CASE AUTH/3102/9/18 ***NO BREACH OF THE CODE***

DIRECTOR v LILLY

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 Lilly 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 Lilly is given below.

General detailed comments from the Panel are given below.

The Panel noted the data in Goldacre *et al* in that results of forty-five of Eli Lilly's due trials had not been reported on EUCTR; the disclosure percentage was 47.7 %.

The Panel considered that as there was no UK involvement in 41 trials, the matter did not come within the scope of the UK Code. No breach of the Code was ruled in relation to those trials.

The Panel noted Lilly' submission with regard to the four trials that were conducted in the UK.

Trial 2012-005477-31 started in August 2013 and ended in March 2016 and involved emibetuzumab. The development of emibetuzumab had been terminated and the product was not licensed or commercially available anywhere in the world.

The Panel noted Lilly's submission that it had published the results on EudraCT in April 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 Lilly. 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. The Panel therefore did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

Trial 2010-022101-18 started in May 2012 and finished in October 2015 and involved tabalumub. Tabalumab was not licensed or commercially available anywhere in the world. The Panel noted Lilly's submission that it had published the results on EudraCT in April 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 Lilly. 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. The Panel therefore did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

Trial 2006-004486-34 started in October 2006 and finished in July 2009 and involved enzastaurin. Enzastaurin was currently in development and was not licensed or commercially available anywhere in the world. The Panel noted Lilly's submission that it had published the results on EudraCT in January 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 Lilly. 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. The Panel therefore did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

Trial 2008-003843-36 started in September 2008 and finished in January 2010 and involved exenatide (Byetta), which received its first licence in the US in April 2005 and was made commercially available there in June 2005. The Panel noted Lilly's submission that the trial was published in December 2010 in Annals of Internal Medicine and hence

met the disclosure requirement. Lilly noted that AstraZeneca acquired exenatide in August 2012.

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 Eli Lilly was not responsible for the disclosure of the trial results of Trial 2008-003843-36.

The Panel considered that in the particular circumstances of this case as far as Eli Lilly was concerned the matter did not come within the scope of the Code and it therefore ruled no breach in relation to Trial 2008-003843-36.

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 the 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 *el al*. In this regard, 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 Lilly had stated that it had 86 trials with results and 41 were due to be published on the EUCTR. The Appeal Board noted the data in Goldacre *et al* in that the disclosure percentage was 47.7%. Lilly submitted that four of the trials at issue were conducted in UK and were, therefore, subject to the Code. Of the remaining four trials with a UK nexus there were three trials at issue in the appeal (trials 2012-005477-31, 2010-022101-18 and 2006-004486-34).

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 Lilly's submission at the appeal that it had noted the non-mandatory EC Guideline and other relevant advice when it was introduced, and it had taken a cautious approach by waiting to see what other pharmaceutical companies would do before it decided what to do. Lilly subsequently decided to follow the EC

Guideline and it published the data from the three trials in question on EUCTR in January and April 2018 which was prior to receipt of the complaint.

Whilst the Appeal Board was concerned about the failure to disclose the summary results of the three trials on EUCTR within the timelines advised by the EC Guideline and other relevant advice and queried whether Lilly's 'wait and see' approach was appropriate. In the exceptional circumstances of this case, the Appeal Board did not consider that the late posting of the results of three trials on the EUCTR as part of a retrospective exercise warranted a breach of the Code. 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 appeals in this case and in Cases AUTH/3079/9/18 (Pfizer), AUTH/3087/9/18 (GlaxoSmithKline) and AUTH/3118/11/18 (Tesaro) 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 Lilly 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 Eli Lilly were as follows:

Sponsors with highest proportion of trials unreported

Sponsors	Total trials on EUCTR	Due trials with results	Due trials	% reported
Eli Lilly	375	41	86	47.7

When writing to Eli Lilly 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

Lilly noted that the BMJ referred to 41 clinical trials conducted by the company for which results were not included in EU Clinical Trials Register (EUCTR).

