ANONYMOUS CONTACTABLE MEMBER OF THE PUBLIC v RECORDATI

Clinical trial disclosure (Silodyx)

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 Silogyx (silodosin).

The detailed response from Recordati is given below.

General detailed comments from the Panel are given below.

The Panel noted the CMRO publication in that one evaluable study had not been disclosed in the timeframe. The disclosure percentage was 75%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 100%.

The Panel noted Recordati's submission that it sponsored two of the trials listed in the CMRO publication. With regard to one study which completed in July 2013 (last patient, last visit), the Panel ruled no breach of the Second 2012 Edition of the Code including Clause 2 as the study results did not need to be disclosed until July 2014.

The Panel noted Recordati submitted data to show that the last patient, last visit, for the open label phase of a second study was 4 January 2008 and a synopsis of the clinical study report was submitted to various groups (competent authorities, ethics committees, investigators) between 22 September and 15 October 2008. An abstract was published in April 2010 and full publication (Chapple *et al*) was in November 2010.

The Panel noted Recordati's submission regarding the various dates of the various marketing authorizations. Silodosin twice daily was first approved for BPH in January 2006 (Kissei Pharmaceuticals in Japan). Silodosin once daily was first approved in October 2008 (Watson Pharmaceuticals, US). Recordati's version – Silodyx was approved for once daily use in January 2010 and first marketed in Germany in June 2010.

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

The Panel considered that it could be argued that Recordati's second study completed after silodosin was first approved and commercially available (January 2006).

However, the Panel noted that the date of the last patient, last visit, 4 January 2008, and the date of the synopsis of the clinical study report, 22 September 2008 were both before there were any disclosure requirements in the Code. The matter was not covered by the 2006 Code and as such there could no breach of it. Thus the Panel ruled no breach of the 2006 Code including Clause 2.

The Panel noted its ruling above. In addition it noted that if the relevant date of the first approval and commercial availability was company specific, ie the date of Recordati's product marketing authorization (June 2010), then the matter would be covered by the 2008 Code and the trial results would need to be disclosed by June 2011, which had happened.

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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 Silogyx (silodosin) were as follows:

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	2	0	0	0%	2	2	100%
Phase III	4	0	4	3	75%	4	4	100%
TOTAL	**6**	**2**	**4**	**3**	**75%**	**6**	**6**	**100%**

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 Recordati.

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

When writing to Recordati, 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

Recordati noted that the CMRO publication reviewed 53 new medicines authorised by the European Commission under the centralised procedure during the three years 2009 – 2011, and assessed whether all completed company-sponsored clinical trials conducted in relation to such products had been

published on a registry or in the scientific literature either (a) within 12 months of the later of the first regulatory approval or trial completion or (b) by 31 January 2013 (the end of the survey). The authors found that, of the studies considered, 77% had results disclosed by 12 months and by 31 January 2013, this figure had increased to 89%. The article did not name or otherwise identify the trials which comprised the 33% where results had not been disclosed within 12 months.

With respect to silodosin (Silodyx), the data provided to Recordati S.p.A. by the authors indicated that 13 clinical trials had been identified (three Phase II, four Phase III, four Phase IV and two observational prospective studies). Two of the identified studies had been sponsored by Recordati Industria Chimica e Farmaceutica S.p.A. (doing business also as Recordati S.p.A.): one of these studies had not yet been completed and was not therefore considered; the remaining study completed in 2008, but, according to the CMRO publication, was not published until after the 12 month period specified. The CMRO publication did not suggest that any of the studies relating to silodosin had been sponsored by Recordati Pharmaceuticals Ltd.

Silodosin was an α-adrenoceptor antagonist originated by Kissei Pharmaceutical (Japan) for benign prostatic hyperplasia (BPH). It was first approved in Japan on 23 January 2006 (International Birth Date). Kissei was the marketing authorization holder of Urief in Japan, where it was administered twice daily.

