CASE AUTH/3087/9/18 ***NO BREACH OF THE CODE***

DIRECTOR v GLAXOSMITHKLINE

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 GlaxoSmithKline 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.

The detailed response from GlaxoSmithKline is given below.

General detailed comments from the Panel are given below.

The Panel noted the data in Goldacre *et al* in that the results of 33 of GlaxoSmithKline's due trials had not been reported on EUCTR; the disclosure percentage was 88.7%.

The Panel noted GlaxoSmithKline's submission that it found 34 rather than 33 trials that appeared to have results due but no results posted.

The Panel noted GlaxoSmithKline's submission that of the 34 trials, 18 had no UK involvement, no UK centres, investigators or patients. The Panel considered that as there was no UK involvement, the matter did not come within the scope of the UK Code. No breach of the Code was ruled in relation to these 18 trials.

The Panel noted GlaxoSmithKline's submission that of the 16 trials with UK involvement, 11 were cancelled prior to enrolling any subjects. There were no results to report. The Panel therefore ruled no breaches of the Code including Clause 2 in relation to these eleven trials.

The Panel noted GlaxoSmithKline's submission that of the five trials with UK involvement and results, three trials were not clinical trials of a licensed medicine or a subsequently licensed medicine. Two (trial 2008-005288-33 and trial 2010-019832-11) of these three studies were exploratory studies of imaging methods (therefore not clinical trials of medicinal products, whether investigational or licensed). The Panel noted that according to Goldacre *et al*, which was the source of the complaint, 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. In the Panel's view, there was no evidence before it that the results of the above two trials which were exploratory studies of imaging methods were required to be disclosed under EC Guidelines. The Panel therefore ruled no breaches of the Code including no breach of Clause 2 in relation to these two trials.

The Panel noted GlaxoSmithKline's submission that trial 2011-005216-28 which completed on 22 August 2012 evaluated an investigational medicine, Vestipitant, that was not approved in any market. The Panel noted GlaxoSmithKline's submission that summary results were disclosed on GlaxoSmithKline's Clinical Study Register on 25 July 2013. The trial results were also published in the British Journal of Anaesthesia, 2015 March; 114(3):423-429. However, 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 GlaxoSmithKline. 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 was unsure whether or not the results were now disclosed on EUCTR but noted that they were published elsewhere as stated above. The Panel therefore did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

The Panel noted that trial 2011-005913-35 was a trial of umeclidinium and vilanterol in combination, compared to the individual component medicines. The product was first marketed on 18 December 2013 in the US and the trial completed on 11 June 2013. The Panel noted GlaxoSmithKline's submission that summary results were posted on GlaxoSmithKline Clinical Study Register on 21 November 2013 and on Clinicaltrials.gov on 11 February 2014. However, 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 GlaxoSmithKline. 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 was unsure whether or not the results were now disclosed on EUCTR but noted that they were published elsewhere as stated above. The Panel therefore did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

The Panel noted that trial 2009-009885-15 involved a trial of lapatinib in combination with vinorelbine or capecitabine which received first market approval on 13 March 2007 in the US. The trial completed on 21 August 2012. The Panel noted GlaxoSmithKline's submission that summary results were posted on GlaxoSmithKline Clinical Study Register on 18 April 2013 and on Clinicaltrials.gov on 18 July 2013. The Panel further noted GlaxoSmithKline's submission that lapatinib was divested by GlaxoSmithKline to Novartis and responsibility of this trial was transferred to Novartis in 2015. The Panel noted Goldacre *et al* which stated that 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. 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. The Panel noted that it appeared from the information provided that the circumstances were such that on 21 December 2016 GlaxoSmithKline was not responsible for the disclosure of the results of trial 2009-009885-15, the matter did not come within the scope of the Code and it therefore ruled no breach in relation to trial 2009-009885-15.

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 EC 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 guideline in question.

