PARAGRAPH 5.1/DIRECTOR v ASTRAZENECA

Clinical trial disclosure (Caprelsa)

A study published online in Current Medical Research & Opinion (CMRO) on 5 May 2015 was entitled 'Clinical trial transparency update: an assessment of the disclosure of results of company-sponsored trials associated with new medicines approved in Europe in 2012'. The study authors were Dr B Rawal, Former Medical Innovation and Research Director, ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and research. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2014. It covered 23 new medicines (except vaccines) from 18 companies that were approved by the European Medicines Agency (EMA) in 2012. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available in the supplemental information via a website link. Neither the study nor the supplemental information identified specific studies. The study did not assess the content of disclosure against any specific requirements.

The Deputy Director decided that the study was such that she had received information from which it appeared that AstraZeneca UK 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 summary output for each medicine set out the sources for all trials found irrespective of sponsor and an analysis of publication disclosure in the form of a table which gave details for the studies for Caprelsa (vandetanib) and Zinforo (ceftaroline fosamil).

The detailed response from AstraZeneca is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that two Caprelsa evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 95%. The disclosure percentage at 31 July 2014 was 95%. A footnote stated that from company communication, two undisclosed Phase II trials pre-dated disclosure requirements.

The Panel noted that Caprelsa was first licensed and commercially available in April 2011. The studies completed in November 2003 and August 2006. The 2008 Code and Joint Position 2005 were thus relevant.

One study which completed in 2003 and under the Joint Position 2005 did not need to be disclosed. The results were published in May 2005. The Panel ruled no breach of the 2008 Code including Clause 2.

The second study completed in August 2006 and was described by AstraZeneca as an exploratory Phase II study which terminated early due to slow enrolment. The Panel noted AstraZeneca's submission that this exploratory study was not of significant medical importance and nor did it impact on the product's labelling. The Panel therefore ruled no breach of the 2008 Code including Clause 2.

The Panel noted the CMRO publication in that three Zinforo evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 70%. The disclosure percentage at 31 July 2014 was 90%. A footnote stated that from company communication, the undisclosed trial was a post-approval Phase I [pharmacokinetic] type study in children, therefore out of scope of the disclosure requirements.

The Panel noted ceftaroline fosamil was first approved and commercially available as Teflaro in January 2011. The Panel noted that two studies which completed in February 2009 and July 2008 were undertaken before AstraZeneca was granted a sublicence in August 2009. These were the responsibility of another pharmaceutical company and this was taken up separately with that company (Case AUTH/2772/6/15).

The Panel noted that Zinforo was first licensed in August 2012 and commercially available in Germany on October 2012.

The Panel noted that the remaining study completed in February 2013 ie after both Zinforo and Teflaro were first licensed and commercially available (August 2012 and January 2011 respectively). The Second 2012 Edition of the Code and thus the Joint Position 2009 were relevant. This stated that if trial results for an investigational product that had failed in development had significant medical importance study sponsors were encouraged to post the results if possible. The Panel noted AstraZeneca's submission that the study was sponsored, designed and conducted by another company. It had no UK involvement and was conducted in the US. AstraZeneca had reimbursed half the cost of the study in order to use it in a paediatric investigation plan for Zinforo. The Panel noted that AstraZeneca was a UK registered company. It could be argued that this meant the UK Code applied however, the Panel considered that the circumstances were

such that AstraZeneca was not responsible for the disclosure of this study under the ABPI Code. The Panel considered that as there was no UK involvement in the study, the matter did not come within the scope of the UK Code and therefore ruled no breach.

A study published online in Current Medical Research & Opinion (CMRO) on 5 May 2015 was entitled 'Clinical trial transparency update: an assessment of the disclosure of results of company-sponsored trials associated with new medicines approved in Europe in 2012'. The study authors were Dr B Rawal, Former Medical Innovation and Research Director, ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and research. Publication support for the study was funded by the ABPI.

