

# ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v GENZYME (SANOFI)

## Clinical trial disclosure (Mozobil and Renvela)

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 Mozobil (plerixafor) and Renvela (sevelamer carbonate).

The detailed response from Sanofi is given below.

General detailed comments from the Panel are given below.

With regard to Renvela, the Panel noted that five of the evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 38%. Two studies had not been disclosed at all. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 75%. A footnote stated that the undisclosed trials were not applicable under FDAAA requirements.

The Panel noted Sanofi's submission that Renvela was first approved on 19 October 2007 and commercially available that month and that only two of the non-disclosed trials had UK patients or involvement in the UK company. These had completed in January and March 2007. The Panel noted that the date of first approval was before the requirement to disclose the results of clinical trials was included in the ABPI Code (1 November 2008). The matter was not covered by the 2006 Code as such and there could be no breach of it. Thus the Panel ruled no breach of the 2006 Code including Clause 2.

With regard to Mozobil, the Panel noted that seven of the evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 61%. Seven trials had not been disclosed at all. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 61%.

The Panel noted Sanofi's submission that Mozobil was first approved and commercially available on 28 December 2008 and that only one Mozobil trial had sites or investigators in the UK. This trial completed in November 2010. The Panel noted that Sanofi had failed to disclose the results of the trial by November 2011. 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. The results had been disclosed and thus the Panel ruled no breach of 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

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 Mozobil (plerixafor) and Renvela (sevelamer carbonate) were as follows:

### Mozobil

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	9	69%	13	9	69%
Phase III	5	0	5	2	40%	5	2	40%
<b>TOTAL</b>	<b>20</b>	<b>2</b>	<b>18</b>	<b>11</b>	<b>61%</b>	<b>18</b>	<b>11</b>	<b>61%</b>

### Renvela

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	2	67%	3	2	67%
Phase III	4	0	4	0	0%	4	3	75%
Phase IV	1	0	1	1	100%	1	1	100%
<b>TOTAL</b>	<b>8</b>	<b>0</b>	<b>8</b>	<b>3</b>	<b>38%</b>	<b>8</b>	<b>6</b>	<b>75%</b>

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 Genzyme.

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

When writing to Genzyme, 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

Although this case was cited as a complaint to Genzyme (which operated as an individual company in the UK) and many of the relevant events were historical, Genzyme on a global and at a research

and development level, was now a part of the Sanofi group. Mozobil and Renvela had been transferred to the Sanofi portfolio within the UK from an operational perspective; however much of what might be considered in this case occurred before that integration took place.

Sanofi noted that the debate around clinical trial transparency was already a very public and inclusive one, with industry engaged in dialogue between concerned parties and working together as an industry to ensure appropriate data could be made available to enable further high quality scientific research and ultimately benefit patients. Sanofi fully supported the ABPI initiative to gain a greater understanding of the degree to which data on approved products was publicly available (the CMRO publication) and was working with the ABPI to implement future guidelines on monitoring and enforcing the established and evolving requirements.

Sanofi asked the Panel to carefully consider the global nature of pharmaceutical research and development. Whilst Sanofi was fully engaged in the debate as well as the industry wide efforts to responsibly share clinical trial data, this debate and any resulting actions were by necessity regional (European) and global in nature. No single country affiliate or industry association could operate in a silo if real progress was to be made.

Sanofi fully supported the five Principles for Responsible Clinical Trial Data Sharing jointly released by PhRMA and EFPIA on 24 July 2013; and its global organisation would make it clear exactly how Sanofi would meet those commitments.