The Appeal Board noted GlaxoSmithKline's submission regarding the retrospective effort involved in posting older trials dating back to May 2004. The Appeal Board noted GlaxoSmithKline's submission that it had to post 718 older trials (344 of which had UK trial sites) on the EUCTR. The Appeal Board noted the data in Goldacre *et al* in that the results of 33 of GlaxoSmithKline's due trials had not been reported on EUCTR; the disclosure percentage was 88.7%. GlaxoSmithKline had submitted that it found 34 rather than 33 trials that appeared to have results due, but no results posted and that 18 had no

UK involvement, no UK centres, investigators or patients. Of the remaining 16 with a UK nexus there were two trials at issue in the appeal.

The Appeal Board noted that the Panel had ruled breaches of the Code for GlaxoSmithKline's failure to disclose results by 21 December 2016 or within the required timeframe in relation to two trials (trial 2011-005216-28 and trial 2011-005913-35) and these were the subject of the appeal.

The Appeal Board noted that for trial 2011-005216-28 posting on EUCTR was delayed because the trial was not tracked correctly as a GlaxoSmithKline-sponsored trial in internal systems and for trial 2011-005913-35, results posting on the EUCTR was delayed due to human error.

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 that both trials were published on GlaxoSmithKline's Clinical Study Register within 12 months of completion and both trials were published in the scientific literature. According to GlaxoSmithKline, both trials were also published on the EUCTR in March 2018 before Goldacre *et al* was published and before the complaint in this case was received in September 2018.

The Appeal Board was concerned about the failure to disclose the summary results of the two trials 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 two trials on the EUCTR as part of a retrospective exercise involving 344 trials with a UK nexus warranted a breach of the Code, particularly as the two trials had already been publicly disclosed and prior to receipt of the complaint. The Appeal Board ruled no breach of the Code in relation to each trial. 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/3118/11/18 (Tesaro) 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 GlaxoSmithKline 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.

Goldacre *et al* gave details of disclosure of clinical trial results for each sponsor. The data for GlaxoSmithKline were as follows:

Sponsors with highest proportion of trials reported

Sponsor	Total trials on EUCTR	Due trials	Due trials with results	% reported
GlaxoSmithKline	1,060	293	260	88.7

When writing to GlaxoSmithKline 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

GlaxoSmithKline noted that the BMJ study asserted that of its 293 company-sponsored clinical trials that should have results posted, results had only been posted for 260. The study authors did not identify the 33 trials that they had asserted did not have results posted on the EU Clinical Trial Register (EUCTR).

GlaxoSmithKline stated that it had accessed the data provided by the BMJ study authors and had identified 34, rather than 33, trials that appeared to have results due, but no results posted (details provided).

GlaxoSmithKline stated that 18 of the studies had no UK involvement (details provided). The remaining 16 trials were sponsored by a GlaxoSmithKline UK company or had UK trial centres and so were within the scope of the Code (details provided).

Of the 16 trials with UK involvement, 11 trials were cancelled before any patients were enrolled (details provided). These trials had protocol summaries registered in the EUCTR because clinical trial applications were filed in expectation of the planned trials. On the EUCTR, these cancelled trials were described as 'prematurely ended' and the date relevant member states were informed the trial was withdrawn was posted as the 'date of the global end of the trial'. As these trials did not enroll any subjects, there were no results to be disclosed.

Of the five trials with UK involvement and results, three trials were not clinical trials of a licensed medicine or a subsequently licensed medicine. Two of these three trials were exploratory studies of imaging methods (therefore not clinical trials of medicinal products, whether investigational or licensed) and one was a trial of an investigational medicine that was not approved in any market. GlaxoSmithKline submitted that these studies were thus not within the scope of Code and so no breach has occurred. The study details were as follows:

Trial 2008-005288-33 – evaluated the exploratory use of an imaging agent with enhanced MRI data acquisition and analysis methods, to characterise macrophage uptake in atherosclerotic plaques within the carotid artery.

Trial 2010-019832-11 – evaluated the uptake of an imaging agent in cancer cells for possible use as a biomarker for measuring response to chemotherapy. This trial was discontinued after enrolling only one subject and results could not be posted without compromising the patient's privacy.

Trial 2011-005216-28 – evaluated an investigational medicine, Vestipitant, that was not approved in any market. The trial completed on 22 August 2012 and its results were posted. Summary results were disclosed on GlaxoSmithKline's Clinical Study Register as GlaxoSmithKline protocol VNK115640 on 25 July 2013. The trial results were also published in the British Journal of Anaesthesia, 2015 March; 114(3):423-429.

