ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v BRISTOL-MYERS SQUIBB

Clinical trial disclosure (Onglyza, Nulojix and Yervoy)

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 Nulojix (belatacept), Onglyza (saxagliptin) and Yervoy (ipilimumab).

The detailed response from Bristol-Myers Squibb is given below.

General detailed comments from the Panel are given below.

With regard to Nulojix (Case AUTH/2656/11/13), the Panel noted the CMRO publication in that two evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 71%. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 86%. A footnote stated that the undisclosed trial was completed in 2004 and was not subject to FDAAA 801 requirements.

The Panel noted Bristol-Myers Squibb's submission that both trials had been published; only one had UK involvement and had been published in 2002, before Nulojix was first approved and commercially available (July 2011). In this regard, the Panel ruled no breach of the Code including Clause 2.

With regard to Onglyza (Case AUTH/2654/11/13), the Panel noted the CMRO publication in that two evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 88%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 100%.

Onglyza was first approved and commercially available in July 2009. The Panel noted Bristol-Myers Squibb's submission that the trial which involved UK patients completed in April 2010 and the results were posted on clinicaltrials.gov in August 2011. As the results were not disclosed by April 2011, Bristol Myers-Squibb had not met the requirements of the Code. The Panel ruled a breach of the 2008 Code. The delay in disclosure of the results meant that high standards had not been maintained and a breach was ruled. As the data had been published, the Panel considered that there was no breach of Clause 2 and ruled accordingly.

With regard to Yervoy (Case AUTH/2656/11/13), the Panel noted the CMRO publication in that six evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 63%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 63%. A footnote stated that the undisclosed trials were not subject to FDAAA 801 requirements.

Yervoy was first approved and commercially available in April 2011. The Panel noted that the one trial that involved UK patients completed in July 2007 and the results should have been disclosed by April 2012. Bristol-Myers Squibb submitted that this trial was presented as a poster in September 2008 and fully published in September 2009. The Panel ruled no breach of the 2008 Code including Clause 2.

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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 Nulojix (belatacept), Onglyza (saxagliptin) and Yervoy (ipilimumab) as follows:

Nulojix

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	6	1	5	3	60%	5	4	80%
Phase III	2	0	2	2	100%	2	2	100%
Phase IV	0	0	0	0	0%	0	0	0%
Other	0	0	0	0	0%	0	0	0%
TOTAL	**8**	**1**	**7**	**5**	**71%**	**7**	**6**	**86%**

Onglyza

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	1	0	1	1	100%	1	1	100%
Phase III	15	0	15	13	87%	15	15	100%
Phase IV	2	1	1	1	100%	1	1	100%
Other	0	0	0	0	0%	0	0	0%
TOTAL	**18**	**1**	**17**	**15**	**88%**	**17**	**17**	**100%**

Yervoy

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	15	2	13	8	62%	13	8	62%
Phase III	3	0	3	2	67%	3	2	67%
Phase IV	0	0	0	0	0%	0	0	0%
Other	0	0	0	0	0%	0	0	0%
TOTAL	**18**	**2**	**16**	**10**	**63%**	**16**	**10**	**63%**

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 Bristol-Myers Squibb.

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

When writing to Bristol-Myers Squibb, 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

Bristol-Myers Squibb stated that Case AUTH/2654/11/13 related to Onglyza which was a joint development project with AstraZeneca. As Bristol-Myers Squibb was solely responsible for the Onglyza trials referred to in the complaint, it had confirmed with AstraZeneca that it would respond to this complaint; AstraZeneca had no part in the arrangements for disclosing the results of the two specific studies.

Bristol-Myers Squibb Limited was most concerned to receive these complaints from a member of the public following the publication of the ABPI commissioned study on disclosure rates of results of company-sponsored trials. Bristol-Myers Squibb fully supported enhancing public access to clinical study information in a way that safeguarded the privacy of patients, respected the national regulatory systems and maintained incentives for investment in research and development.

The company's practice was to provide patients, clinicians and others with information about Bristol-Myers Squibb sponsored clinical trials that were conducted on investigational compounds and marketed products. During 2014 it would initiate publication of all Bristol-Myers Squibb Clinical Study Report Synopses from trials conducted on marketed products on the company website www.BMS.com.

Bristol-Myers Squibb submitted that its policy was to comply with all regulatory and legal obligations for transparency of clinical trial information for all markets in which it conducted clinical research. For example, when Bristol-Myers Squibb conducted clinical research in the US it was bound by the requirements of Section 801 of the Food and Drug Administration Amendments Act (FDAAA). As a result Bristol-Myers Squibb used the www.clinicaltrials.gov (National Institutes of Health) website for the registration and publication of clinical trial results. A brief summary of the FDAAA and International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) provision was provided.