After a thorough investigation, and reference to Clause 13.1, 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, general comments from the Panel in the previous cases and the PMCPA decision tree, Lilly concluded that only four of the trials at issue were conducted in UK and were, therefore, subject to the scope of the Code. These were:

1 An emibetuzumab trial (2012-005477-31) which started in August 2013 and ended in March 2016.

Emibetuzamab's development had been terminated and the product was not licensed or commercially available anywhere in the world. There was thus no Code requirement to disclose the data from this trial. Lilly had, however, published the results on EudraCT in April 2018.

2 A trial on tabalumub (2010-022101-18) started in May 2012 and finished in October 2015.

Tabalumab was not licensed or commercially available anywhere in the world. Hence, based on the decision tree, there was no Code requirement to disclose the data from this trial. Lilly had, however, published the results on EudraCT in April 2018.

3 A trial on enzastaurin (2006-004486-34) started in October 2006 and finished in July 2009.

Enzastaurin was currently in development and was not licensed or commercially available anywhere in the world. Hence, based on the decision tree, there was no Code requirement to disclose the data from this trial. Lilly had, however, published the results on EudraCT in January 2018.

4 This trial (2008-003843-36) compared exenatide with placebo and started in September 2008 and finished in January 2010.

Exenatide (Byetta) received its first licence in the US in April 2005 and was made commercially available there in June 2005.

Based on the decision tree, the 2008 Code and 2005 Joint Position applied to the above trial and required disclosure within 1 year of completion of the trial. The trial was published in December 2010 in Annals of Internal Medicine and hence met the disclosure requirement. Lilly noted that AstraZeneca acquired exenatide in August 2012.

Following a request for further information, Lilly noted that there was an error in its response and acknowledged that there were in fact 45 and not 41 due trials for which results were not included in the EUCTR. For these additional 4 studies, and the 37 trials that Lilly had previously stated were not conducted in the UK, Lilly submitted that there was no direct or indirect connection between the trials and the UK; there were no UK investigators, none of these trials were conducted by or on behalf of Eli Lilly UK and there was no UK funding or any other UK involvement.

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*, Clause 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/3102/9/18

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 the data in Goldacre *et al* in that results of forty-five of Eli Lilly's due trials had not been reported on EUCTR; the disclosure percentage was 47.7 %.

The Panel noted Eli Lilly's submission that only four of the forty-five trials were conducted in the UK and were, therefore, subject to the Code; there were no UK investigators, funding or any other UK involvement in the other 41 trials.

The Panel considered that as there was no UK involvement in 41 trials, the matter did not come within the scope of the UK Code. No breach of the Code was ruled in relation to those trials.

The Panel noted Lilly' submission with regard to the four trials that were conducted in the UK.

Trial 2012-005477-31 started in August 2013 and ended in March 2016 and involved emibetuzumab. The development of emibetuzumab had been terminated and the product was not licensed or commercially available anywhere in the world.

The Panel noted Lilly's submission that it had published the results on EudraCT in April 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. The Panel therefore did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

Trial 2010-022101-18 started in May 2012 and finished in October 2015 and involved tabalumub. Tabalumab was not licensed or commercially available anywhere in the world. The Panel noted Lilly's submission that it had published the results on EudraCT in April 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. The Panel therefore did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

Trial 2006-004486-34 started in October 2006 and finished in July 2009 and involved enzastaurin. Enzastaurin was currently in development and was not licensed or commercially available anywhere in the world. The Panel noted Lilly's submission that it had published the results on EudraCT in January 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. The Panel therefore did not consider that in the circumstances a breach of Clause 2 was warranted and ruled accordingly.

Trial 2008-003843-36 started in September 2008 and finished in January 2010 and involved exenatide (Byetta), which received its first licence in the US in April 2005 and was made commercially available there in June 2005. The Panel noted Lilly's submission that the trial was published in December 2010 in Annals of Internal Medicine and hence met the disclosure requirement. Lilly noted that AstraZeneca acquired exenatide in August 2012.

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 Eli Lilly was not responsible for the disclosure of the trial results of Trial 2008-003843-36.

