overseas affiliate of Tesaro UK, the sponsor of the trial.

Tesaro submitted that the history of the compound in question, rolapitant, was complex. The ruling stated that 'The authority understood the medicine in question was transferred out of Merck Sharp & Dohme by Tesaro in January 2014'. As stated in Tesaro's initial response, but not acknowledged in the Panel's ruling, this description was inaccurate.

Tesaro submitted that the trial took place in 2007 and its sponsor was the Schering Plough Research Institute in the US, a division of Schering Corporation. From publicly available information, Tesaro understood that Schering Corporation merged with Merck & Co in 2009. Schering Corporation sold certain compounds, including rolapitant, to OPKO Health, Inc in

2009. OPKO Health owned the patent rights and know-how related to the rolapitant and in late 2010 granted Tesaro Inc., Tesaro UK's US parent company, the right to develop and commercialise rolapitant under a licence agreement. Under that agreement, Tesaro Inc. had the right to use certain intellectual property rights and know-how, including the results of clinical trials, to further develop the compound. Tesaro Inc did not acquire the underlying ownership of the compound rolapitant or of OPKO Health.

Tesaro submitted that Tesaro Inc. developed rolapitant for the current authorised indication of prevention of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults. Tesaro Inc. did not develop further the indication investigated in the trial, chronic idiopathic cough, and data relating to that indication was not pertinent to rolapitant's current authorised use.

Tesaro submitted that the Panel appeared to have assumed, though this was not expressly stated in the ruling, that the sponsor's obligation to post the summary report of the results of the Trial was transferred to Tesaro Inc. by virtue of the 2010 licence agreement. Even if this were possible, there was no such provision in the licence agreement that transferred the historic and future obligations of the sponsor of the Trial to Tesaro Inc.

Tesaro submitted that whether the fulfilment of the sponsor's obligations was transferred as part of the sale from the sponsor's group to OPKO Health and therefore was even capable of being transferred under the licence agreement to Tesaro Inc. would be subject to the terms of the underlying sale agreement, to which Tesaro Inc. was not a party.

Tesaro submitted that it held the EU marketing authorisation for rolapitant (for the indication of prevention of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults) when it was first granted in April 2017, ie after the EC Guidance disclosure deadline, and which had now been transferred to another Tesaro group company.

Tesaro submitted that, however, the EC Guidance applied only to the sponsor and there was no requirement for a company to disclose the summary report of the results of a trial relating to a product on the basis of holding a licence to the rights to develop a product or holding a marketing authorisation for that product.

Tesaro submitted that the Panel's ruling suggested that the basis for holding Tesaro responsible for the publication of the summary report of the results of the trial was by virtue of Tesaro being the 'overseas affiliate' of the company required to post the results. The ruling stated that:

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

Tesaro submitted that taking the elements raised in the text from the ruling above:

- The trial was not conducted 'on behalf of' Tesaro UK, either directly or via a third party. The trial was carried out in 2007. Tesaro UK's parent company did not licence the rights to develop the product until 2010 and Tesaro UK did not exist at the time the clinical trial took place nor when Tesaro Inc. licensed the rights to the product.

- The trial was run by a non-UK company. There was UK involvement as the trial was conducted at a UK site. Based on text quoted above, it is 'likely' that the Code would apply to the trial.

- Applying the principle that UK pharmaceutical companies are responsible for the activities of 'overseas affiliates' if those activities come within the scope of the Code, if the trial was assumed as coming with the scope of the Code by virtue of being conducted at a UK site, Tesaro UK should only be held responsible for the trial under the Code if the trial was the activity of an 'overseas affiliate'.

- Tesaro UK was not, and had never been, an 'overseas affiliate' of the trial sponsor or its successors. Under English law, 'affiliate' was used to describe companies within the same corporate group or under common control. The Oxford dictionary definition of 'affiliate' was a person or organisation that was affiliated with a larger body or a fellow member of a larger body. Tesaro UK was not part of the same corporate group as the sponsor or its successors, nor under common control or part of the same larger body as the sponsor or its successors.

