TRANSPARENCY OF CLINICAL TRIAL DATA: CURRENT STATE OF PLAY

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EU institutions have been promoting increased disclosure of pre-clinical and clinical trial data for some time, and the European Medicines Agency ('the EMA') seems determined to release as much data as possible after a marketing authorisation has been granted, considering there to be no legitimate impact on the companies concerned. In particular, since 2010 the significant change has been that the EMA has stated that it does not consider data from clinical trials supporting marketing authorisations to be commercially confidential.

The authorities claim to be responding to widespread public pressure for greater transparency, and, at times, it has seemed that there is little that companies can do to stem the tide. Industry and intellectual property associations are objecting to the EMA's increasingly unqualified policy in favour of disclosure, whereas researchers and national competent authorities have supported the EMA's position. However, in pending litigation, the European Court will finally have an opportunity to review the legality of the new approach being adopted by the EMA.

Against this background, this comment sets out a summary of the current position in relation to disclosure of clinical trial data, and highlights some of the areas of development for the future.

The Pro-active Disclosure of Clinical Trial Data

The authorities release a large amount of data concerning clinical trials used to obtain marketing authorisations once the authorisation has been granted (or refused or withdrawn). This is to satisfy the obligations of transparency both in relation to human research and the decisions of the regulatory agencies. For example, on authorisation of a medicinal product, the EMA (or the national equivalent for products subject to national approval and assessment through the decentralised and mutual recognition procedures) publishes a detailed European Public Assessment Report ('EPAR'), which includes a summary of, and the conclusions reached on, the documentation submitted by the applicant.

Information, including results-based information, is also published on clinical trial registries. Member States have an obligation under section 11 of the Clinical Trials Directive 2001/20/EC to enter certain information about trials conducted in their territory onto the EudraCT database, and are required to make some of that information public.[1] Commission guidance from October 2012 sets out the information to be made public, and states that, for all trials, result-related information should be supplied and made public after the completion of the trial, and not only after the grant of the marketing authorisation.[2] The publication of clinical trial data is becoming an increasingly 'hot topic' with the EMA and national competent authorities, and while historically not many results-based data are included on the registries, it is likely that authorities will increasingly rely on this guidance to 'force' disclosure. In addition, due to the increased interest in clinical trial data, many companies have signed up to voluntary databases to increase the information that is made available, or have pledged to release data they hold.

However, the Commission guidance has been met with significant opposition from some companies, who consider the results of clinical trials to be confidential at least until the grant of the corresponding marketing authorisation. The lack of a common approach by industry has led some to believe

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1) See https://eudract.ema.europa.eu/ and www.clinicaltrialsregister.eu.

2) Commission Guideline – Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 (2012/C 302/03).

that companies are hiding data and cannot be trusted to release data about their products. As a result, there is a large amount of negative press relating to clinical trial transparency, particularly surrounding the new initiatives being proposed (discussed below). Much of this fails to recognise the complexity of the issues and the legitimate concerns that companies have, including in relation to protection of intellectual property in respect of which many commentators, perhaps understandably, fail to appreciate the implications of basic patent law.

Recent Developments Relating to Pro-active Disclosure

The EMA is committed to the pro-active publication of data supporting marketing authorisations, and, on 24 June 2013, published a draft policy on pro-active access to clinical trial data. The draft policy divides data into three categories:[3]

- Category 1: documents containing confidential information which will not be disclosed. However, the EMA states that this will only be a small number of documents '*in duly justified cases*', and the EMA does not, in principle, consider clinical trial data to be commercially confidential;
- Category 2: documents not containing confidential information or personal data which will be made available on the EMA's website at the same time as publication of the EPAR;
- Category 3: patient-level data containing personal information, for which controlled access is necessary. In such cases, access will only be granted where appropriate assurances are in place, and a data-sharing agreement has been signed.

The consultation on the draft ended on 30 September 2013, and the EMA had intended the policy to come into force on 1 January 2014. However, due to the large number of responses received, implementation has been delayed. The EMA has stated that "the final policy and an implementation plan will be presented to the Management Board for endorsement at its June 2014 meeting." However, it is unclear in what form the policy will take. In addition, it is as yet unclear how this policy would apply for products authorised through the decentralised or mutual recognition procedures, and how it would be implemented by national competent authorities.