The Panel considered that in the particular circumstances of this case as far as Eli Lilly was concerned the matter did not come within the scope of the Code and it therefore ruled no breach in relation to Trial 2008-003843-36.

APPEAL BY LILLY

Lilly submitted that it was fully committed to the transparent publication of clinical trial data and compliance with the Code and it shared industry's commitments in this important area and recognised the interest of the PMCPA in preserving high standards.

Lilly appealed the Panel's ruling.

Lilly submitted that Clause 13.1 of the 2019 Code together with its supplementary information, the PMCPA Decision Tree and the Joint Position on the Disclosure of Clinical Trial Information via Clinical trial Registries and Databases to which they referred were explicit on the standards which UK pharmaceutical companies were expected to meet on trial data disclosure. Lilly had complied with these provisions in full.

Lilly submitted that EU legislation required that certain information contained in EudraCT be made accessible to the public. These requirements applied to clinical trials of paediatric as well as non-paediatric patients and applied primarily to trials which led to commercially available medicines. Lilly had complied with this legislation in full.

Lilly noted that Goldacre *et al* relied upon Commission Guideline (2012/C302/03) on the posting and publication of result-related information on clinical trials as the basis for the requirement to publish results, and this also formed the basis for the decision of the Panel. The Appeal Board

would be aware, however, that the Code made no mention of this guideline, and that an EU guideline did not impose legally enforceable obligations on pharmaceutical companies.

Lilly noted that as it stated in its ruling, the Panel was required only to consider the matter with regard to the Code. Lilly submitted that had complied in full with the extensive provisions in the Code. The Panel made no ruling on Clause 13.1 and found no breach of Clauses 1.11 and 2. As the Panel ruling also stated, there had been no formal finding by any judicial authority or appropriate body that Lilly was in breach of the Code.

Lilly submitted that in circumstances where a company had complied with the Code and the explicit provisions of the Code, supplementary material and Joint Positions and where the Code itself defined the standard that was to be met on a particular issue, it was neither fair nor reasonable to conclude that that the company had failed to maintain high standards.

Lilly had published the data from the three trials in question on EUCTR in January and April 2018. Lilly's corporate policy on the disclosure of clinical trial data was publicly available and was now in full alignment with the Guideline.

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 the 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 *el al*. In this regard, 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 and the failure to do so would potentially be covered by another code of practice in the relevant jurisdiction.

The Appeal Board noted Lilly had stated that it had 86 trials with results and 41 were due to be published on the EUCTR. The Appeal Board noted the data in Goldacre *et al* in that the disclosure percentage was 47.7%. Lilly submitted that four of the trials at issue were conducted in UK and were, therefore, subject to the Code. The Appeal Board noted its comment above about trials with no UK nexus. Of the remaining four trials with a UK nexus there were three trials at issue in the appeal.

The Appeal Board noted that the Panel had ruled breaches of Clauses 9.1 for Lilly's failure to disclose within the time indicated by the guidance in relation to three trials. The Appeal Board noted that three trials (trials 2012-005477-31, 2010-022101-18 and 2006-004486-34) were subject to the appeal.

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 Lilly's submission at the appeal that it had noted the non-mandatory EC Guideline and other relevant advice when it was introduced, and it had taken a cautious approach by waiting to see what other pharmaceutical companies would do before it decided what to do. Lilly subsequently decided to follow the EC Guideline and it published the data from the three trials in question on EUCTR in January and April 2018 which was prior to receipt of the complaint.

Whilst the Appeal Board was concerned about the failure to disclose the summary results of three trials (trials 2012-005477-31, 2010-022101-18 and 2006-004486-34) on EUCTR within the timelines advised by the EC Guideline and other relevant advice and queried whether Lilly's 'wait and see' approach was appropriate. In the exceptional circumstances of this case, the Appeal Board did not consider that the late posting of the results of three trials on the EUCTR as part of a retrospective exercise warranted a breach of Clause 9.1. 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/3087/9/18 (GlaxoSmithKline) and AUTH/3118/11/18 (Tesaro) 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**