CASE AUTH/2664/11/13

ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v TAKEDA

Clinical trial disclosure (Mepact, Edarbi and Daxas)

An anonymous, contactable member of the public complained about the information published as 'Clinical Trial Transparency: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved recently in Europe'. The study was published in Current Medical Research & Opinion (CMRO) on 11 November 2013. The study authors were Dr B Rawal, Research, Medical and Innovation Director at the ABPI and B R Deane, a freelance consultant in pharmaceutical marketing and communications. 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 from 27 December 2012 to 31 January 2013. It covered 53 new medicines (except vaccines and fixed dose combinations) approved for marketing by 34 companies by the European Medicines Agency (EMA) in 2009, 2010 and 2011. 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 via a website link and was referred to by the complainant. The study did not aim to assess the content of disclosure against any specific requirements.

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

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 Mepact (mifamurtide), Edarbi (azilsartan medoxomil) and Daxas (roflumilast).

The detailed response from Takeda is given below.

General detailed comments from the Panel are given below.

With regard to Daxas, the Panel noted the CMRO publication in that eleven evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 39%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 44%. Ten evaluable trials had not been disclosed. A footnote stated that all the undisclosed trials were now publicly available on the Takeda website.

The Panel noted that Daxas was first approved and commercially available in August 2010. This meant that for studies completing before that date the 2008 Code and Joint Position 2005 were thus relevant. The Panel examined the data provided by Takeda. This related to 15 completed studies with UK involvement. The Panel noted the discrepancy between Takeda's data and the CMRO publication and the further data provided by Takeda regarding the eight trials referred to in the CMRO publication. The Panel noted that trials completed after 5 January 2005 and before the date Daxas was first approved and commercially available (August 2010) needed to be disclosed by August 2011. Four studies had not been disclosed in the timeframe. The Panel ruled a breach of the 2008 Code. The delay in disclosure meant that high standards had not been maintained and a breach was ruled. As the results had been disclosed, the Panel considered there was no breach of Clause 2 and ruled accordingly.

A further three studies were listed with last patient last visit dates of 29 April 2008, 3 July 2007 and 31 January 2008 and 'Results Submission Dates' as 17 March 2011. The Panel noted Takeda's submission that the date of publication of the results was not known. These could have been publicly disclosed anytime between 30 days and 60 days after the results were submitted to clinicaltrials.gov. The Panel noted this gave a theoretical latest date of publication and thus disclosure of the results as 60 days from 17 March 2011, ie 16 May 2011. This was before one year after Daxas was first approved and commercially available, ie August 2011. The Panel ruled no breach of the 2008 Code including Clause 2.

Eight studies completed before 6 January 2005 and therefore the results did not need to be disclosed under the Joint Position 2005. No breach of the 2008 Code including Clause 2 was ruled.

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COMPLAINT

The complainant stated that the study detailed a number of companies which had not disclosed their clinical trial results in line with the ABPI for licensed products. The complainant provided a link to relevant information which included the published study plus detailed information for each product that was assessed.

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 each product. The data for Mepact (mifamurtide), Edarbi (azilsartan medoxomil) and Daxas (roflumilast) was as follows:

Mepact

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	11	0	11	6	55%	11	6	55%
Phase III	1	0	1	1	100%	1	1	100%
TOTAL	**12**	**0**	**12**	**7**	**58%**	**12**	**7**	**58%**

Edarbi

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	3	0	3	1	33%	3	1	33%
Phase III	17	2	15	15	100%	15	15	100%
TOTAL	**20**	**2**	**18**	**16**	**89%**	**18**	**16**	**89%**

Daxas

Total by phase	Total	Unevaluable	Evaluable	Disclosed in timeframe	Disclosure percentage	Complete before end January 2012	Disclosed at all	Disclosure percentage at 31 January 2013
Phase I & II	2	1	1	0	0%	1	1	100%
Phase III	18	1	17	7	41%	17	7	41%
Phase IV	2	2	0	0	0%	0	0	0%
TOTAL	**22**	**4**	**18**	**7**	**39%**	**18**	**8**	**44%**

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

total	total number of trials identified which were completed and/or with results disclosed
unevaluable	trials within the total which could not be evaluated (due to either trial completion date or publication date being missing or unclear) – excluded from the analysis
evaluable	trials with all criteria present including dates, and hence the base which could be evaluated for the assessment
results disclosed in timeframe	evaluable trials which fully complied with publication requirements, ie summary results disclosed (in registry or journal) within 12 months of either first regulatory approval date or trial completion date, whichever was later
disclosure percentage	proportion of evaluable trials which were fully disclosed
completed before end of January 2012	number of studies completed before end January 2012 (or already disclosed)
results disclosed at all	number of trials with any publication of results at any time
disclosure percentage at 31 January 2013	proportion of trials completed by end January 2012 which were now disclosed

The complainant listed the companies he/she would like to complain about and this included Takeda.