### **Scope of the Code**

Sanofi also asked the Panel to carefully consider the degree to which any country affiliate of an international pharmaceutical company such as Sanofi was involved in the separate activities that made up the conduct of global clinical trials and, importantly in this case, the degree to which local affiliates were involved in the specific activity of registration, disclosure and publication of global clinical trial information. Sanofi was not headquartered in the UK and had no UK research and development facility. Even when a global clinical trial had UK investigators or sites, the activity consisted of an investigator or trial site which recruited and treated patients within the global study protocol (as predefined outside of the UK), together with the infrastructure and activity required to administer and monitor the sites in line with Good Clinical Practice. The specific activity which was the subject of this complaint was the registration, disclosure and publication of clinical trial information. For Sanofi global clinical trials and trials undertaken by other regions/countries, these activities, and indeed the analysis and writing of the information which was disclosed, were all activities conducted wholly outside of the UK by company teams elsewhere in the world. It was only locally initiated and conducted studies undertaken to produce local information by the UK affiliate which

would have such activities undertaken in the UK. Sanofi drew attention to the supplementary information to Clause 1.8 that 'Activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European Country as well as the national code of the country in which the activity takes place or the materials are used'.

In order to fully understand the information in the CMRO publication and to establish a clear view of the applicability of the Code, Sanofi analysed the list of trials that were considered by the authors. None of the trials were conducted by the Sanofi UK affiliate. Registration, disclosure and publication for each of the trials listed where Sanofi was a sponsor, were managed outside of the UK, by non-UK teams.

Sanofi submitted therefore that the complaint about the CMRO publication was outside of the scope of the Code as per Clause 1.8 and should not be further considered by the Panel.

### **Response to the complaint**

Notwithstanding the above, Sanofi noted that it was the Panel's responsibility to interpret the breadth of the complaint and whether the matter was covered by the UK Code and so, as requested, it responded to the points raised by the case preparation manager.

To inform its response, Sanofi sought further information from the author of the CMRO publication, concerning the intent, purpose and methodology of the study. The reply was provided. In summary, it was clear that the ABPI study had been undertaken to produce a quantitative benchmark of disclosure rates for industry sponsored clinical trials and to provide the industry with information with which to respond to media and professional body enquiries and inform a response to the Science and Technology Select Committee.

In relation to the complaint the relevant clause of the Code was Clause 21.3. The methodology described by the author, both in the publication and in the email to Sanofi was that this study did not audit or compare disclosure rates against any given disclosure requirement and did not limit assessment to any given laws or requirements in specific territories. Nor did the CMRO publication present any detailed information from which the degree of compliance with the detailed aspects of the IFPMA Joint Position (such as defined timelines or availability on the specific types of registries), and therefore Clause 21 of the Code, could be ascertained.

Sanofi stated that, although the CMRO publication listed overall disclosure rates for Mozobil and Renvela as defined within that study, it did not list Genzyme/Sanofi as a company which had not disclosed its clinical trial results in line with the Code. It followed therefore, that Sanofi did not believe this publication provided any evidence of a breach of Clauses 21, 9 or 2 of the Code.

## Additional Information

Notwithstanding Sanofi's view on the applicability of the Code or, in spite of that, in its response to the complaint, the company gave some more detail on some aspects of the trials which were considered by the authors in preparation for the CMRO publication.

Mozobil was first approved in the US on 15 December 2008.

Renvela was first approved in the US on 19 October 2007.

Sanofi submitted that when analysing the list of trials that were considered by the authors of the CMRO publication, and cross referencing that with its clinical trials management systems and databases, it was clear that only three company sponsored studies on Mozobil and Renvela had sites or investigators in the UK.

For each of those three trials, the following tables provided the information requested by the PMCPA and copies of the relevant public registry entries were provided.