- Tesaro Inc. was not the sponsor of the trial and did not acquire the company that was the sponsor of the trial.

In conclusion, Tesaro submitted that the Panel had provided no adequate basis for its ruling that the posting of the summary report of the results of the trial in question after the deadline in the EC Guidelines constituted a failure to maintain high standards by Tesaro UK under Clause 9.1. A ruling that Tesaro had failed to maintain 'high standards' on the basis of the late disclosure of the summary report of the results of a clinical trial in accordance with a non-mandatory guideline where the trial took place before Tesaro was incorporated and Tesaro Inc. had the right to develop the product and for which neither Tesaro UK nor its group company was the sponsor, and where no breach of Clauses 13.1 and 1.11 or any other provision of the Code had been ruled, would significantly extend the current scope of the 'high standards' provision in Clause 9.1.

APPEAL BOARD RULING

The Appeal Board noted that a series of cases had been taken up by the PMCPA as a result of the data published in Goldacre *et al*. Four cases were the subject of an appeal by the respondent companies. Each would be determined on their own merits but there were a number of common themes.

The Appeal Board noted that Goldacre *et al* formed the basis of the complaint. Goldacre *et al* did not refer to disclosure of clinical trial results and the Joint Position which was covered by Clause 13.1 of the Code. The article assessed companies' compliance with EC Guideline 2012/c302/03. The Appeal Board noted that disclosure of clinical trial results on EUCTR was not mentioned in Clause 13 and its supplementary information, or indeed elsewhere in the Code. The Appeal Board noted that the Code was not exhaustive and in such circumstances

the Appeal Board did not consider it unreasonable to consider the subject matter of the complaint in relation to Clause 9.1. In this regard the Appeal Board noted the long-established broad application of Clause 9.1 to promotional and non-promotional materials and activities including matters within the scope of the Code but not expressly referred to. The Appeal Board did not consider that a ruling of a separate clause was required as a condition precedent to ruling under Clause 9.1; in the Appeal Board's view, Clause 9.1 could be ruled upon in isolation.

The Appeal Board noted that Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 required that clinical trial data be published on EUCTR. European Commission (EC) Guideline 2012/c302/03 gave guidance as to when the clinical trial results data should be published. According to the guideline posting of results of clinical trials which ended one year or more prior to finalisation of the programming of the relevant database, should be done within 24 months of finalisation of that programming. According to the 'What's New' section of EudraCT public website (post-dated 13 January 2016) the deadline for submission of these results was 21 December 2016. This date was referred to in Goldacre *et al*. It appeared to the Appeal Board that whilst the regulation mandated disclosure of results on EUCTR, the EC Guideline and other material advised companies how to comply with the regulation including in relation to the timing of such disclosures. The Appeal Board considered that it was within the spirit of the Code and good practice to comply with the EC Guideline in question.

The Appeal Board noted that, where companies had merged or the rights to a particular product had been bought or sold, there appeared to be difference of opinion as to which company would be responsible for posting the retrospective results. There were also difficulties in correcting information once posted.

The Appeal Board also noted that according to Goldacre *et al*, Phase I trials that were not part of a paediatric plan did not need to be disclosed.

The Appeal Board noted that Goldacre *et al* assessed all relevant trials on the EUCTR database including those with no UK nexus which were not covered by the Code. There might therefore be a difference between a company's overall disclosure rate and the disclosure rate of those clinical trials with a UK nexus. The results of trials on the registry which did not have a UK nexus and were not disclosed still needed to be disclosed on the registry according to the relevant regulation and the failure to do so would potentially be covered by another code of practice in the relevant jurisdiction.

The Appeal Board noted Tesaro had results due for one trial (trial 2006-002164-26), but no results had been posted. The Appeal Board noted the data in Goldacre *et al* in that as the results for Tesaro's one due trial had not been reported on EUCTR; the disclosure percentage was therefore 0%.