The complainant alleged that all of the companies listed had breached Clauses 2, 9 and 21 of the Code.

When writing to Takeda, the Authority drew attention to Clauses 1.8 and 21.3 of the Second 2012 Edition of the Code and noted that previous versions of the Code might also be relevant.

RESPONSE

Takeda understood that the original intent of the ABPI study was to demonstrate that there was greater transparency than the public commonly believed about research conducted by the pharmaceutical industry. It was not to highlight non-compliance with the ABPI Code. Takeda contacted the ABPI to confirm the intent of the CMRO publication and a copy of the response was provided.

Takeda willingly participated in line with its commitment to the principles of transparency. Since the survey, it had continued its commitment by completing ongoing results disclosure in line with its planned revised transparency policy (which went beyond the transparency required legally or by the Code).

Takeda did not consider that the complaint about disclosure of the results of clinical trials was within the scope of the ABPI Code Second 2012 Edition which clearly stated in Clause 21.3 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'. Previous Codes (2008 and 2011) stated 'Companies must disclose details of clinical trials'. Supplementary information stated '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'.

The clinical trials concerned, according to the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005 and 2008 respectively were 'all clinical trials, other than exploratory trials ... initiated on or after July 1, 2005' (Joint Position, 2005) or 'all confirmatory clinical trials ... initiated on or after July 1, 2005 ... and all exploratory efficacy trials ... initiated 6 months prior the publication of this Joint Position' (Joint Position, 2008).

The 2008 and 2011 Codes only specified disclosure of the details of clinical trials on databases such as clinicaltrials.gov. Disclosure of results was not specified until the 2012 Code.

Takeda submitted that the UK Code applied where the study involved some UK centres or patients or alternatively if a medicine was available in the UK, then the details of the studies must be disclosed. This was the case with each of these products except Edarbi. The ABPI Code for disclosure of details applied to Mepact and Daxas. Given that the disclosure of details was not the subject of the complaint Takeda had restricted its response to the matter of results disclosure. Should the PMCPA, however, determine that additional data regarding disclosure of details were required, data could be provided on the expectation that this would be supporting information and not the subject of the complaint.

Takeda stated that it acquired Mepact from IDM Pharma in June 2009 and it was granted its first marketing authorization globally by the European Commission on 6 March 2009. The first countries in which it was commercially available were Austria, Germany and the UK in February 2010 and thus Takeda submitted that the 2008 Code applied.

Edarbi was granted its first marketing authorization by the FDA in February 2011. The first country in which it was commercially available was the US in April 2011. Therefore Takeda submitted that the 2011 ABPI Code applied.

Takeda became responsible for Daxas on the

acquisition of Nycomed in 2011. Daxas was granted its first marketing authorization globally by the European Commission on 5 July 2010. It was first commercially available in Germany in August 2010. Therefore Takeda submitted that the 2008 ABPI Code applied.

Turning to the specific studies highlighted in the complaint, the Mepact trials were sponsored by another company, IDM Pharma, and were completed between 1988 and 1996. This was before the implementation of the 2005 Joint Position referred to in the 2008 Code. Therefore regardless of the complaint about results being outside the scope of the Code, the Mepact studies predated the remit of the 2005 Joint Position.

The azilsartan trials referred to in the CMRO publication only concerned Azilva. The clinical trials for Azilva (which contained the active form of azilsartan vs azilsartan medoxomil found in Edarbi) were outside the scope of the Code as there were no links to the UK and the product was only available in Japan. No studies relating to Edarbi were cited in the CMRO study. As such Takeda submitted that this negated the complaint.

All clinical trial details for Daxas were disclosed on clinicaltrials.gov as required by the 2008 ABPI Code. This information was provided as guidance to PMCPA and not for the purposes of responding to the complaint which referred to results; Takeda referred to its position on the scope of the Code set out above.