Investigation of the complaint

Bristol-Myers Squibb submitted that the complaint related specifically to two overall measures for disclosure rates contained in the tabulated supplementary material which accompanied the CMRO publication:

- disclosure within 12 months of either the first EMA/FDA approval, or within 12 months of the completion of the trial if later, and
- disclosure at 31 January 2013.

The authors' conclusions in relation to disclosure rates for the relevant studies which involved Nulojix, Onglyza and Yervoy were as follows:

Product	**Disclosure within 12 months of either the first EMA/FDA approval, or within 12 months of the completion of the trial if later**	**Disclosure at 31 January 2013**
Nulojix	71% (5 of 7 studies)	86% (6 of 7 studies)
Onglyza	88% (13 of 15 studies)	100% (15 of 15 studies)
Yervoy	63% (10 of 16 studies)	63% (10 of 16 studies)

Bristol-Myers Squibb identified and reviewed the ten studies which the authors concluded had not been disclosed within the mentioned timelines (two Nulojix, two Onglyza and six Yervoy studies). Details of these studies were provided.

Nulojix studies
Bristol-Myers Squibb stated that Nulojix was first authorized in June 2011.

One of the two studies (IM103-002) was a historic study which was published in 2002 before the Code included an obligation to post clinical trial data at Clause 21.3 and prior to the implementation of the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 2005.

The remaining Nulojix study (IM103-045), completed in June 2011 and was eligible for disclosure under the Joint Position in force at the time (2009). Results were published on www.clinicaltrials.gov approximately 15 months after the end of the study. In addition the study was submitted for full publication in May 2013 to the American Journal of Transplantation however, the study did not involve any UK patient.

Onglyza studies
Bristol-Myers Squibb stated that Onglyza was first authorized in July 2009.

Both Onglyza studies (CV181-085 and CV181-057), completed after the first authorization, in May 2010 and April 2010 respectively. Results of both studies were published on www.clinicaltrials.gov approximately 16 months after the end of the study. Both were eligible for disclosure under the Joint Position (2009).

Study CV181-057 involved one UK site and eight UK patients (1.7% of the total). The study results were published in March 2012 in Current Medical Research and Opinion. Study CV185-085 was fully published in July 2013 in Diabetes Therapy.

Yervoy studies
Bristol-Myers Squibb acquired Medarex (the company which developed ipilumumab) in 2009. Yervoy was first authorized in March 2011.

Study MDX010-07/CA184-019 completed in November 2004, which predated the implementation date of 1 July 2005 cited in the Joint Position 2008. No UK patients were involved.

Three of the Yervoy studies were completed after 1 July 2005 and before 1 July 2008. The first two of these studies (MDX011-12/CA184-015, MDX010-15/CA184-001) were exploratory (non-efficacy) studies and were excluded from disclosure requirements under the Joint Positions in force at the time (2005/2008). Neither of these studies involved UK patients.

The third (CA184-007) was a confirmatory trial which started in December 2005 and completed in July 2007 and involved a small number of UK patients (1.7% of the total). When the trial started the applicable Joint Position (2005) did not require disclosure as Yervoy was not approved for marketing and was not commercially available. From January 2006 to June 2012, Bristol-Myers Squibb actively posted on to its corporate website, clinical study report (CSR) synopses from trials conducted on marketed products. Bristol-Myers Squibb subsequently stopped posting this information on BMS.com as much of it was already posted to www.ClinicalTrials.gov. However, from cached internet history, it could clearly be seen that the CA184-007 trial was posted by Bristol-Myers Squibb along with other trials. Bristol-Myers Squibb was not able to establish the timing for this posting (http://webcache.googleusercontent.com/search?q=cache:2yl4aiaI1sQJ:ctr.bms.com/pdf//CA184-007%2520ST.pdf+&cd=2&hl=en&ct=clnk&gl=uk). This trial was also presented as a poster at the ESMO Congress in September 2008 and fully published in Clinical Cancer Research in August 2009.

Study MDX101-28 was an observational study, which completed in April 2009 and was not required to be reported under the Joint Position in force at the time (2008). This study did not involve UK patients.

Study CA184-027 was a phase 1 exploratory trial completed in October 2009. This trial was also not required to be reported under the applicable Joint Position (2008). This study did not involve UK patients.

Response to complaint

It was Bristol-Myers Squibb's opinion that in relation to this specific complaint it was not unreasonable to consider this as an ABPI Code matter.

Publication of clinical trial results was dealt with by Bristol-Myers Squibb's clinical research groups in the US, it was thus outside the remit of Bristol-Myers Squibb UK. Nevertheless, UK companies remained responsible for ensuring adherence to the UK Code.