The study surveyed various publicly available information sources for clinical trial registration and disclosure of results searched between 1 May and 31 July 2014. It covered 23 new medicines (except vaccines) from 18 companies that were approved by the European Medicines Agency (EMA) in 2012. It included all completed company-sponsored clinical trials conducted in patients and recorded on a clinical trial registry and/or included in a European Public Assessment Report (EPAR). The CMRO publication did not include the specific data for each product. This was available in the supplemental information via a website link. Neither the study nor the supplemental information identified specific studies. The study did not assess the content of disclosure against any specific requirements.

The Deputy Director decided that the study was such that she had received information from which it appeared that AstraZeneca UK Limited might have with Paragraph 5.1 of the Constitution and Procedure to take the matter up as a complaint.

COMPLAINT

The study assessed the proportion of trials for which results had been disclosed on a registry or in the scientific literature either within 12 months of the later of either first regulatory approval or trial completion, or by 31 July 2014 (end of survey). Of the completed trials associated with 23 new medicines licensed to 18 different companies in 2012, results of 90% (307/340) had been disclosed within 12 months and results of 92% (312/340) had been disclosed by 31 July 2014.

The supplemental information gave details of disclosure of clinical trial results for each product irrespective of sponsor. The data for Caprelsa (vandetanib) were as follows:

Phase	Total	Un-evaluable	Evaluable	Disclosed in 12-month timeframe	Disclosure Percentage	Complete before 31 July 2014	Disclosed at 31 July 2014	Disclosure percentage at 31 July 2014
Phase I & II	37	2	35	33	94%	35	33	94%
Phase III	6	0	6	6	100%	6	6	100%
Phase IV	1	1	0	0		0	0	
Other	1	1	0	0		0	0	
Total	**45**	**4**	**41**	**39**	**95%**	**41**	**39**	**95%**

Footnote (company communication): Two undisclosed phase II trials pre-dated disclosure requirements.

The data for Zinforo (ceftaroline fosamil) were as follows:

Phase	Total	Un-evaluable	Evaluable	Disclosed in 12-month timeframe	Disclosure Percentage	Complete before 31 July 2014	Disclosed at 31 July 2014	Disclosure percentage at 31 July 2014
Phase I & II	3	0	3	1	33%	3	3	100%
Phase III	8	3	5	5	100%	5	5	100%
Phase IV	4	3	1	0	0%	1	0	0%
Other	1	0	1	1	100%	1	1	100%
Total	**16**	**6**	**10**	**7**	**70%**	**10**	**9**	**90%**

Footnote (company communication): The single undisclosed trial is a post-approval phase I PK type study in children, therefore out of scope of disclosure requirements.

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

total	total number of company sponsored trials identified which were completed by 31 July 2014
unevaluable	trials with completion date within the last 12 months or key dates missing – excluded from the analysis
evaluable	trials with all criteria present including dates, and hence the base number of trials which could be evaluated for the assessment
results disclosed in 12 month timeframe	evaluable trials which were disclosed within the target 12 months measured from the later of either first regulatory approval date in Europe or the US, or trial completion date
disclosure percentage	proportion of evaluable trials which were disclosed within 12 months measured from the later of either first regulatory approval date in Europe or the US, or trial completion date
completed before 31 July 2014	number of evaluable trials completed before 31 July 2014
Disclosed at 31 July 2014	number of evaluable trials with results disclosed by 31 July 2014
disclosure percentage at 31 July 2014	proportion of evaluable trials which were disclosed by 31 July 2014

AstraZeneca was asked to respond in relation to Clauses 2, 9.1 and 13.1 of the 2015 Code. The Authority noted that previous editions of the Code would be relevant and provided details.

RESPONSE

AstraZeneca stated that it had long been committed to making information about its clinical research publicly available to enhance the scientific understanding of how its medicines worked and in the medical interest of patients. The disclosure policies exceeded the current legal requirements for disclosure.

AstraZeneca stated that investigational clinical trials were registered on the US National Library of Medicine's website (www.clinicaltrials.gov) prior to the first patient being enrolled and to other websites within timelines as required by law or policy. Additionally, basic information was on the company's publicly accessible website (www.astrazenecaclinicaltrials.com).

AstraZeneca submitted that transparency of clinical trial results and applicable information from its clinical trials contributed to public confidence in medicines and improved public health and scientific knowledge. AstraZeneca recognised that increased requirements for transparency, within the reactive and proactive disclosure contexts, must also be balanced with the protection of personal data, intellectual property and confidential information.