The discussions around the policy highlight, in particular, the significant differences of opinion on whether any data within the marketing authorisation dossier, other than manufacturing information, should be kept confidential. However, the EMA is committed to the policy, and sees greater openness as being in the public interest. Comments from industry have largely been met with suspicion, and there appears to be a lack of appreciation of how disclosure can affect the commercial interests of companies, particularly outside the EU.

Secondly, in July 2012, the European Commission published a Proposal for a new Clinical Trials Regulation, which includes the creation of a revised EU-wide database to contain details of clinical trials and which will be accessible to the public.[4] After intense debate, in December 2013, the European Parliament and Council agreed on amendments to the draft. The agreed text states that the sponsor of a clinical trial conducted in the EU should submit a summary of the results of the clinical trial to the EU database within a year of the end of the trial. In addition, where the trial was intended to be used for obtaining a marketing authorisation, the applicant should submit the clinical study report 30 days after the marketing authorisation has been granted (or refused or withdrawn). However, although the recitals state that '*... in general the data included in clinical study reports should not be considered commercially confidential once a marketing authorisation has been granted ...*', the (draft) Regulation does acknowledge that the EU database shall be publically accessible unless confidentiality is justified on the grounds of '*protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product unless there is an overriding public interest in disclosure*'. The Regulation, however, provides no definition of commercially confidential information. The text of the proposal was adopted by the European Parliament on 2 April, and it is expected that the Council will endorse the Regulation in a formal Council sitting, paving the way for final adoption before the Parliament breaks for the May elections.

3) Publication and access to clinical trial data, POLICY/0070, 24 June 2013.

4) Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, 17 July 2012, COM(2012) 369 final, 2012/0192 (COD), Articles 34 and 78.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) and the US Pharmaceutical Research and Manufacturers of America (PhRMA) have responded to the public's concerns by committing to increase the amount of information available to researchers, patients, and the public. In January, PhRMA and EFPIA's joint 'Principles for Responsible Clinical Trial Data Sharing' came into operation.[5] Under these principles, pharmaceutical companies will release, on request, anonymised patient- and study-level clinical trial data, along with full clinical study reports and protocols for US- and EU-approved medicines to '*qualified scientific and medical researchers*'. Such release is subject to contractual prohibitions, patient privacy protections, and confidential commercial information protections. Data requestors are required to provide a rationale for their proposed research, along with their analysis, publication and posting plans; any potential conflicts of interest, including potential competitive use of the data and the source of any research funding. Companies should establish scientific boards to review requests, and should commit to making the data request process transparent by publicly posting their review processes and the identity of external board members, including their existing relationships with the company.

Responding to Requests under Freedom of Information Legislation

The Treaty on the European Union (and its previous versions) notes that the European Union institutions should conduct their work as openly as possible, and that any citizen of the Union, and any natural or legal person residing or having its registered office in a Member State, should have a right of access to documents of the Union's institutions. To implement this, Regulation 1049/2001/EC on access to documents grants EU citizens and legal entities an express right to access documents held by European institutions (this Regulation is not concerned only with bodies involved in pharmaceutical matters). Article 4 Regulation 1049/2001/EC contains exemptions to the right of disclosure, in particular where disclosure would undermine the protection of the commercial interests of a natural or legal person, including intellectual property, unless there is an overriding public interest in disclosure.

This general right of access to documents applies to documents held by the EMA, and the EMA has published a number of policy and guidance documents on access to documents (many Member States have equivalent legislation in their particular country, although the operation is different across the EU). Under previous versions of the policy, the EMA treated clinical trial data as confidential, and refused disclosure of such data. However, in 2010, the European Ombudsman, who investigates complaints of maladministration by EU institutions, delivered two decisions critical of the approach of the EMA. As a result, on 30 November 2010, the EMA published a new policy defining how it would respond to requests for access to documents.[6] The EMA also published guidance on the application of Regulation 1049/2001/EC and the new policy to particular categories of documents and types of information held by the EMA. In relation to the documents within an application for a marketing authorisation (although the guidance does not specifically refer to clinical trial data), it is said that such documents will be considered as confidential prior to the final decision (approval, refusal, or withdrawal). However, once the relevant decision has been made, the documents will be considered to be public, and will be disclosed (subject to appropriate redactions).