In relation to Clause 21.3, Bristol-Myers Squibb had identified the three studies above where disclosure was delayed by 3-4 months. Only one of these studies involved UK patients and all three had since been submitted, or fully published, in the scientific literature, reinforcing Bristol-Myers Squibb's commitment to transparency. Bristol-Myers Squibb acknowledged that the PMCPA would need to determine how these isolated delays aligned with the applicable clause however Bristol-Myers Squibb considered that the fact of disclosure of this data broadly fulfilled its obligations under Clause 21.3. Bristol-Myers Squibb did not believe that the complainant had provided any evidence to suggest a breach of either Clauses 21.1 or 21.2.

Bristol-Myers Squibb did not consider that it was in breach of Clause 1.8 due to the explanations provided for each individual trial noted above.

In relation to Clause 9, Bristol-Myers Squibb submitted that the situation surrounding the short delay in disclosing the results of these three studies did not represent a significant failure to maintain high standards. Only study CV181-057 involved UK patients and all three studies had submitted to, or already published in peer-reviewed publications.

For similar reasons, its actions did not represent a breach of Clause 2. The short delays in disclosing the results of these three studies did not represent a risk to patient safety or competent care, nor did they discredit or reduce confidence in the pharmaceutical industry.

Bristol-Myers Squibb submitted that it should be recognised that these three studies represented a very small percentage (5.8%) of the 52 studies for the Bristol-Myers Squibb products Eliquis, Nulojix, Onglyza and Yervoy that were identified in the publication. Results of all of the Eliquis studies were disclosed in full accordance with the requirements of the Code.

Bristol-Myers Squibb would provide any of the CSR synopses to any individual that requested the synopses of a study.

As requested, Bristol-Myers Squibb provided copies of the summaries of product characteristics (SPCs) for Onglyza, Yervoy and Nulojix and also the following internal documents

- Clinical Trial Directive 003.02 Disclosure: Clinical Trial Registrations and Posting of Results
- Clinical Trial Directive 003.02 amendment 2 (GDMA Procedural document Variance Request Form)
- PRI Policy 010 Public Disclosure of BMS Pharmaceutical Information
- Standard Operating Procedure 007 Public Disclosure of BMS Pharmaceutical Information

However, based on the wording of the complaint, which Bristol-Myers Squibb noted clearly referred to the 'information published in the study', it appeared that the other information requested by the PMCPA was out of scope. Before providing this additional information Bristol-Myers Squibb would like to better understand the PMCPA's rationale for requesting it in light of the original complaint and the full and transparent explanation provided.

Bristol-Myers Squibb submitted that it acted with the best intentions with regard to data transparency and adhered to the requirements of the Code to ensure transparency. It had provided a full response to the specific complaint made to the PMCPA.

In response to a request for further information Bristol Myers-Squibb stated that Nulojix, Onglyza and Yervoy were first approved and commercially available in July 2011, July 2009 and April 2011 respectively.

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.

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 CASES AUTH/2654/11/13 AND AUTH/2656/11/13

The Panel noted Bristol-Myers Squibb's submission regarding the date of the trial completion in relation to which joint position was relevant. As set out above, the Panel considered that the determining factor was when the product was first approved and commercially available and if the trial completed after this date then the date of the trial completion was relevant.

Nulojix (Case AUTH/2656/11/13)
The Panel noted the CMRO publication in that two evaluable studies had not been disclosed within the timeframe. The disclosure percentage was 71%. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 86%. A footnote stated that the undisclosed trial was completed in 2004 and was not subject to FDAAA 801 requirements.