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

- AstraZeneca registered and posted results from all Phase I-IV interventional trials, including healthy volunteer trials, on ClinicalTrials.gov and other applicable legally required websites, as well as on its own website

- AstraZeneca registered non-interventional studies and disclosed the results of those trials conducted on marketed (commercially available) products on all legally required websites in addition to its own website

- AstraZeneca posted trial results, synopses and other information on its website for products approved in countries that did not legally require disclosure

- AstraZeneca's timelines for disclosure were:
  - Results of trials with already commercially available medicines were posted within one year of trial completion. Results of trials with medicines in development were posted within 30 days of first regulatory approval for the new medicine where trials had completed at least one year. When a medicine in development was discontinued, results were published within one year of the public announcement of the decision, unless analysis and interpretation of the data were not sufficiently complete, in which case the company posted an explanation for the delay and the anticipated date when the results would be posted.
  - For marketed medicines and recently approved medicines where AstraZeneca considered there to be good cause to delay posting of results, it sought necessary approval according to applicable law. Where approved, an explanation for the delay and the anticipated date when the results would be posted.

AstraZeneca submitted that, in essence, it posted the results of all its clinical trials in all stages of clinical development on several public websites – regardless of outcome (positive or negative) – including for medicines which were discontinued in development.

Scope of complaint and AstraZeneca UK response

The basis of the complaint was the recently published CMRO survey which identified from the cohort of all completed company-sponsored clinical trials, carried out in patients and relating to new medicines approved by the EMA in 2012, studies for which results were not posted in a 'timely' manner. This included, according to the survey protocol, studies identified through searching clinical trial registries and/or included in a European Public Assessment Report (EPAR) for which results had not been disclosed within twelve months of the later of either first regulatory approval or trial completion. The survey also indicated if the clinical trial results had been disclosed by the end of the survey, 31 July 2014.

The supplemental information referred to two AstraZeneca products, Caprelsa (vandetanib) and Zinforo (ceftaroline fosamil), where the researchers considered that the disclosure of some clinical trial results had not been 'timely'. The percentage of evaluable studies disclosed within the twelve-month timeframe, as set out in the survey protocol, was 95% and 70% respectively.

The authors of the article stated that there were no unevaluable trials where the key dates were missing. All unevaluable trials had completed in the last 12 months and were within the required results disclosure timeframe disclosure.

Caprelsa

Vandetanib was first licensed in the US by the Food and Drug Administration (FDA) on 6 April 2011; it became commercially available without a trade name in the US on 25 April 2011. AstraZeneca did not wait for a trade name approval because, at that time, there were no other FDA-approved medicines available for the treatment of medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. The FDA approved the trade name Caprelsa in August 2011.

The supplemental information to the CMRO article stated that there were forty-one evaluable Caprelsa studies and of these thirty-nine were disclosed in a 'timely' manner in accordance with the survey protocol. A footnote to the Caprelsa data stated 'Two undisclosed phase II trials pre-dated disclosure requirements'.

The researchers had provided AstraZeneca UK with details of the Caprelsa studies included in the survey. AstraZeneca identified the studies which, in the opinion of the researchers, were not in accordance with the survey protocol.

As Caprelsa was launched in April 2011 and the studies in question were completed before 1 November 2008, the 2008 Code applied and this referred to the Joint Position 2005 which stated:

> 'The results of all clinical trials, other than exploratory trials, conducted on a drug that is approved for marketing and is commercially available in at least one country should be publicly disclosed on a free, publicly accessible, clinical trial results database, regardless of outcome. Trial results from exploratory trials also should be publicly disclosed if they are deemed to have significant medical importance and may have an impact on a marketed product's labeling.'

Study NCT00034918 was an exploratory Phase II study; it completed in November 2003 and thus did not need to be disclosed as it predated the Joint Position 2005. The study results were published in the journal Clinical Cancer Research in May 2005.

Study D4200C00045 was an exploratory, Phase II study; it completed in August 2006. This study terminated early due to slow enrolment and, therefore, was not of significant medical importance nor did it have an impact on the product's labelling. As per the Joint Position 2005, the results were not required to be disclosed.