GlaxoSmithKline noted that the two remaining trials with UK involvement were clinical trials of licensed medicines. Results of these studies were posted on an Internet register within 12 months of first market approval or within 12 months of trial completion for an already approved medicine, in compliance with the Code. Importantly the Code did not state which register should be used to meet this requirement. These studies were also submitted for publication

within 18 months of first market approval or of trial completion in compliance with the Code. The two studies were as follows:

Trial 2011-005913-35 (GlaxoSmithKline protocol DB2116132) was a trial of umeclidinium and vilanterol in combination, compared to the individual component medicines.

The disclosure of this trial was summarised:

- First market approval: 18 December 2013 (US).
- Trial completed: 11 June 2013.
- Summary results posted:
    - GlaxoSmithKline Clinical Study Register: 21 November 2013 (within 12 months of first market approval).
    - Clinicaltrials.gov: 11 February 2014 (within 12 months of first market approval).
- Publication:
    - Manuscript submitted: 27 November 2014 (within 18 months of first market approval).
    - Revised Manuscript submitted: 30 October 2015.
    - Publication issued: 1 March 2016; in 'Magnitude of meclidinium/vilanterol lung function effect depends on monotherapy responses: results from two randomised controlled trials'. Respir Med. 2016;112 :65-74.

Trial 2009-009885-15 (GlaxoSmithKline protocol LAP112620) was a trial of lapatinib in combination with vinorelbine or capecitabine. GlaxoSmithKline noted that lapatinib was divested by GlaxoSmithKline to Novartis and responsibility for this trial was transferred to Novartis as part of a transaction between the two companies in 2015.

The disclosure of this trial was summarised:

- First market approval: 13 March 2007 (US).
- Trial completed: 21 August 2012.
- Summary results posted:
    - GlaxoSmithKline Clinical Study Register: 18 April 2013 (within 12 months of trial completion).
    - ClinicalTrials.gov: 18 July 2013 (within 12 months of trial completion).
- Publications:
    - 'A phase II, randomized, multicentre study evaluating the combination of lapatinib and vinorelbine in women with ErbB2 overexpressing metastatic breast cancer', Breast Cancer Res Treat. 2014; 143: 493-505 (published and therefore submitted within 18 months of completion).

GlaxoSmithKline submitted that of the 5 trials with UK involvement and results, 3 were subject to legal requirements to disclose summary results on the EUCTR as they were clinical trials of medicinal products conducted in the EU (unlike Clause 13.1, these legal requirements applied to trials of either investigational or licensed medicines). GlaxoSmithKline submitted that as there had been no finding by any regulatory or judicial authority that the company had not complied with law and regulation, there was no breach of Clause 1.11.

For the trials in question, between the time the authors reviewed postings on 17 January 2018 and the BMJ article published on 12 September 2018, GlaxoSmithKline had posted results on the EUCTR for the three clinical trials of medicines that were required by regulation to have results posted to EUCTR (details below). These trials were now categorised by the BMJ article authors' online EU Tracker as 'Reported Results' and counted there as compliant. As the three trials' results were posted on the EUCTR as required by law and regulation, there was no breach of Clause 1.11.

Trial 2009-009885-15 (licensed medicine) results posted 21 July 2018.

Trial 2011-005913-35 (licensed medicine) results posted 21 March 2018.

Trial 2011-005216-28 (investigational medicine) results posted 8 March 2018.

GlaxoSmithKline submitted that it had maintained high standards regarding the disclosure of clinical trials results: its conduct had not brought discredit upon, or reduced confidence in, the pharmaceutical industry.

GENERAL COMMENTS FROM THE PANEL

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.

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

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 the data in Goldacre *et al* in that the results of 33 of GlaxoSmithKline's due trials had not been reported on EUCTR; the disclosure percentage was 88.7%.

The Panel noted GlaxoSmithKline's submission that it found 34 rather than 33 trials that appeared to have results due but no results posted.