As per contractual agreements with Kissei, other companies were responsible for the clinical development and subsequent marketing of silodosin in their territories, in particular:

- The US where silodosin had been developed for use once daily by Watson Pharmaceuticals (now Actavis Inc.), which marketed the product as Rapaflo (approved by the FDA in October 2008).
- In the Republic of Korea clinical trials had been performed by JW Pharmaceutical, which marketed silodosin as Thrupas.
- Recordati S.p.A had been responsible for the clinical development programme in Europe. Recordati Ireland Ltd had been granted two marketing authorizations for silodosin (Silodyx, Urorec) by the European Commission under the centralised procedure on 29 January 2010. Silodosin was first marketed in the EU (Germany) in June 2010. Other national marketing authorizations had been granted to Recordati or to Recordati licensees in other non EU countries. The list of countries where silodosin was presently authorised under the name of Recordati or under the name of a Recordati licensee was provided.
- Silodosin was not marketed in the UK by Recordati Pharmaceuticals Ltd, Recordati Ireland Ltd or Recordati S.p.A. or any other company of the Recordati group.

Details of the clinical trials conducted in relation to silodosin were provided.

As indicated to Recordati by the authors of the CMRO publication, only two of these trials were sponsored by Recordati (both by Recordati Industria Chimica e Farmaceutica S.p.A). Recordati stated that its response did not consider or comment on silodosin trials sponsored by companies outside the Recordati group.

With respect to the two studies sponsored by Recordati Industria Chimica e Farmaceutica S.p.A, the approach to publication was determined by the Recordati standard operating procedure (SOP) 06SC01R05 'Standard format of a Recordati clinical study protocol and procedures for its internal approval'. Accordingly, at the end of a study, results were communicated to investigators, ethics committees and competent authorities and, with the exception of Phase I studies, were published.

Study KMD3213-IT-CL 0215 (EudraCT No 2005-005665-11; ClinicalTrials.gov Identifier: NCT00359905), an international, randomized, double-blind, placebo- and active-controlled Phase III clinical trial performed in Europe, with a 9 month open label extension period (completed)

This trial was conducted at 72 sites in 11 European countries, of which 5 sites were located in the UK (2 additional UK sites did not recruit any patient). 1228 patients with benign prostatic hyperplasia were enrolled, of whom 18 were recruited in the UK. The trial was included on the public registry Clinicaltrials.gov in August 2006.

The results of the double-blind placebo and active controlled phase were first presented in abstract form at the EAU Congress 2010 (Eur Urol Suppl. 2010 April; 9 (2): 313) and then fully published (Eur Urol. 2011; 59 :342-52. Epub 2010 Nov 10).

Data related to the open label extension phase were included in a review on silodosin in 2011 (Curran MP. Silodosin. Treatment of the sign and symptoms of benign prostatic hyperplasia. Drugs 2011; 71: 897-907) and a full publication was in preparation.

Study KMD 3213 IT-CL 0376 (EudraCT No 2011-000045-20; ClinicalTrials.gov Identifier: NCT01757769), an international, open-label, single-arm, Phase IV clinical trial (not yet completed)

The trial, included in Clinicaltrialsregister.eu in March 2011, was not yet completed (Last Patient Last Visit on July 2013, clinical study report in preparation). In circumstances where this trial had not been completed and did not form part of the assessment by the authors. Recordati did not comment on it further.

The complaint against Recordati Pharmaceuticals Ltd

1 Applicability of the UK Code

Recordati submitted that Recordati Pharmaceuticals UK did not appear to fall within the definition of 'company', provided by Clause 1.8 and its supplementary information:

'[…] 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 activities take place or the materials are used. […]

By 'company' is meant any legal entity that organises or sponsors promotion which takes place within Europe, whether such entity be a parent company (e.g. the headquarters, principal office, or controlling company of a commercial enterprise), subsidiary company or any other form of enterprise or organisation.[…]'

Recordati Pharmaceuticals UK was a subsidiary of Recordati S.p.A which was based in Milan (Italy). Recordati Pharmaceuticals UK did not have an active sales force and was not involved in the organisation or the sponsoring/promotion of medicines anywhere in Europe. In particular, Recordati Pharmaceutical Ltd did not participate in any of the promotional activities listed at Clause 1.2. The activities of Recordati Pharmaceuticals Ltd were limited to: regulatory activities (maintenance of current UK marketing authorizations), pharmacovigilance activities and product distribution activities. In these circumstances, the complaint directed towards Recordati Pharmaceuticals Ltd appeared inappropriate.