Takeda stated that although clinical trial results disclosure was not mandated by the ABPI Code before the 2012 Code, and then only for specific studies falling into certain criteria, Takeda was committed to transparency and thus had spent significant time to ensure that the results for these acquired products were disclosed according to a consistent standard applied to all of Takeda's other products. As such, the company noted its ongoing actions that supported its commitment to transparency whereby all of the studies discussed for the medicines referred to in the complaint had had results disclosed by the time the CMRO study was published and thus before the complaint was made.

Thus in response to the complaint regarding clinical trial disclosure concerning Mepact, Edarbi and Daxas, Takeda sincerely believed that the 2008 and 2011 Codes did not apply to the disclosure of results of clinical studies and as such the complaint was not within the scope of the relevant Codes. In addition it strongly refuted the complaint and all alleged breaches of the Code.

Takeda submitted that the supplementary information to Clause 1.8 that 'Pharmaceutical companies must ensure that they comply with all applicable codes, laws and regulations to which they are subject' could refer to the 2005 and 2008 Joint Positions on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases. However, it believed that these joint positions were not within the scope of Clause 1.8 as they were guidance rather than governmental-issued legislation/edicts or directives or codes of practice mandating adherence as issued by an industry association. This was reinforced by the ABPI's own position in changing the wording of Clause 21.3 in the 2012 edition of the Code.

Takeda submitted it was committed to the spirit and letter of the Code as well as the principle of transparency. As stated above, the results of all the studies referred to were available in the public domain. Since 2010 Takeda had had a global policy on 'Registration and Results Disclosure of Clinical Trial Information'; a new version came into force in January 2014 and confidential copies were provided.

In response to a request for additional information, Takeda provided more information about the Daxas trials. In response to a request for yet more information, the company confirmed that the phrase 'Results Submission Dates' on the spreadsheet detailing the Daxas trials was the date that results were submitted to clinicaltrials.gov. The dates when these studies were publicly disclosed after submission was unknown. Clinicaltrials.gov did not publicly document when results were disclosed publicly (ie when results were published on the website) it only documented when results were first submitted. It took approximately 30 to 60 days for clinicaltrials.gov to review results submissions and it would only publish information once submissions were accepted without requiring further clarification from the submitting organization.

Takeda submitted, therefore, that the date of submission was the date that the data were disclosed to clinicaltrials.gov. It was impossible to be completely accurate on the date clinicaltrials.gov actually publicly disclosed the data.

Takeda stated it had provided this information in the spirit of transparency but it referred to its comments above where it clearly stated that the disclosure of results for these medicines was outside the scope of the relevant codes.

In response to a request for further information about Daxas, Takeda submitted that eight of the fifteen completed trials listed in appendix 4 to the company's response were referred to in the CMRO publication. They were BY217/M2-012, BY217/M2-013, BY217/M2-112, BY217/M2-121, BY217/M2-124, BY217/M2-125, BY217/M2-127 and BY217/M2-128 and details of the studies and results had been disclosed.

The differences between the various study lists in this complaint were because of the differences in lists from the CMRO publication and the scope of the complaint whereby the focus was upon studies with UK involvement. The complete study lists to include all countries involved had been provided.

GENERAL COMMENTS FROM THE PANEL

The Panel noted the ABPI involvement in the study. However, a complaint had been received and it needed to be considered in the usual way in line with the PMCPA Constitution and Procedure. The Panel noted that all the cases would be considered under

the Constitution and Procedure in the Second 2012 Edition as this was in operation when the complaint was received. The addendum (1 July 2013 which came into effect on 1 November 2013) to this Code only related to Clause 16 and was not relevant to the consideration of these cases.

The Panel noted that the study concluded that the results of over three quarters of all company-sponsored clinical trials were disclosed within a year of completion or regulatory approval and almost 90% were disclosed by 31 January 2013 which suggested transparency was now better than had sometimes been reported previously.

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 related to UK health professionals or were carried out in the UK.

Clause 21.3 of the Second 2012 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 patients enrolment) and completed trials for medicines licensed for use in at least one country. Further information was to 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.

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. The Second 2012 Edition of the ABPI Code fully reflected the requirements of the IFPMA Code. The changes introduced in the ABPI Code were to update the date of the Joint Position on the Disclosure of Clinical Trial Information and to include the new requirement to disclose in accordance with the Joint Position on the Publication of Clinical Trial Results. 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 by the complainant 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 would come into effect on 1 May 2014 for newly introduced requirements following a transition period from 1 January 2014 until 30 April 2014.

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 complaint 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 applied, and thus which joint position, was complicated. It noted that the 2011 Code which, taking account 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 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 Code). 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.