The Panel noted GlaxoSmithKline's submission that of the 34 trials, 18 had no UK involvement, no UK centres, investigators or patients. The Panel considered that as there was no UK involvement, the matter did not come within the scope of the UK Code. No breach of the Code was ruled in relation to these 18 trials.

The Panel noted GlaxoSmithKline's submission that of the 16 trials with UK involvement, 11 (EUCTR 2004-005058-30, 2005-001122-87, 2007-000779-40, 2007-004025-20, 2007-005954-22, 2009-011782-92, 2010-019390-15, 2010-024087-17, 2011-000241-21, 2011-002818-37, and 2014-001959-274) were cancelled prior to enrolling any subjects. The Panel considered that there were no results to report. The Panel therefore ruled no breaches of Clauses 1.11, 9.1 and 2 in relation to these 11 trials.

The Panel noted GlaxoSmithKline's submission that of the five trials with UK involvement and results, three trials were not clinical trials of a licensed medicine or a subsequently licensed medicine. Two (trial 2008-005288-33 and trial 2010-019832-11) of these three studies were exploratory studies of imaging methods (therefore not clinical trials of medicinal products, whether investigational or licensed).

The Panel noted that according to Goldacre *et al,* which was the source of the compliant, 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. In the Panel's view, there was no evidence before it that the results of the above two trials which were exploratory studies of imaging methods were required to be disclosed under EC Guidelines. The Panel therefore ruled no breach of Clauses 1.11, 9.1 and 2 in relation to these two trials.

The Panel noted GlaxoSmithKline's submission that trial 2011-005216-28 which completed on 22 August 2012 evaluated an investigational medicine, Vestipitant, that was not approved in any market. The Panel noted GlaxoSmithKline's submission that summary results were disclosed on GlaxoSmithKline's Clinical Study Register as GlaxoSmithKline protocol VNK115640 on 25 July 2013. The trial results were also published in the British Journal of Anaesthesia, 2015 March; 114(3):423-429. However, 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 was unsure whether or not the results were now disclosed on EUCTR but noted that they were published elsewhere as stated above. The Panel therefore did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

The Panel noted that trial 2011-005913-35 was a trial of umeclidinium and vilanterol in combination, compared to the individual component medicines. The product was first marketed on 18 December 2013 in the US and the trial completed on 11 June 2013. The Panel noted GlaxoSmithKline's submission that summary results were posted on GlaxoSmithKline Clinical

Study Register on 21 November 2013 and on Clinicaltrials.gov on 11 February 2014. However, 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 was unsure whether or not the results were now disclosed on EUCTR but noted that they were published elsewhere as stated above. The Panel therefore did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

The Panel noted that trial 2009-009885-15 involved a trial of lapatinib in combination with vinorelbine or capecitabine which received first market approval on 13 March 2007 in the US. The trial completed on 21 August 2012. The Panel noted GlaxoSmithKline's submission that summary results were posted on GlaxoSmithKline Clinical Study Register on 18 April 2013 and on Clinicaltrials.gov on 18 July 2013. The Panel further noted GlaxoSmithKline's submission that lapatinib was divested by GlaxoSmithKline to Novartis and responsibility of this trial was transferred to Novartis as part of a transaction between the two companies in 2015.

The Panel noted Goldacre *et al* which stated that 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. 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.

The Panel noted that it appeared from the information provided that the circumstances were such that on 21 December 2016 GlaxoSmithKline was not responsible for the disclosure of the trial results of trial 2009-009885-15.

The Panel considered that in the particular circumstances of this case as far as GlaxoSmithKline was concerned the matter did not come within the scope of the Code and it therefore ruled no breach in relation to trial 2009-009885-15.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline appealed the Panel's rulings of a breach of Clause 9.1 with respect to transparency of the results for clinical trials 2011-005216-28 and 2011-005913-35.

GlaxoSmithKline submitted that clinical trial transparency was fundamentally important in the conduct of good science and helped the medical community and patients have access to the latest information to make decisions about healthcare. GlaxoSmithKline was a recognised leader in this area and had played a pivotal role in setting high standards for clinical trial transparency, including:

- In 2004, GlaxoSmithKline was the first pharmaceutical company to establish a clinical trial register to provide result summaries of its trials. This register now contained results from over 6,000 clinical studies.
- In 2013 GlaxoSmithKline was the first pharmaceutical company to commit to publicly disclose clinical study reports from its trials. Over 2,000 were now publicly available.