The only completed trial of silodosin sponsored by a company in the Recordati group was sponsored by Recordati Industria Chimica e Farmaceutica S.p.A, the parent company of Recordati Pharmaceuticals Ltd. Recordati Pharmaceuticals Ltd was not involved in the trial and had no control over publication of the data. While five study sites were located in the UK, the contribution of the UK to the number of trial participants was minimal.

Recordati submitted that it was significant that the ABPI's 'Best Practice Model for the Disclosure of Results and Transparent Information on Clinical Trials' was directed towards 'ABPI members and all industry sponsors of clinical trials who are required to publish their trial results ....' and did not suggest that the model applied to subsidiaries such as Recordati Pharmaceuticals Ltd, which did not sponsor the relevant trial.

In these circumstances, Recordati submitted that to impose responsibility for publication of trial data on the UK company was unreasonable and impractical. Trials were conducted on a global basis and many factors might influence the date of publication of the associated trial data. A local affiliate (particularly one, such as Recordati Pharmaceutical Ltd, that had played no part in the relevant trial) could have no control over publication of data or responsibility where there was delay.

Clause 21.3

The complainant referred to the CMRO publication, as grounds for his/her complaint. This publication stated with regard to the assessment methodology that,

'Disclosure was assessed and recorded for two time points: firstly, within 12 months (of either the first regulatory approval by either the EMA or FDA [if applicable], or the date of completion of the trial if after the first approval); and secondly, at 31 January 2013, the end of the study period. While presentations at international conferences often represent the first public disclosure of results, there are no comprehensive and publicly available sources for reliably identifying all conference abstracts. Therefore we made no additional attempt to locate conference abstracts other than the routine search of PubMed, but if their existence was brought to our attention by the European marketing authorisation holder, abstracts published in journal supplements were accepted as valid evidence of disclosure of the trial and its results for the purely quantitative purpose of this study'.

Recordati submitted that the conclusions of the CMRO publication that the relevant Recordati study failed to comply with appropriate reporting requirements (whether in accordance with Clause 21.3 or with the joint position), were incorrect and that, in fact, Study KMD3213-IT-CL 0215 was properly reported.

Clause 21.3 of the 2008 Code provided no further details about what details should be disclosed and when; however the supplementary information to Clause 21.3 indicated that 'this clause requires the provision of details about ongoing clinical trials .... and completed trials for medicines licensed for use in at least one country'. Reference was made to the Joint Position 2005 as providing further information, but (in contrast to the Second 2012 Edition of the Code) there was no suggestion that compliance with the provisions of the Joint Position constituted a binding obligation and any construction of Clause 21.3 to impose such obligations in the absence of clear direction, would be unreasonable and unfair.

As described above, the results from Study KMD3213-IT-CL 0215 were published in abstract form at the EAU Congress 2010 and then in full in November 2010. The results of the open label extension phase were included in a review on silodosin in 2011 and a full publication was in preparation. It was Recordati's position that such publication satisfied the requirements of Clause 21.3.

However, whilst Recordati did not believe this was required under the 2008 Code, it believed that Recordati's actions were, in any event, also consistent with the principles underlying the joint position. On 29 November 2013, the ABPI, Clinical Development Manager, sent Recordati an email, on behalf of the authors, attaching an excel file, used for the purposes of the publication; this stated that the above Recordati study had missed compliance by 13 months. This conclusion was based on the Joint Position and arose from the use of 9 October 2008 as the first date of regulatory approval, which preceded publication of the results of Study KMD3213-IT-CL 0215 by more than 12 months. However, 9 October 2008 was the date of FDA approval obtained by Watson Pharmaceuticals, an independent company

unrelated to Recordati. Recordati Ireland Ltd in fact obtained its first approval for silodosin in the EU in January 2010; the publication of the abstract for the study was in April 2010 and the full publication of the double blind Phase occurred in November 2010 (well within 12 months of the date of approval). The publication of the open label extension was performed only later (2011); however these data were included in the EPAR from January 2010 and therefore in the public domain.

Recordati thus considered that reporting by Recordati Industria Chimica e Farmaceutica S.p.A was consistent with the Code and the principles of the joint position.