The Appeal Board noted that the Panel had ruled a breach of Clause 9.1 for Tesaro's failure to disclose results by 21 December 2016 or within the required timeframe in relation the trial (trial 2006-002164-26) and this was the subject of the appeal.

The Appeal Board noted from Tesaro's submission that trial 2006-002164-26, posting on EUCTR was delayed because the trial was related to asset SCH619734, now known as Varuby (rolapitant), which was originally developed by Schering Plough; as a consequence of Schering Plough's merger with Merck & Co in 2009, rolapitant was divested to OPKO Health Inc. in

October 2009. In December 2010, OPKO Health Inc. granted Tesaro Inc. an exclusive licence of the worldwide rights to develop and commercialise rolapitant. The Appeal Board noted that Tesaro understood that the trial in question was conducted and completed at a single UK site by its sponsor, the US based Schering Plough Research Institute, a division of Schering Corporation.

The Appeal Board considered that there would be a difference between action to deliberately hide clinical trial data or systematic failure resulting in non or late disclosure and late disclosure of results as part of a retrospective exercise contrary to non-mandatory timelines due to mitigating factors. The Appeal Board, nonetheless, noted its view above about good practice and disclosure in accordance with the EC Guideline.

The Appeal Board noted from Tesaro's submission that, on 19 October 2018 before Tesaro was notified of the complaint, the trial results (trial 2006-002164-26) were provided to EUCTR by Tesaro Inc following a request from Merck Sharp & Dohme, which no longer had a right to access the report. The Appeal Board noted Tesaro's submission about sponsorship of the trial and that it was not an affiliate of, nor did it acquire, the sponsor. Nonetheless, bearing in mind its comments above, the Appeal Board noted that Tesaro Inc had access to, and posted, the trial results.

The Appeal Board was concerned about the failure to disclose the summary results of one trial (trial 2006-002164-26) on EUCTR within the timelines advised by the EC Guideline and other relevant advice. In the exceptional circumstances of this case, the Appeal Board did not consider that the late posting of the results of this trial on the EUCTR as part of a retrospective exercise warranted a breach of Clause 9.1, particularly as the results of the trial had already been publicly disclosed and prior to receipt of the complaint. The Appeal Board ruled no breach of Clause 9.1. The appeal was successful.

Following its completion of the consideration of the appeal in this case and in Cases AUTH/3079/9/18 (Pfizer), AUTH/3087/9/18 (GlaxoSmithKline) and AUTH/3102/9/18 (Lilly) the Appeal Board noted that the respondent companies in Case AUTH/3084/9/18 (Boehringer Ingelheim), Case AUTH/3091/9/18 (UCB), Case AUTH/3097/9/18 (Teva), and Case AUTH/3099/9/18 (Allergan), accepted the Panel's rulings of breaches of the Code and had not appealed.

The Appeal Board agreed that Boehringer Ingelheim, UCB, Teva and Allergan should be contacted and informed of the outcome of the appeals in Cases AUTH/3079/9/18, AUTH/3087/9/18, AUTH/3118/11/18 and AUTH/3102/9/18. The PMCPA Constitution and Procedure did not cover this unusual situation where more than one company was involved in a similar set of circumstances and the Appeal Board had taken a different view to the Panel. Boehringer Ingelheim, UCB, Teva and Allergan should each be offered the opportunity to appeal out of time and the appeal process would operate in the usual way. The Appeal Board noted that each cases' circumstances might differ, and the result of any appeal could not be guaranteed. The reports for Case AUTH/3084/9/18 (Boehringer Ingelheim), Case AUTH/3091/9/18 (UCB), Case AUTH/3097/9/18 (Teva) and Case AUTH/3099/9/18 (Allergan), should be updated to reflect the situation and to cross refer to the cases which were successfully appealed. Allergan and UCB declined the opportunity to appeal. Boehringer Ingelheim and Teva successfully appealed the Panel's rulings of breaches of Clause 9.1.

Complaint received	**21 November 2018**
Case completed	**18 September 2019**