On the basis of the information detailed above and the information regarding the studies not disclosed within the study protocol, AstraZeneca denied breaching Clause 21.3 of the 2008 Code, as the Joint Position 2005 did not require disclosure of the two trials identified as not being disclosed in 'timely' manner.

Zinforo

AstraZeneca submitted that ceftaroline fosamil was initially synthesized by Takeda Pharmaceutical Co Ltd and developed by Cerexa Inc and Forest Laboratories, Inc. In 2006, Forest Laboratories, Inc acquired Cerexa Inc. In August 2009, Forest Laboratories, Inc granted AstraZeneca an exclusive sub-licence including worldwide commercial rights and co-exclusive development rights for ceftaroline fosamil, excluding US, Canada and Japan. On 29 October 2010, Forest Laboratories obtained FDA approval for ceftaroline fosamil in the US and it became commercially available there as Teflaro on 3 January 2011. AstraZeneca was granted a licence for Zinforo by the EMA on 23 August 2012 and first made the product commercially available in Germany on 1 October 2012.

The supplemental information to the CMRO article stated that there were ten evaluable Zinforo studies and of these seven were disclosed in accordance with the survey protocol. One of these studies remained undisclosed on 31 July 2014. A footnote to the Zinforo data stated 'The single undisclosed trial is a post-approval phase I PK type study in children, therefore out of scope of the disclosure requirements'.

The researchers provided AstraZeneca UK details of the Zinforo studies included in the survey. AstraZeneca had identified the studies which, in the opinion of the researchers, were not in accordance with the survey protocol.

Two studies (NCT00633126 and NCT00633152) were exploratory studies. As Teflaro was first licensed and commercially available in January 2011 and the

studies completed in February 2009 and July 2008 respectively, the 2008 Code and the Joint Position 2005 were relevant. The Joint Position 2005 did not require the results from exploratory studies to be disclosed. Both these studies had results disclosed before the issue of a marketing authorization and commercial availability in territories that AstraZeneca was responsible for under the licensing agreement.

AstraZeneca submitted that these studies were sponsored, designed and conducted by Cerexa Inc and/or Forest Laboratories, Inc. The studies were not conducted on behalf of AstraZeneca and were conducted entirely in the US. There was no involvement of any UK centres, investigators or patients. The decision tree developed by the PMCPA for considering a previous clinical trial disclosure complaint and the subsequent case rulings, indicated that where the clinical trial had no involvement from a UK company and there was no involvement of UK centres, investigators or patients, then the ABPI Code did not apply.

The remaining study (NCT01298843) was a pharmacokinetic study in children aged younger than 12 years. As this study completed in February 2013, the Second Edition 2012 Code of Practice and the Joint Position 2009 were relevant. AstraZeneca UK recognised that this trial did not report results within the timelines required by the Joint Position 2009. However, as both Zinforo and Teflaro were licensed for use in those 18 years and over, this study was conducted in an unlicensed population.

AstraZeneca stated that this study was sponsored, designed and conducted by Forest Laboratories in order to fulfil an FDA paediatric post-marketing requirement. AstraZeneca reimbursed Forest Laboratories half of the cost of the study, in order to use the study as part of the paediatric investigation plan (PIP) for Zinforo. However, the study was not conducted on behalf of AstraZeneca. Furthermore, there was no involvement of any UK centres, investigators or patients in this study. The study was conducted entirely in the US and therefore the ABPI Code did not apply.

AstraZeneca's Global Procedure on Disclosure of Trial Information to Public Websites stated that the company was responsible for disclosure of study information where AstraZeneca had sponsored the study. The licensing agreement between AstraZeneca and Forest Laboratories for ceftaroline fosamil stated that each party was responsible for conducting their development activities in compliance with all applicable laws and guidelines in each party's respective territory. Therefore, as clearly set out in the documents detailed above, disclosure of these studies was the responsibility of Forest Laboratories not AstraZeneca.

AstraZeneca provided details of this complaint to Actavis, which acquired Forest Laboratories in July 2014, and Actavis informed AstraZeneca that the results for study NCT01298843 would be posted on EudraCT by 21 July 2015.