Clause 2

In the context of the submissions above, in particular the lack of any involvement by Recordati Pharmaceuticals Ltd in the relevant trial and that the trial was reported in accordance with the time limits under Clause 21.3 in any event, Recordati submitted that there had been no activity by Recordati Pharmaceuticals Ltd that warranted particular censure and that there had been no breach of Clause 2.

Clause 9

Recordati Pharmaceuticals UK maintained high standards at all times. Again, in the context of the above, Recordati submitted there had not been a breach of Clause 9.

In response to a query from the case preparation managing regarding trials sponsored by other companies mentioned in the analysis for CMRO publication but not included in Recordati's response, the company provided details of the six trials considered in the analysis for CMRO publication.

The following four Phase III clinical trials were considered because they were included in the dossier to obtain the EU marketing authorization:

EudraCT No 2005-005665-11 (NCT00359905), sponsored by Recordati in Europe
S104009 (ClinicalTrials.gov Identifier: NCT00224107), sponsored by Watson in US
S104010 (ClinicalTrials.gov Identifier: NCT00224120), sponsored by Watson in US
S104011 (ClinicalTrials.gov Identifier: NCT00224133), sponsored by Watson in US.

In addition, for completeness Recordati also mentioned the Phase IV clinical study it sponsored after the approval in EU (EudraCT No 2011-000045-20, NCT01757769), that was excluded from the CMRO publication because it was ongoing at the time of the analysis.

The following studies were included in the CMRO publication but not in Recordati's response because they were Phase II studies performed in not yet approved indications of silodosin (neither in EU or in US):

Study S108001 (NCT00740779), a Phase II multicentre, double-blind, placebo-controlled study in patients with abacterial chronic prostatitis/chronic pelvic pain syndrome sponsored by Watson in US.

Study S108005 (NCT00793819), a Phase II double-blind, placebo-controlled Phase II study in patients with nocturia, sponsored by Watson in US.

In response to a request for further information Recordati submitted that the first marketing authorization was not granted to Recordati but to Kissei Pharmaceuticals in Japan on 23 January 2006 as Urief, which was first launched in May 2006. A second marketing authorization was granted to Kissei's licensee Watson Pharmaceuticals (now Actavis Inc) on 8 October 2008 (Rapaflo) which was launched in April 2009. Two marketing authorizations were granted to Recordati on 29 January 2010 (Silodyx and Urorec) first launch in June 2010.

Recordati was not the marketing authorization holder in Japan or US. Neither Urief nor Rapaflo were marketed in the EU.

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.