### Renvela

Study Identifier as used by author of CMRO publication.	NCT00267514 / SVCARB00205
Study Type	Phase 3 Clinical Trial
Study Description	Study to Demonstrate Equivalence of Sevelamer Carbonate Powder and Sevelamer HCl Tablets in Haemodialysis Patients
Date of Commencement of the Trial	31 January 2006
Listing of Trial on Public Registry (Y/N)	Yes
Date of Public Registry Entry	20 December 2005
Location of Public Registration at Commencement	Clinical trials.gov
Date of Trial Completion	15 March 2007
Date and location of Disclosure of Results on a Public Database	January 2009, Genzymeclinicalresearch.com
Submitted for Publication in Scientific Literature within 12-18 months Y/N	No – Study Completed prior to the 2010 declaration on Publication of Clinical Trial Information in Scientific Literature

Publication	Fan <i>et al.</i> A randomized, crossover design study of sevelamer carbonate powder and sevelamer hydrochloride tablets in chronic kidney disease patients on haemodialysis. <i>Nephrol Dial Transplant.</i> 2009 Dec; 24(12):3794-9. doi: 10.1093/ndt/gfp372. Epub 2009 Aug 7. posted on Genzyme results website: <a href="http://www.genzymeclinicalresearch.com/results/output/product/gzcr_res_Renvela_study3.aspx#TopOfPage">http://www.genzymeclinicalresearch.com/results/output/product/gzcr_res_Renvela_study3.aspx#TopOfPage</a>
Comment	Registration on public registry was within 21 days. Posting of results to a public registry was made but exceeded the 12 month period. The reason for this delay was not documented or recalled by current staff. Submission for peer review publication was not subject to IFPMA declaration as trial completed prior to 2010.  Sanofi submitted that as the study completed prior to the inclusion of the requirement to disclose clinical trial information as per IFPMA declarations being incorporated into the 2008 edition of the Code (effective from 1 July 2008) none of the IFPMA declaration requirements would have been covered by the Code.

Study Identifier as used by author of CMRO publication.	NCT00681941 / SVCARB00105 / ACTRN012606000380594
Study Type	Phase 3
Study Description	An Open Label Dose Titration of Sevelamer Carbonate Tabs 3 Times a Day in Hyperphosphatemic CKD Patients Not On Dialysis
Date of Commencement of the Trial	January 2006
Listing of Trial on Public Registry (Y/N)	Yes
Date of Public Registry Entry	19 May 2008
Location of Public Registration at Commencement	Clinicaltrial.Gov
Date of Trial Completion	January 2007
Date and location of Disclosure of Results on a Public Database	November 2008, genzymeclinicalresearch.com

Submitted for Publication in Scientific Literature within 12-18 months Y/N	No – Study Completed prior to the 2010 declaration on Publication of Clinical Trial Information in Scientific Literature
Comment	<p>Trial commencement was registered on a public registry but not within 21 days. Trial results were posted to a public registry but not within 12 months of completion. The reason for these delays was not documented and was not recalled by current staff. There was no submission for publication in scientific literature as the completion date preceded the IFPMA declaration of 2010.</p> <p>Sanofi submitted that as this study completed prior to the inclusion of the requirement to disclose clinical trial information as per IFPMA declarations being incorporated into the 2008 edition of the Code (effective from 1st July 2008) none of the IFPMA declaration requirements would have been covered by the Code.</p>

Publication	Russell <i>et al</i> , Plerixafor and granulocyte colony-stimulating factor for first-line steady-state autologous peripheral blood stem cell mobilization in lymphoma and multiple myeloma: Results of the prospective PREDICT trial. <i>Haematologica</i> 2013 98:2 (172-178).
Comment	<p>The commencement of this trial was posted to a public registry but not within the 21 day time frame. The results had not been posted on a public registry. The reasons for the delay in registration and lack of posting of results on public registry was not documented and not recalled by current staff.</p> <p>A manuscript was submitted for publication in scientific literature on 7 June and accepted by <i>Haematologica</i> on 26 July 2012. This fell outside the requirements of the 2010 IFPMA declaration to submit within 18 months by three weeks.</p>