AstraZeneca UK denied breaching Clause 21.3 of both the 2008 ABPI Code and Second 2012 Edition of the Code as the studies were conducted outside the UK and were not sponsored by AstraZeneca nor were they conducted by or on behalf of AstraZeneca.

Summary

AstraZeneca denied breaching Clause 13 (2015 Code) and Clause 21.3 (2008 Code and Second 2012 Edition of the Code), as the studies identified by the researchers, were in compliance with the applicable ABPI Code and Joint Position or they fell out with the jurisdiction of the ABPI Code. Consequently, AstraZeneca denied breaching Clause 9.1 and Clause 2.

General comments from the Panel

The Panel noted that all the cases would be considered under the Constitution and Procedure in the 2015 Code as this was in operation when the CMRO study was published and the complaint proceedings commenced. The Panel noted that the study concluded that of the completed trials associated with 23 new medicines licensed to 18 different companies in 2012, results of 90% had been disclosed within 12 months and results of 92% had been disclosed by 31 July 2014.

The Panel noted that the CMRO study in question was an extension of a previously reported study of trials related to new medicines approved in Europe in 2009, 2010 and 2011 which found that over three-quarters of all these trials were disclosed within 12 months and almost 90% were disclosed by the end of the study. That study was the subject of an external complaint which gave rise to 27 cases in 2013 and 2014. The present case was not the subject of external complaint. The study itself formed the basis of the complaint.

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

Clause 13.1 of the 2015 edition of the Code stated that companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

The relevant supplementary information stated that this clause required the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patient enrolment) and the results of completed trials for medicines licensed for use and commercially available in at least one country. Further information was to be found in the current Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the current Joint Position on the Publication of Clinical Trial Results in the Scientific Literature, both at www.ifpma.org.en/ethics/clinical-trials-disclosure.html. Companies must include on the home page of their website, information as to where details of their clinical trials could be found.

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

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

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

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

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

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

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

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

> 'Companies must disclose details of clinical trials.'

The relevant supplementary information stated:

> **'Clause 21.3 Details of Clinical Trials**
>
> This clause requires the provision of details about ongoing clinical trials (which must be registered within 21 days of initiation of patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information can be found in the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 (http://clinicaltrials.ifpma.org).
>
> Details about clinical trials must be limited to factual and non-promotional information. Such information must not constitute promotion to health professionals, appropriate administrative staff or the public.'

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

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

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

The relevant supplementary information stated:

'Clause 21.3 Details of Clinical Trials

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

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

The Panel noted that in the 2014 ABPI Code the disclosure requirements which had previously been stated in Clause 21 had been moved to Clause 13. In addition, the supplementary information stated that companies must include on their website information as to where details of their clinical trials could be found. The 2014 Code came into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014. These requirements were to be found in Clause 13.1 of the 2015 Code. The relevant supplementary information had been amended in the 2015 Code to replace the year of the relevant joint positions with the word 'current', to add a reference to the medicine being licensed and 'commercially available' and to update the website address. The 2015 Code came into effect on 1 May 2015 for newly introduced requirements following a transition period from 1 January 2015 until 30 April 2015. The study at issue was posted online on 5 May 2015.

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

The Panel noted that the matter for consideration related to the disclosure of clinical trial results.

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

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

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

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

Having examined the various codes and joint positions, the Panel noted that the Joint Position

2005 excluded any clinical trials completed before 6 January 2005. The position changed on 18 November 2008 as the Joint Position 2008 did not have any exclusion relating solely to the date the trial completed. The Joint Position 2009 was similar to the Joint Position 2008 in this regard.

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

The Panel concluded that from 1 November 2008, (allowing for the transition period) until 30 April 2011 under the 2008 Code companies were required to follow the Joint Position 2005. From 1 May 2011 until 30 April 2012 under the 2011 Code and 1 May 2012 until 31 October 2012 under the 2012 Code companies were required to follow the Joint Position 2008. Since 1 November 2012 companies were required to follow the Joint Position 2009. The Panel considered that since the 2008 Code companies were, in effect, required to comply with the joint position cited in the relevant supplementary information. The relevant supplementary information gave details of what was meant by Clause 21.3 (Clause 13.1 in the 2014 and 2015 Codes). The Panel accepted that the position was clearer in the Second 2012 Edition of the Code. The Panel noted that the 2011 Code should have been updated to refer to the Joint Position 2009.