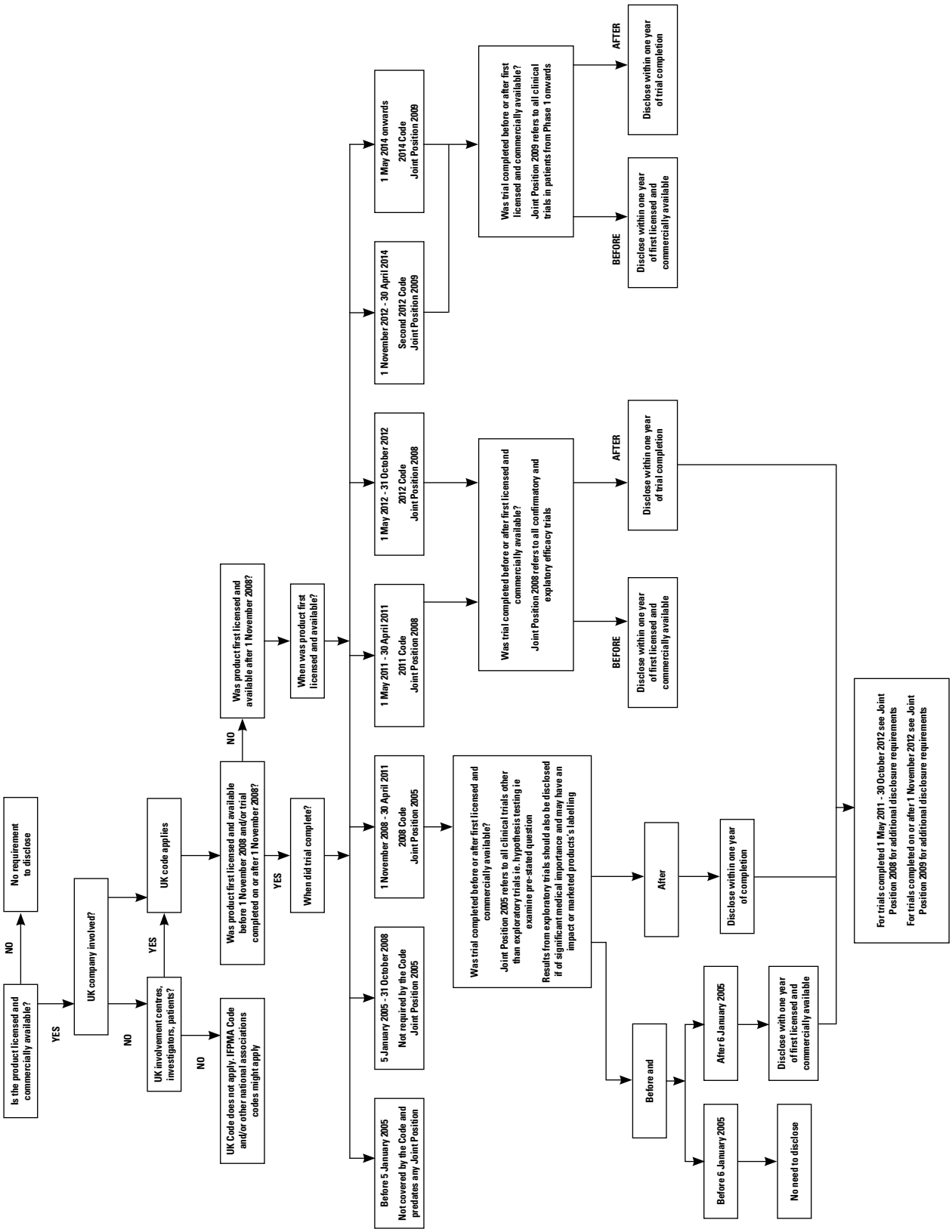
The Panel considered the complaint could be read in two ways: firstly that the companies listed had not disclosed the data referred to in the CMRO publication relating to the products named or secondly, more broadly, that the companies had not disclosed the clinical trial data for the product named ie 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.

Decision Tree

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



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/2673/11/13

The Panel noted the CMRO publication in that one evaluable study had not been disclosed in the timeframe. The disclosure percentage was 75%. The disclosure percentage at 31 January 2013 of trials completed by end of January 2012 was 100%.

The Panel noted Recordati's submission that it sponsored two of the trials listed in the CMRO publication. With regard to Study NCT01757769 which completed in July 2013 (last patient, last visit), the Panel ruled no breach of Clauses 21.3, 2 and 9.1 of the Second 2012 Edition of the Code as the study results did not need to be disclosed until July 2014. The clinical study report was expected in March 2014.

The Panel noted Recordati submitted data to show that the last patient, last visit, for the open label phase of Study NCT00359905 was 4 January 2008 and a synopsis of the clinical study report was submitted to various groups (competent authorities, ethics committees, investigators) between 22 September and 15 October 2008. An abstract was published in April 2010 and full publication (Chapple *et al*) was in November 2010.

The Panel noted Recordati's submission regarding the various dates of the various marketing authorizations. Silodosin twice daily was first approved for BPH in January 2006 (Kissei Pharmaceuticals in Japan). Silodosin once daily was first approved in October 2008 (Watson Pharmaceuticals, US). Recordati's version – Silodyx was approved for once daily use in January 2010 and first marketed in Germany in June 2010.

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

The Panel considered that it could be argued that Recordati's second study in question completed after silodosin was first approved and commercially available (January 2006).

However, the Panel noted that the date of the last patient, last visit, 4 January 2008, and the date of the synopsis of the clinical study report, 22 September 2008 were both before there were any disclosure requirements in the Code. The matter was not covered by the 2006 Code and as such there could no breach of it. Thus the Panel ruled no breach of Clauses 9.1 and 2 of the 2006 Code.

The Panel noted its ruling above. In addition it noted that if the relevant date of the first approval and commercial availability was company specific, ie the date of Recordati's product marketing authorization (June 2010), then the matter would be covered by the 2008 Code and the trial results would need to be disclosed by June 2011, which had happened.

Complaint received **21 November 2013**

Case completed **24 March 2014**