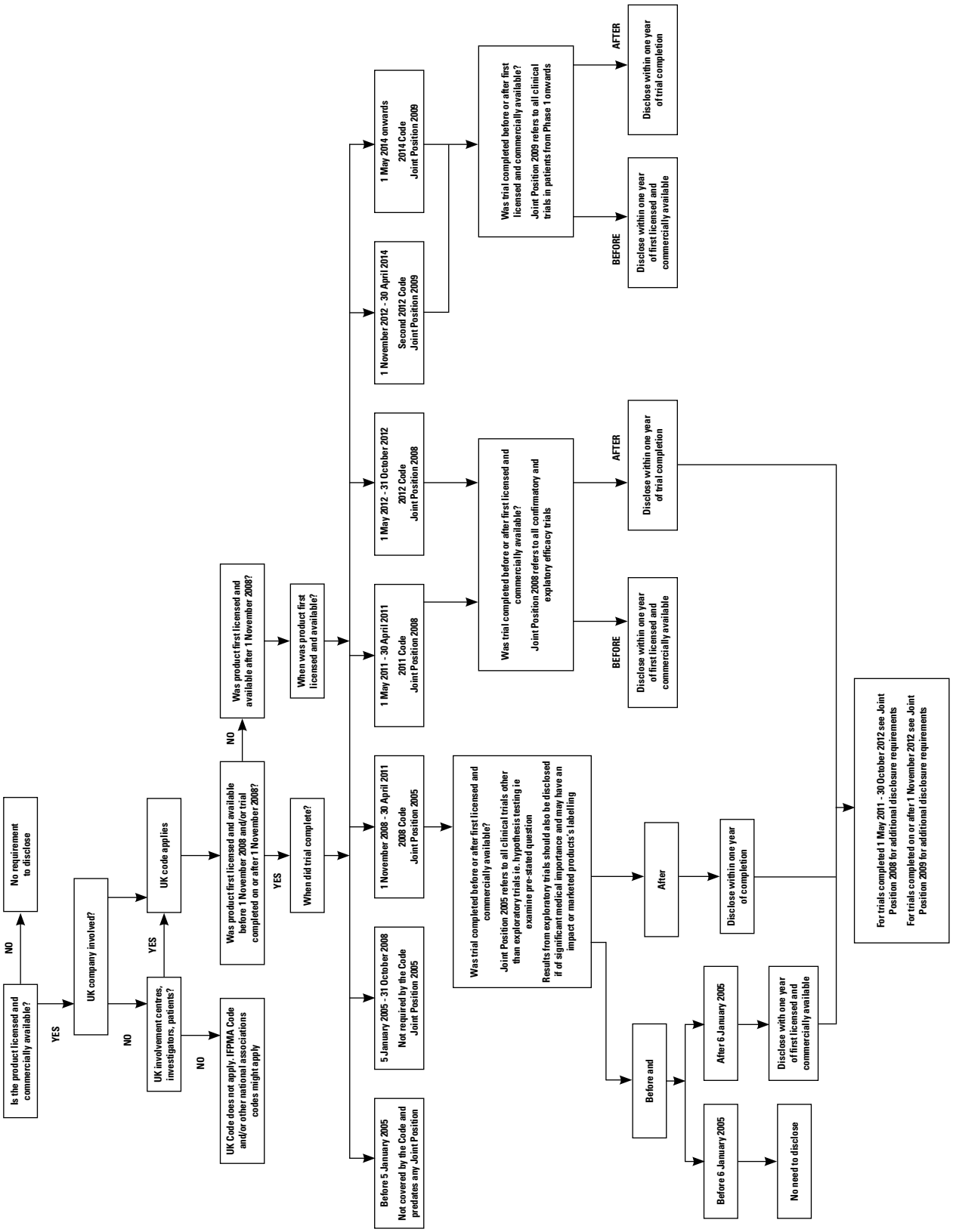
The Panel noted Bristol-Myers Squibb's submission that both trials had been published. One study had been published in 2002 which was before Nulojix was first approved and commercially available (July 2011). In this regard, the Panel ruled no breach of Clause 21.3 of the 2011 Code and consequently no breach of Clauses 9.1 and 2. The Panel considered that as the second trial had no UK involvement, the matter did not come within the scope of the Code and therefore ruled no breach.

Onglyza (Case AUTH/2654/11/13)
The Panel noted the CMRO publication in that two evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 88%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 100%.

Onglyza was first approved and commercially available in July 2009. The Panel noted Bristol-Myers Squibb's submission that both trials had been published. Only one involved UK patients and this

Decision Tree

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



completed in April 2010 and the results were posted on clinicaltrials.gov in August 2011. As the results were not disclosed by April 2011, Bristol Myers-Squibb had not met the requirements of the Code. The Panel ruled a breach of Clause 21.3 of the 2008 Code. The delay in disclosure of the results meant that high standards had not been maintained and a breach of Clause 9.1 was ruled. As the data had been published, the Panel considered that there was no breach of Clause 2 and ruled accordingly.

The Panel considered that as the second trial had no UK involvement, the matter did not come within the scope of the Code and therefore ruled no breach.

Yervoy (Case AUTH/2656/11/13)
The Panel noted the CMRO publication in that six evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 63%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 63%. A footnote stated that the undisclosed trials were not subject to FDAAA 801 requirements.

The Panel noted Bristol-Myers Squibb's submission that five of the non-disclosed trials did not involve UK patients. The Panel considered that as there was no UK involvement the matter did not come within the scope of the UK Code and therefore ruled no breach.

Yervoy was first approved and commercially available in April 2011. The Panel noted that the one trial that involved UK patients completed in July 2007 and the results should have been disclosed by April 2012. Bristol-Myers Squibb submitted that this trial was presented as a poster in September 2008 and fully published in September 2009. The Panel ruled no breach of Clause 21.3 of the 2008 Code and consequently no breach of Clauses 9.1 and 2.

Complaint received **21 November 2013**

Case completed **31 March 2014**