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

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

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

The Panel referred to the decision tree in the previous cases (for example 2654/11/13 *et al*) which it updated to include the 2015 Code.

The Panel considered that companies would be well advised to ensure that all the clinical trial results were disclosed as required by the codes and joint positions. The Panel considered that there was no complaint about whether the results disclosed met the requirements of the joint positions so this was not considered. In the Panel's view the article and thus the matter for consideration was only about whether or not study results had been disclosed and the timeframe for such disclosure. The CMRO publication focussed on the disclosure of evaluable trial results and the Panel only considered those evaluable trials.

The Panel noted that its consideration of these cases relied upon the information provided by the respondent companies. The CMRO publication did not identify the studies evaluated; it only provided quantitative data. The Panel noted that the study related to products approved for marketing by the EMA in 2012 and searched for the data between 1 May and 31 July 2014. The study was published online on 5 May 2015. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the date the product was first licensed and commercially available anywhere in the world might predate EMA approval.

PANEL RULING IN CASE AUTH/2763/5/15

Caprelsa

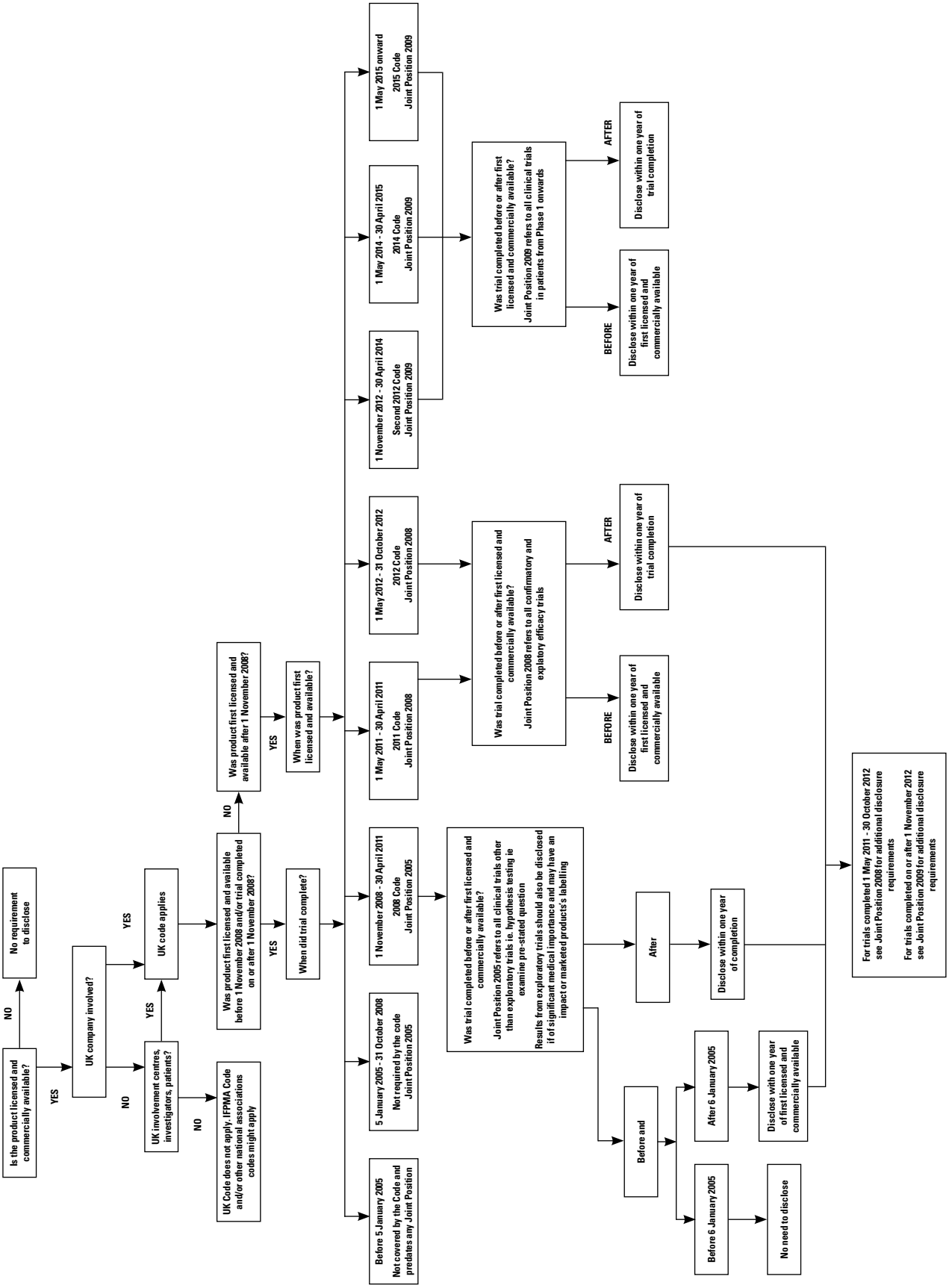
The Panel noted the CMRO publication in that two Caprelsa evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 95%. The disclosure percentage at 31 July 2014 was 95%. A footnote to the information stated that from company communication, two undisclosed Phase II trials pre-dated disclosure requirements.