- In 2013 GlaxoSmithKline was the first pharmaceutical company to establish a system for sharing anonymised patient level data from its trials with other researchers. GlaxoSmithKline had now listed over 2,000 clinical trials as available for data sharing.

GlaxoSmithKline submitted that its policy on clinical trial transparency was industry leading. The policy covered all aspects of clinical study transparency, including commitments to post information on registers, publish studies in the scientific literature and share patient level data.

GlaxoSmithKline set high standards for clinical trial disclosure and delivered on those high standards. An independent review published in 2017 rated GlaxoSmithKline first among forty-six pharmaceutical companies for the scope and content of its transparency policies. Furthermore, independent trial trackers assessing compliance with US and EU regulations showed compliance at 100% and 99.8% (the single case currently listed on the EU Trial Tracker (one out of 436) as having results due but not posted was compassionate use access of a medicine that GlaxoSmithKline had divested, for which GlaxoSmithKline had no results to post) respectively (GlaxoSmithKline Performance on Current US and EU Trial Trackers was provided).

GlaxoSmithKline submitted that regarding trials 2011-005216-28 and 2011-005913-35, it publicly disclosed the trials' results on registers within 12 months of trial completion and published trial results in the scientific literature. For both trials GlaxoSmithKline posted summary results on the EUCTR in March 2018, prior to the PMCPA complaint in the present case which GlaxoSmithKline received on 28 September 2018. The public disclosure of these two studies was described in detail in GlaxoSmithKline's response to the complaint and repeated here.

<u>Trial 2011-005216-28 evaluated an investigational product, vestipitant</u>

- First Market Approval of study medicine: None (vestipitant was not approved as a GlaxoSmithKline product in any market, and to GlaxoSmithKline's knowledge, was not approved in any market under the auspices of any other entity).
- Trial Completed: 22 August 2012.
- Summary results posted:
    - GlaxoSmithKline's Clinical Study Register as GlaxoSmithKline protocol VNK115640 on 25 July 2013 (within 12 months of trial completion).
- Publication:
    - Publication Issued: March 2015 'Comparison of Vestipitant with Ondansetron for the Treatment of Breakthrough Postoperative Nausea and Vomiting after Failed Prophylaxis with Ondansetron'. British Journal of Anaesthesia, 114(3):423-429.

<u>Trial 2011-005913-35 evaluated umeclidinium and vilanterol in combination, compared to the individual component drugs</u>

- First Market Approval of study medicine: 18 December 2013 (US).
- Trial Completed: 11 June 2013.
- Summary results posted:

    - GlaxoSmithKline Clinical Study Register as GlaxoSmithKline protocol DB2116132: 21 November 2013 (within 12 months of trial completion and of first market approval).
    - Clinicaltrials.gov: 11 February 2014 (within 12 months of first market approval).
- Publication:
    - Manuscript Submitted: 27 November 2014 (within 18 months of first market approval).
    - Revised Manuscript Submitted: 30 October 2015.
    - Publication Issued: 1 March 2016; in 'Magnitude of umeclidinium/vilanterol lung function effect depends on monotherapy responses: results from two randomised controlled trials'. Respir Med. 2016;112 :65-74.

GlaxoSmithKline submitted that this record of public disclosure of the results demonstrated that GlaxoSmithKline set and maintained high standards for clinical trial transparency.

Posting older trials on the EU Register was a major retrospective effort and timelines were not mandatory

GlaxoSmithKline submitted that the history of the EUCTR was complex; various EU regulations, coming into effect over time and acting in combination, retroactively required summary results posting of clinical trials that began after May 2004. These postings of older trials could not be carried out, however, until after the EUCTR became available in July 2014.

It was also important to note that the timeframes recommended for posting such older trials on the EU register were not the subject of a mandatory regulation but were included in the Guideline EC 2012/C 302/03 and modified by informal advice, as detailed below. Both trials 2011-005216-28 and 2011-005913-35 ended more than a year before the EUCTR programming was finalised.