### Mozobil

Study Identifier as used by author of CMRO publication.	NCT00838357 MOZ00808, 2008-000689-21
Study Type	Phase 4 (Expanded Access Program)
Study Description	Plerixafor and G-CSF for the Mobilisation of Peripheral Blood Stem Cells for Autologous Stem Cell Transplantation in Patients With Non-Hodgkin's Lymphoma (NHL), Hodgkin's Disease (HD) or Multiple Myeloma (MM) – Safety Study in a General Autologous Transplant Population
Date of Commencement of the Trial	September 2008
Listing of Trial on Public Registry (Y/N)	Yes
Date of Public Registry Entry	5 February 2009
Location of Public Registration at Commencement	clinicaltrials.gov
Date of Trial Completion	18 November 2010
Date and location of Disclosure of Results on a Public Database	Results not publicly disclosed
Submitted for Publication in Scientific Literature within 12-18 months	No

### Summary

Sanofi stated that although the matters raised in the complaint were not covered by the UK Code, in providing a response to a potentially broader interpretation of the complaint, Sanofi believed the CMRO publication did not, as alleged, provide any evidence as to the compliance or otherwise of Sanofi or Genzyme with the specific requirements of Clauses 21, 21.3, 9 or 2 or the IFPMA declarations, as evidenced by the methodology of the study detailed by the authors.

In a response to a request for further information regarding what appeared to be an inconsistency between Sanofi's response and the attachments, Sanofi confirmed that only two Renvela trials had sites or investigators in the UK. The additional trial referred to in the attachments was conducted on a different product, Renagel and thus was not relevant.

In response to a request for further information, Sanofi confirmed that Mozobil was first approved and commercially available on 28 December 2008.

### 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.

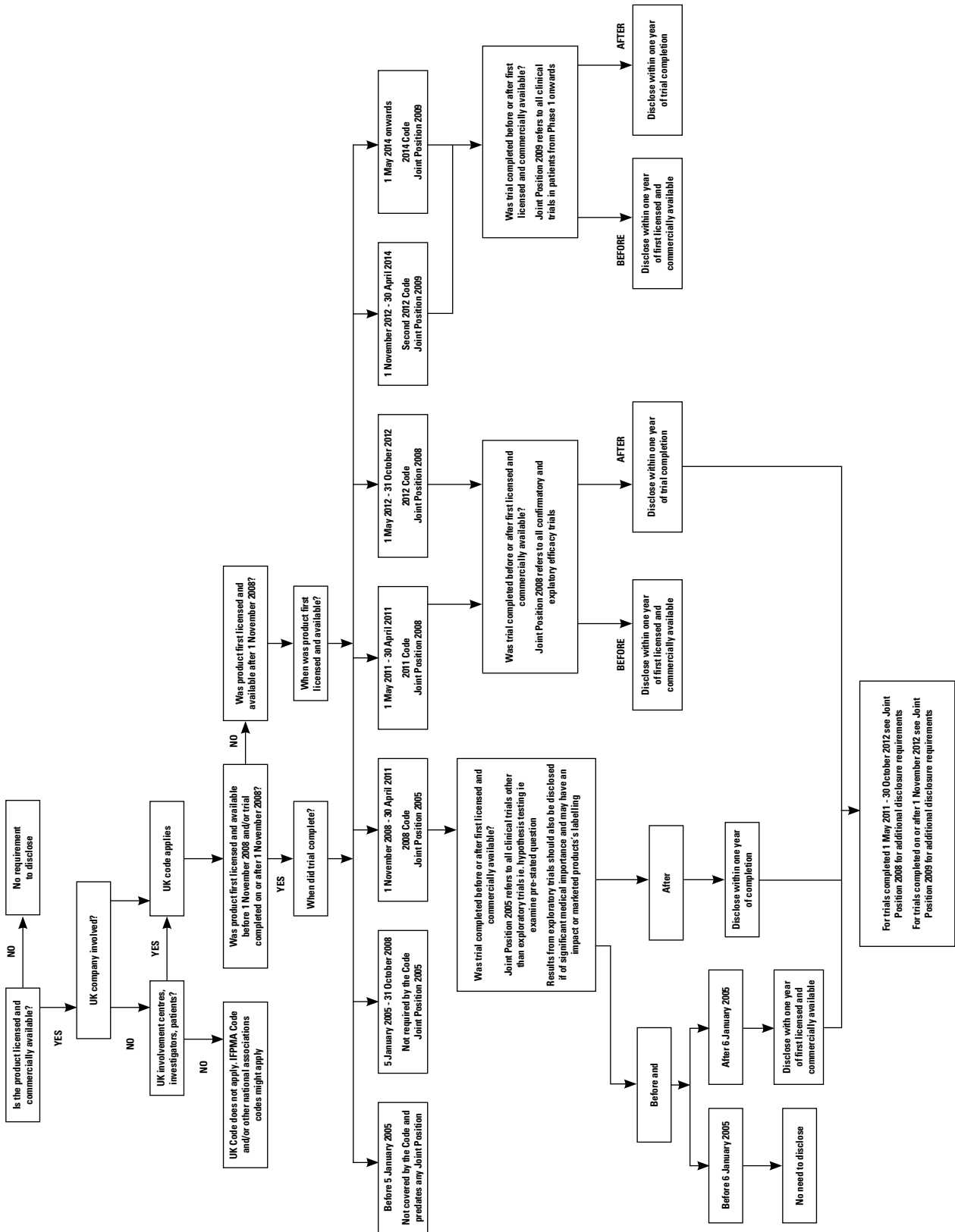
During its development of the decision tree, the Panel sought advice from Paul Woods, BPharm MA (Medical Ethics and Law) of Paul Woods Compliance Ltd who provided an opinion. Mr Woods was not provided with details of the complaint or any of the responses. The advice sought was only in relation to the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