The Panel noted that Caprelsa was first licensed and commercially available in April 2011. The studies completed in November 2003 and August 2006. The 2008 Code and Joint Position 2005 were thus relevant.

Study NCT00034918 completed in 2003 and under the Joint Position 2005 did not need to be disclosed. The results were published in Clinical Cancer Research in May 2005. The Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

Decision Tree

Updated Decision tree developed by the Panel



Study D4200C00045 completed in August 2006 and was described by AstraZeneca as an exploratory Phase II study which terminated early due to slow enrolment. The Panel noted AstraZeneca's submission that this exploratory study was not of significant medical importance and nor did it impact on the product's labelling. The Panel therefore ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

Zinforo

The Panel noted the CMRO publication in that three Zinforo evaluable studies had not been disclosed in the timeframe. The disclosure percentage was 70%. The disclosure percentage at 31 July 2014 was 90%. A footnote to the information stated that from company communication, the undisclosed trial was a post-approval Phase I PK [pharmacokinetic] type study in children, therefore out of scope of the disclosure requirements.

The Panel noted ceftaroline fosamil was first approved and commercially available as Teflaro in January 2011. The Panel noted that two studies (NCT00633126 and NCT00633152) which completed in February 2009 and July 2008 were part of work undertaken before Forest Laboratories granted a sublicence to AstraZeneca in August 2009. These were the responsibility of another pharmaceutical company and this was taken up separately with that company (Case AUTH/2772/6/15).

The Panel noted that Zinforo was first licensed in August 2012 and commercially available in Germany on October 2012.

The Panel considered that it could be argued that the date a product was first approved and commercially available was not brand specific if there were a number of different brand names for the same product as for ceftaroline fosamil. The Panel noted, however, that the joint positions referred to maintaining protection for intellectual property rights. Further it was not clear whether the reference to first approved and commercially available was medicine specific or company specific.

The Panel noted that the remaining study (NCT01298843) completed in February 2013. This was after the dates that both Zinforo and Teflaro were first licensed and commercially available (August 2012 and January 2011 respectively). The Second 2012 Edition of the Code and thus the Joint Position 2009 were relevant. This stated that if trial results for an investigational product that had failed in development had significant medical importance study sponsors were encouraged to post the results if possible. The Panel noted AstraZeneca's submission that the study was sponsored, designed and conducted by Forest Laboratories. It had no UK involvement and was conducted in the US. AstraZeneca had reimbursed half the cost of the study in order to use it in the paediatric investigation plan for Zinforo. The Panel noted that AstraZeneca was a UK registered company. It could be argued that this meant the UK Code applied.

The Panel considered that although AstraZeneca was a UK registered company, the circumstances were such that AstraZeneca was not responsible for the disclosure of Forest's study under the ABPI Code. The Panel considered that as there was no UK involvement in study NCT01298843, the matter did not come within the scope of the UK Code and therefore ruled no breach.

Complaint proceedings commenced **14 May 2015**

Case completed **2 July 2015**