- EC 2012/C 302/03 § 4.6.1 recommended that 'Result-related information on clinical trials which ended one year or more prior to finalisation of the programming [of the relevant databases] … should be done within 24 months of the finalisation of the programming' (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf).
- 'Trial results: Modalities and timing of posting' dated the 'finalisation of the programming' at 21 July 2014 and recommended posting trials that ended more than a year earlier (before 21 July 2013) by 21 July 2016 (https://eudract.ema.europa.eu/docs/guidance/Trial%20results_Modalities%20and%20timing%20of%20posting_V2.0.pdf).
- Due to problems with the EU Registry, via news updates, EMA postponed the 21 July 2016 date: 'In addition, for trials categorised as to be posted ≤ 24 months after finalisation of the programming (see document "Trial results: modalities and timing of posting"), the deadline for submission of summary results will be 21 December 2016, being five months from the current deadline in July 2016' (https://eudract.ema.europa.eu/whatsnew_archive.html).

For GlaxoSmithKline, posting these older trials dating back to May 2004 on the EUCTR required identifying, collecting and posting available results of 718 clinical trials (344 of which had UK trial sites). Trials 2011-005216-28 and 2011-005913-35 represented 0.003% (2/718) of this

overall effort. Again, as described above, summary results of trials 2011-005216-28 and 2011-005913-35 were posted on public registers before the EUCTR was launched and the trials were published in the scientific literature in a timely manner.

In addition, to the fact that the trials' results were already publicly available before the creation of the EUCTR, the inadvertent delay in posting the two trials' results on the EUCTR did not pose any risk to patient welfare; the investigational medicine in trial 2011-005216-28 had never been licensed and trial 2011-005913-35 evaluated a combination product against its individual components but was not pivotal to regulatory approval.

In the case of trial 2011-005216-28, results posting on the EUCTR was delayed because the trial was not tracked as a GlaxoSmithKline-sponsored trial in internal systems. For trial 2011-005913-35, results posting on the EUCTR was delayed because, in collecting the 718 'older trials' dating back to 2004 for posting when the EUCTR became operational in 2016, the trial was omitted due to human error.

Therefore, GlaxoSmithKline submitted that it was not reasonable for the Panel to measure high standards against a hypothetical 100% compliance rate with a non-mandatory timeline guideline related to retrospective posting that included hundreds of trials, when the two trials' results were posted on public registers before the creation of the EU register and published in the scientific literature and were posted to the EU register in March 2018. As the two trials were publicly disclosed promptly and, as discussed below, in accordance with the Code standards, GlaxoSmithKline submitted that high standards were maintained.

The ABPI Code of Practice's standard for clinical trial transparency were set by Clause 13.1, which was not considered by the Panel

In the present case, GlaxoSmithKline responded with respect to Clauses 13.1, 1.11, 9.1 and 2.

However, in its decision, the Panel declined to evaluate trials 2011-005216-28 and 2011-005913-35 under Clause 13.1. This was not consistent with past PMCPA cases on clinical trial transparency. Clause 13.1 set the Code specific standard for clinical trial transparency. Clause 13.1 stated 'Companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature'. In turn, the two Joint Positions set out specific transparency standards.

In previous PMCPA cases related to clinical trial transparency, the Panel had focused on Clause 13.1 or its precursor Clause 21.3 to evaluate whether the transparency requirement of the Code was met. In each of those prior clinical trial transparency cases, a breach of Clause 9.1 was only found as an extension of a breach first found of Clause 13.1 or its precursor Clause 21.3. Similarly, in each case in which no breach of Clause 13.1 or its precursor Clause 21.3 was found, no breach of Clause 9.1 was found.