# Decision Tree

Developed by the Panel when considering the complaint about the disclosure of clinical trial 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 CASE AUTH/2665/11/13**

##### **Renvela**

The Panel noted that five of the evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 38%. Two studies had not been disclosed at all. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 75%. A footnote stated that the undisclosed trials were not applicable under FDAAA requirements.

The Panel noted Sanofi's submission that Renvela was first approved on 19 October 2007 and commercially available that month and that only two of the non-disclosed trials had UK patients or involvement in the UK company. These had completed in January and March 2007. The Panel noted that the date of first approval was before the requirement to disclose the results of clinical trials was included in the ABPI Code (1 November 2008). The matter was not covered by the 2006 Code as such and there could be no breach of it. Thus the Panel ruled no breach of Clauses 9.1 and 2 of the 2006 Code.

##### **Mozobil**

The Panel noted that seven of the evaluable trials had not been disclosed within the timeframe. The disclosure percentage was 61%. Seven trials had not been disclosed at all. The disclosure percentage at 31 January 2013 of trials completed by the end of January 2012 was 61%.

The Panel noted Sanofi's submission that Mozobil was first approved and commercially available on 28 December 2008 and that only one Mozobil trial had sites or investigators in the UK. This trial completed in November 2010. The Panel noted that Sanofi had failed to disclose the results of the trial by November 2011. It was not clear why the results had not been disclosed. The applicable Joint Position 2005 gave some flexibility if results were to be published in a peer reviewed medical journal so as not to compromise such publication. In any event Sanofi acknowledged that it had missed the deadline. The Panel ruled a breach of Clause 21.3 of the 2008 Code.

The Panel noted that the study was submitted for publication on 7 June 2012 and accepted on 26 July 2012. In the Panel's view the delay in disclosure meant that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that the results had been disclosed and considered that in the circumstances the matter was covered by its rulings of breaches of Clauses 9.1 and 21.3. It thus ruled no breach of Clause 2.

The Panel noted Sanofi's submission that of the trials referred to in the CMRO publication, only the one detailed above had any UK involvement. With regard to the other studies, the Panel considered that as there had been no UK involvement, the matter did not come within the scope of the Code and therefore ruled no breach.

**Complaint received**                      **21 November 2013**

**Case completed**                              **24 March 2014**