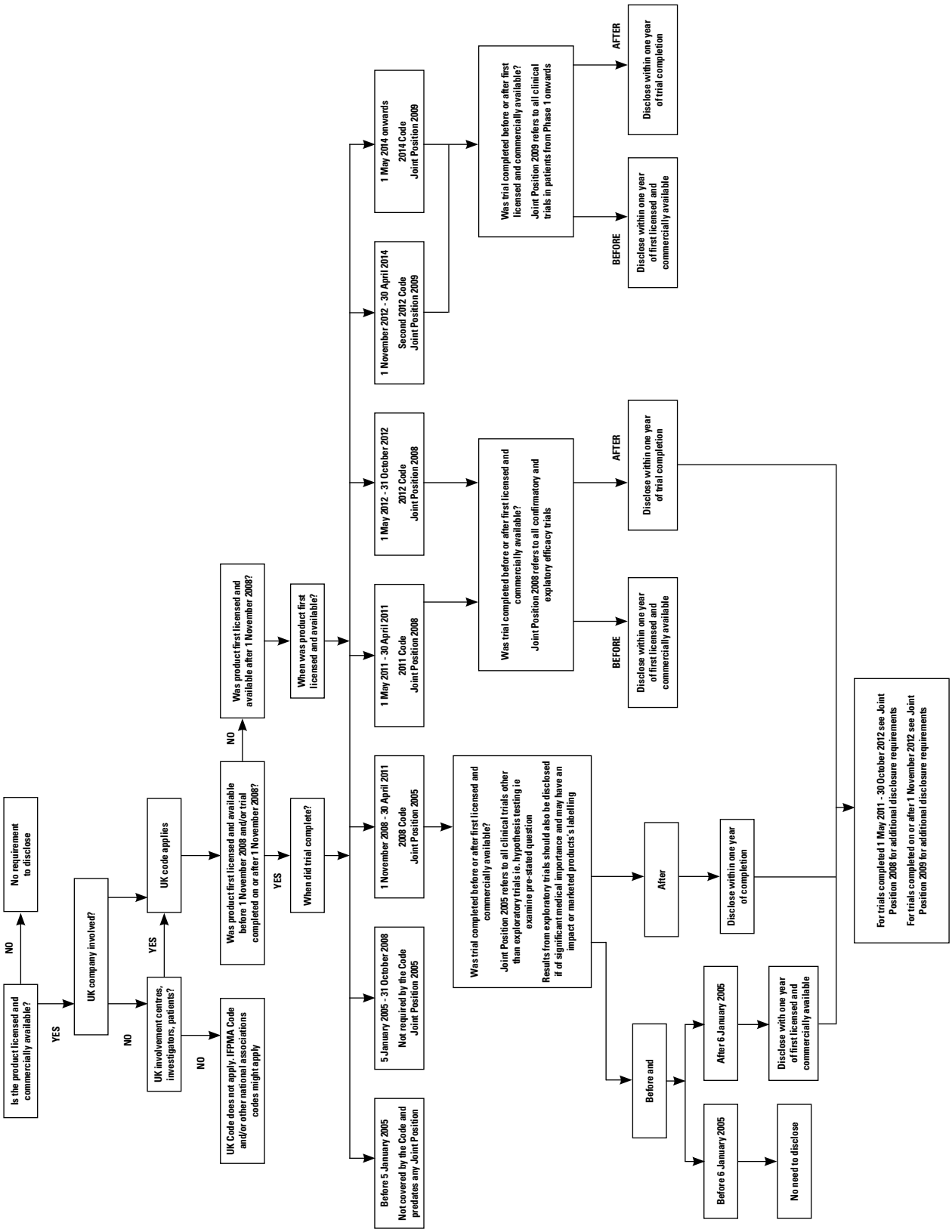
Noting that the complaint concerned licensed products the Panel considered that the trigger for disclosure was the date the product was first approved and commercially available anywhere in the world. This would determine which version of the Code (and joint position) applied for trials completed prior 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 1 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 complaint was about 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 followed the decision tree set out below which it considered set out all the relevant possibilities.

During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the codes and joint positions.

The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie there could be studies in addition to those looked at in the CMRO publication. The Panel decided that it would consider these cases in relation to the studies covered by the CMRO publication and not on the broader interpretation. 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 complaint was only about whether or not study results had been disclosed and the timeframe for such disclosure.

Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial results



The CMRO publication stated that as far as the IFPMA Joint Position was concerned implementation had been somewhat variable in terms of completeness and timing. The Panel noted that a number of studies were referred to in the CMRO publication as 'unevaluable' and these were not specifically mentioned by the complainant. 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 ran from 27 December 2012 to 31 January 2013 and was published in November 2013. The Panel considered that companies that might not have been in line with various disclosure requirements had had a significant period of time after the study completed and prior to the current complaint being received to have disclosed any missing information. It appeared that the authors of the CMRO publication had contacted various companies for additional information.

The Panel noted that the case preparation manager raised Clause 1.8 of the Second 2012 Edition with the companies. The supplementary information to Clause 1.8, Applicability of Codes, *inter alia*, referred to the situation when activities involved more than one country or where a pharmaceutical company based in one country was involved in activities in another country. The complainant had not cited Clause 1.8. The Panel noted that any company in breach of any applicable codes, laws or regulations would *defacto* also be in breach of Clause 1.8 of the Code; the converse was true. The Panel thus decided that as far as this complaint was concerned, any consideration of a breach or otherwise of Clause 1.8 was covered by other rulings and it decided, therefore, not to make any ruling regarding this clause (or its equivalent in earlier versions of the Code).

PANEL RULING IN CASE AUTH/2664/11/13

The Panel noted Takeda's comments about the various codes. It disagreed with its submission about when the need to disclose data was first introduced in the Code and considered this aspect was covered in its general comments above.

The Panel considered that Takeda was responsible under the Code for the publication of the Nycomed studies.

Mepact
The Panel noted the CMRO publication in that five evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 58%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 58%. A footnote stated that the undisclosed trials were sponsored by IDM Pharma and completed in 1993 and that Takeda was in the process of sourcing the information for disclosure.

The Panel noted that the Mepact trials which were completed after 6 January 2005 would need to be disclosed, however according to Takeda's submission, the studies highlighted in the CMRO publication were not sponsored by Takeda and had no UK involvement. The Panel considered that as there was no UK involvement, the matter did not come within the scope of the Code, and therefore ruled no breach.

Edarbi
The Panel noted the CMRO publication in that two evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 89%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 89%. A footnote stated that all studies had now been disclosed on Takeda.com. The two outstanding studies primarily related to the Japanese version of azilsartan (Azilva) which was approved in May 2012 and the studies were disclosed within one year of that approval.

The Panel noted Takeda's submission that there was no UK involvement in the two trials that had not been disclosed. It also noted that the results of these two trials were disclosed within a year of Azilva being approved. The Panel considered as there was no UK involvement, the matter did not come within the scope of the UK Code and therefore ruled no breach.

Daxas
The Panel noted the CMRO publication in that eleven evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 39%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 44%. Ten evaluable trials had not been disclosed. A footnote stated that all the undisclosed trials were now publicly available on the Takeda website (address provided).

The Panel noted that Daxas was first approved and commercially available in August 2010. This meant that for studies completing before that date the 2008 Code and Joint Position 2005 were thus relevant. The Panel examined the data provided by Takeda. This related to 15 completed studies with UK involvement. The Panel noted the discrepancy between Takeda's data and the CMRO publication and the further data provided by Takeda regarding the eight trials referred to in the CMRO publication. The Panel noted that trials completed after 5 January 2005 and before the date Daxas was first approved and commercially available (August 2010) needed to be disclosed by August 2011. Four studies (ref BY217/M2-012, -013, -121 and -124) had not been disclosed in the timeframe. The Panel ruled a breach of Clause 21.3 of the 2008 Code. The delay in disclosure meant that high standards had not been maintained and a breach of Clause 9.1 was ruled. As the results had been disclosed, the Panel considered there was no breach of Clause 2 and ruled accordingly.

A further three studies were listed with last patient last visit dates of 29 April 2008, 3 July 2007 and 31

January 2008 and 'Results Submission Dates' as 17 March 2011. The Panel noted Takeda's submission that the date of publication of the results was not known. These could have been publicly disclosed anytime between 30 days and 60 days after the results were submitted to clinicaltrials.gov. The Panel noted this gave a theoretical latest date of publication and thus disclosure of the results as 60 days from 17 March 2011, ie 16 May 2011. This was before one year after Daxas was first approved and commercially available, ie August 2011. The Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

Eight studies completed before 6 January 2005 and therefore the results did not need to be disclosed under the Joint Position 2005. No breach of Clause 21.3 and consequently Clauses 9.1 and 2 of the 2008 Code was ruled.

Complaint received **21 November 2013**

Case completed **27 March 2014**