Court Proceedings in the EU

The implementation of the policy by the EMA has been controversial. In particular, the EMA has said it does not consider data from clinical trials (or pre-clinical studies) to be commercially confidential, and that it has released a substantial number of documents since the operation of the policy. However, many companies consider documentation within the authorisation dossier to be confidential, and that disclosure would undermine the protection of their commercial interests (including intellectual property). As a result, the EMA is currently subject to two challenges to its policy.[7] In both cases, the companies applied to the European General Court for annulment of the EMA's decisions to disclose all the research-related documents contained in the marketing authorisation applications, and applied for interim orders preventing the EMA from disclosing that information pending the court's decision. Several EU

5) 'Principles for Responsible Clinical Trial Data Sharing: Our Commitment to Patients and Researchers', 18 July 2013.

6) European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use), 30 November 2010, EMA/110196/2006.

7) Cases T-44/13 and T-29/13 *AbbVie v EMA*, and Case T-73/13, *InterMune UK and Others v EMA*.

and US pharmaceutical trade and intellectual property rights associations have sought to intervene in relation to the substantive aspects of that litigation to support the applicants.

On 25 April 2013, the President of the General Court granted the applications for interim relief, with the result that the EMA may not disclose the contested parts of the requested documents pending the hearing of the substantive applications. The EMA expressed disappointment at the decision and, in July 2013, appealed to the Court of Justice. On appeal, on 28 November 2013, the Vice President of the Court of Justice found that the President of the General Court had made an error in law in his approach to determining whether the test for grant of interim measures was met. He therefore referred the case back to the President of the General Court for him to make a further assessment of the arguments and evidence. The application for interim measures, therefore, remains outstanding and the timeline for a final decision by the President of the General Court on whether interim relief should be granted is uncertain. The hearing in the substantive case is not expected to take place before the end of 2014.

As a result of the imminent legal analysis of its new policy as part of pending proceedings, the EMA appears to have adjusted its unqualified approach that pre-clinical and clinical data are never commercially confidential by arguing that, to the extent that the data can be treated as confidential (the disclosure of which might cause the company in question some commercial damage), the public interest in disclosure overrides the commercial interest in confidentiality.

Discussion

Since 2010, the EMA has taken a position of greater disclosure, and considers that all data should be disclosed after a marketing authorisation has been granted. The issue has become one that engages all stakeholders and has elicited strong debate, partly conditioned by the view that, in the past, industry demonstrated (it is said) that it could not be trusted to disclose adverse results of clinical trials or to present results in an unbiased fashion. In addition, the lack of common approach by the industry has led the EMA and others to question the concerns raised by some companies, particularly when there has been limited challenge to the increased disclosure until recently.

The debate is likely to be influenced by the outcome of the cases before the European Court which, while not being concerned with pro-active disclosure, raise the common underlying issues of whether companies can be harmed by disclosure and how far the public interest really requires disclosure. The cases should also clarify what can be considered to be confidential information within a marketing authorisation dossier, and what can be disclosed. This clarification will also be relevant to the interpretation of the new Clinical Trials Regulation, which does not define what is commercially confidential within the marketing authorisation dossier.

Given the EMA's current stance, if a company is concerned that documents provided to the EMA contain commercially confidential information, it is advisable to tell the EMA that this is the case, and request to be notified if any request for access is received. The EMA has previously commented that consultation with the owner of the document is not always required, although recent practice suggests that the EMA is now notifying companies if requests are made for their documents. If a company is concerned about disclosure, it is important to explain why disclosure could damage the commercial interests of the company. We would also advise companies to participate in and respond to the various consultations and proposals that are being discussed in the EU, whether through the relevant industry body or directly, in order to highlight concerns they may have about disclosure.