In the response to the complaint, GlaxoSmithKline submitted that it had showed that the requirements of Clause 13.1 were met for trials 2011-005216-28 (which, under Clause 13.1, was not required to have results disclosed, as the investigational study medicine was never licensed) and 2011-005913-35. This reliance on Clause 13.1 as the relevant standard for results disclosure was emphasised in the PMCPA Clinical Trial Transparency Decision Tree published as part of past clinical trial transparency cases and available as 'Advice' on the

PMCPA's website. The first step in the Decision Tree was to apply a requirement from the Joint Positions as codified in Clause 13.1 – 'Is the [trial] product licensed and commercially available?'. If the answer was 'No', the Decision Tree's direction was 'No requirement to disclose'. By not addressing the present case through Clause 13.1, the Panel did not apply the Code's specific standards for clinical trial transparency, and therefore did not apply the Code's consistent basis for measuring whether high standards were maintained under Clause 9.1: this consistent basis was Clause 13.1 and the Joint Positions.

The Panel's Use of EC Guidelines in its decision on Clause 9.1 was inconsistent with past cases

GlaxoSmithKline submitted that as the Panel did not apply the specific standards in Clause 13.1 for clinical trial transparency in this case, the Panel decision stated: '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 Commission Guideline 2012/C302/03'.

GlaxoSmithKline noted that with respect to the Commission Guidelines, the Panel ruled no breach of Clause 1.11, noting that there had been no finding of non-compliance with the Commission Guidelines with respect to the trials by any authority charged with determining such compliance.

GlaxoSmithKline noted that the Panel's ruling on Clause 1.11 could be understood as either recognition that the Panel was not authorised to evaluate the EC Guidelines independently, or that the EC Guidelines did not constitute a binding legal or regulatory standard against which to measure behaviour. Both understandings were true.

GlaxoSmithKline submitted that in a previous case (Case AUTH/2956/5/17) the Panel acknowledged that judgements on compliance with standards outside of the Code were not within its purview. Considering a complaint alleging potential data protection violations, the Panel found:

> 'The Panel was concerned about activities in relation to the Code. It was not for the Panel to determine whether Napp's activities were in line with data protection requirements per se' (emphasis added).

GlaxoSmithKline submitted that the Panel in the present case acted consistently with this principle, finding no breach of Clause 1.11 by referring to the fact that no external authority with appropriate accountability had found a breach of law or regulation with respect to trials 2011-005216-28 and 2011-005913-35.

However, in Case AUTH/2956/5/17 cited above, where no breach of Clause 1.11 was found, no breach of Clause 9.1 was found.

> '[T]he complainant had not provided evidence that the companies had been found in breach of data protection requirements. Given the circumstances the Panel therefore ruled no breach of Clause 9.1' (emphasis added).

Therefore, following Case AUTH/2956/5/17, GlaxoSmithKline submitted that it was not appropriate for the Panel, in the absence of a finding by an external authority with appropriate accountability, to find that high standards were not met with respect to the EC Guidelines. In

short, when considering clinical trial transparency, the Panel should not find no breach of law or regulation under Clause 1.11 but then turned to find that high standards were not met by reference to the EC Guidelines timeline recommendations.

GlaxoSmithKline submitted that as discussed above, the timelines in the EC Guidelines were recommendations and not a binding standard against which to measure behaviour. The EC Guidelines uniformly used 'should', rather than 'shall' or 'must', in discussing timelines for trial result summary posting, and this advisory guideline on timing for posting was informally modified due to operational delays of the readiness of the EUCTR.

GlaxoSmithKline was not aware of clinical trial transparency cases in which a breach of Clause 9.1 alone was found, without an associated breach of Clause 1.11 or Clause 13.1. (GlaxoSmithKline was aware that in some past PMCPA cases, a Panel had found a breach of Clause 9.1, without an associated predicate finding of breach of a more specific Code requirement that defined a high standard. However, a review of recent (2018-19) such cases indicated that they were all related to promotional activities or materials. Clinical trial transparency was, by definition, non-promotional activity.

Whilst Clause 9.1 had been applied to clinical trial transparency cases, it was applied only in association with Clause 13.1. Applying Clause 9.1 alone, rather than in association with a specific Code standard, according to the supplementary information, should be reserved for complaints related to promotional activities or materials. The supplementary information for Clauses 9.1 and 9.2 in the Code stated 'The special nature of medicines and the professional audience to which the material is directed require that the standards set for the promotion of medicines are higher than those which might be acceptable for general commodity advertising' (emphasis added).

GlaxoSmithKline submitted that for the Panel to apply Clause 9.1 to find breaches of high standards that were: (a) not related to pharmaceutical promotion; (b) not found in the Code of Practice; (c) non-binding and advisory in nature and (d) had not been found to have been violated by authorities charged with administering the standards, created a precedent which could allow rulings related to high standards which might go beyond the remit of the Code.

For example, GlaxoSmithKline submitted that pharmaceutical companies were required to report certain adverse events associated with prescription medicines to regulatory authorities, within defined timelines. Despite dedicated systems and focused processes and overall timeline compliance greater that 90%, not all such reports were submitted within timelines; this was routinely accepted by regulators as unavoidable and acceptable, as long as overall compliance with timelines was high and appropriate systems were in place.

Similarly, with respect to clinical trials generally, the UK Medicines and Healthcare products Regulatory Agency (MHRA) had stated that high standards were represented by quality systems and oversight – not by perfection:

> 'Sometimes things do not go to plan and errors occur on trials. The mere unpredictability of real-life means that clinical trials are not perfect and do not always run according to the planned trial protocol. Reporting of serious breaches correctly and managing them appropriately demonstrates an effective quality management system and effective quality oversight within the organisation.' (https://mhrainspectorate.blog.

gov.uk/2019/05/24/gcp-serious-breaches-the-2018-edition/).

GlaxoSmithKline submitted that it had maintained high standards regarding clinical trial disclosure, evidenced by an industry leading policy and recognition of high disclosure rates by independent sources. Maintaining high standards should be gauged by the entirety of clinical trials that were disclosed in an appropriate and timely manner.

In summary, GlaxoSmithKline did not believe the late posting (according to non-mandatory EC Guidelines) of the results of the two trials on the EUCTR as part of a retrospective exercise involving hundreds of trials warranted a breach of Clause 9.1, particularly as the two trials had already been publicly disclosed on registers and in the scientific literature and met the Code requirements for clinical study transparency under Clause 13.1.

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 EC 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 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 said to be 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 GlaxoSmithKline's submission regarding the retrospective effort involved in posting older trials dating back to May 2004. The Appeal Board noted GlaxoSmithKline's submission that it had to post 718 older trials (344 of which had UK trial sites) on the EUCTR. The Appeal Board noted the data in Goldacre *et al* in that the results of 33 of GlaxoSmithKline's due trials had not been reported on EUCTR; the disclosure percentage was 88.7%. GlaxoSmithKline had submitted that it found 34 rather than 33 trials that appeared to have results due, but no results posted and that 18 had no UK involvement, no UK centres, investigators or patients. The Appeal Board noted its comment above about trials with no UK nexus. Of the remaining 16 with a UK nexus there were two trials at issue in the appeal.

The Appeal Board noted that the Panel had ruled breaches of Clauses 9.1 for GlaxoSmithKline's failure to disclose results by 21 December 2016 or within the required timeframe in relation to two trials (trial 2011-005216-28 and trial 2011-005913-35) and these were the subject of the appeal.

The Appeal Board noted that for trial 2011-005216-28 posting on EUCTR was delayed because the trial was not tracked correctly as a GlaxoSmithKline-sponsored trial in internal systems and for trial 2011-005913-35, results posting on the EUCTR was delayed due to human error.

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 that both trials were published on GlaxoSmithKline's Clinical Study Register within 12 months of completion and both trials were published in the scientific literature. According to GlaxoSmithKline, both trials were also published on the EUCTR in March 2018 before Goldacre *et al* was published and before the complaint in this case was received in September 2018.

The Appeal Board was concerned about the failure to disclose the summary results of two trials (trial 2011-005216-28 and trial 2011-005913-35) 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 two trials on the EUCTR as part of a retrospective exercise involving 344 trials with a UK nexus warranted a breach of

Clause 9.1, particularly as the two trials had already been publicly disclosed and prior to receipt of the complaint. The Appeal Board ruled no breach of Clause 9.1 in relation to each trial. 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/3118/11/18 (Tesaro) 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 **12 September 2018**

Case completed **18 September 2019**