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European Medicines Agency Disclosure Rules for Clinical Trial Data and Other Parts of the Marketing Authorization Dossier

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Pharma and Biotech

The European Medicines Agency's ("EMA") disclosure of clinical trials data has been discussed for more than five years. Certain disclosures have been opposed before the EU Courts, and the first judgments can be expected in the coming months. Two of the pending cases (case T-729/15 *MSD-Intervet* and case T-718/15 *PTC Therapeutics*) concern non-clinical and clinical trial data and other studies in applications for marketing authorizations. The oral hearing in *MSD-Intervet* took place on May 16, 2017 and the oral hearing in *PTC Therapeutics* is scheduled for July 14, 2017. Decisions on the merits can be expected in the autumn. They will be directly relevant for the reactive transparency policy of the EMA, but may also have an impact on its proactive disclosure, and the new clinical trial database.

In summary, there are three different EU transparency initiatives currently in operation or in preparation by the EMA: (i) reactive disclosure of clinical trial data and other documents held by the agency; (ii) proactive disclosure of clinical trial data; and (iii) the transparency aspects of the new clinical trial database under the EU Clinical Trial Regulation EU (No) 536/2014 ("CTR").

This note provides an overview of the current situation.

Reactive Disclosure Policy

In November 2010, the EMA published a policy on access to documents relating to medicinal products for human and veterinary use (Policy 0043 or the "Reactive Disclosure Policy"). At the same time, the EMA also published an output table to support the Reactive Disclosure Policy that lists the possible access status of many documents held by the EMA. In March 2012, the EMA, together with the Heads of Medicines Agencies supplemented this policy with guidance on the release of information about a medicine following the grant of marketing authorization. These documents are currently being revised.

Reactive disclosure covers all documents held by the EMA. It thus goes beyond documents related to a marketing authorization application and can, for instance, also cover orphan

designations, paediatric investigation plans, marketing update reports and opinions on medicinal ingredients used in medical devices.

What does the Reactive Disclosure Policy cover?

The Reactive Disclosure Policy provides general principles that apply to the EMA's handling of access to document requests under the Transparency Regulation 1049/2001. Under the Transparency Regulation and EMA's implementation of it, any person can submit a request for access to any content—regardless of medium—relating to the policies, activities and decisions falling within the EMA's sphere of responsibility.[1] This broad spectrum of documents includes documents and data submitted by third parties to the EMA, such as marketing authorization applicants/holders, and documents created by the EMA itself, such as assessment reports. The EMA's press release that accompanied the Policy states that once a marketing authorization has been granted, documents submitted as part of a marketing authorization application, such as clinical trial reports, can be released subject to the redaction of commercially confidential information. However, the March 2012 supplemental guidance states that as a general rule, data included in clinical study reports are considered as "data that can be released as such data is not considered either commercially confidential or personal data that should be protected. In the case of exceptional and substantiated cases, particularly where innovative study designs and/or innovative analytical methods have been used, consideration will be given to the need for redaction."

Can protected personal data ("PPD") or commercially confidential information ("CCI") be redacted from documents?

The Reactive Disclosure Policy explains that access to a document will only be denied if one of the exceptions in Article 4 of the Transparency Regulation applies. The two most relevant exceptions are if the disclosure would (i) undermine the privacy and the integrity of the individual concerned (PPD); or (ii) undermine the protection of commercial interests of a natural or legal person (CCI).

The Reactive Disclosure Policy defines CCI as any information that is not in the public domain or publicly available, and where disclosure may undermine the economic interest or competitive position of the owner of the information. According to the Reactive Disclosure Policy, any information that can be found in the public domain cannot be considered to be CCI.

Information or parts of a document that should not be disclosed may be redacted to prevent disclosure of such information while allowing access to the rest of the document. However, irrespective of any applicable exception, access to documents or parts of a document relating to CCI may be granted if an overriding public interest in disclosure can be identified (and in the case of environmental information, such overriding public interest is automatically presumed).

[1] Although strictly speaking the right of access rests with EU citizens, institutions may decide to grant access to non-EU citizens and this is EMA common practice.

Does the EMA notify third parties if an access to document request is made that concerns the third party's medicinal product?

The Reactive Disclosure Policy explains that the EMA notifies third parties of access to document requests concerning documents produced by those third parties (e.g., clinical study reports). In practice, the EMA usually notifies third parties about (the first request for) access to document requests for EMA documents (e.g., Assessment Reports) that concern a third party's medicinal product as well.

Does the EMA consult third parties regarding whether or not the information in requested documents should be disclosed?

Typically, the EMA provides third parties with a five working day consultation period to review, identify and redact information in the requested documents that should not be disclosed (unless the same document has already been released in the past). Concretely, the third party should identify proposed redactions of information in the requested documents and produce a detailed justification table. It should explain the rationale for the proposed redactions and be as specific as possible. Sometimes additional response time can be agreed upon.

Before releasing a requested document to a requestor, the EMA usually issues a decision letter to a concerned third party following the EMA's review of any proposed redactions. The EMA typically releases the requested document 10 working days after issuing a decision letter, during which time a third party must commence legal action before the EU General Court if it wishes to challenge the EMA's decision to disclose the requested document. Documents released to requestors are not subject to any particular controls (e.g., in the form of terms of use that restrict what the requestor can do with the documents).

Have any companies challenged EMA decisions regarding access to document requests?

A number of pharmaceutical companies have challenged EMA decisions to release requested documents, including clinical study reports. It is expected that the EU General Court will issue decisions on the merits in the autumn, including in the *PTC* case in which EUCOPE is an intervening party.

One of the key legal issues in these cases is whether there is a presumption of confidentiality for certain documents in the marketing authorization dossier (e.g., clinical trial data). Regulation 726/2004 already provides for transparency of medicinal products and marketing authorization procedures through EPARs, SmPCs, meeting minutes, etc. The Court is asked to rule whether the balance between CCI and transparency in that Regulation would be unstable if more documents could routinely be obtained through the general Transparency Regulation.

Has the EMA published any guidance on CCI in marketing authorization documents?

The EMA has supplemented the Reactive Disclosure Policy with a number of additional guidance documents. Please see section "Proactive Disclosure Policy" below.

Proactive Disclosure Policy

In October 2014, the EMA published a policy on the publication of clinical data for medicinal products for human use (Policy 0070 or the "Proactive Disclosure Policy"). The policy applies to clinical trial data submitted in marketing authorization applications (or variations to existing products) under the centralized procedure after January 1, 2015 and July 1, 2015 respectively. This includes clinical reports previously submitted to the EMA that are cross-referred to in the regulatory application.

What is the aim of the Proactive Disclosure Policy?

The EMA's Proactive Disclosure Policy operates separately to the reactive system of disclosure described above. Essentially, the policy aims to make clinical data as accessible as possible, but with certain controls ("terms of use") in place to reduce the risk that the data could be misused for commercial purposes.

What documents are covered by the policy?

Clinical data published by the EMA normally includes clinical overviews, clinical summaries, study reports and appendices, which correspond to modules 2.5, 2.7 and 5.3 of the common technical document.

The EMA announced the intention to later on broaden the scope of publication to individual patient data, but that will require specific data privacy safeguards. It is unclear whether this will ultimately be pursued.

Will clinical data containing commercially confidential information be redacted?

Although the Proactive Disclosure Policy states that the EMA will not divulge CCI, there is a general presumption that clinical data is not considered CCI. However, Annex 3 of the Proactive Disclosure Policy includes redaction principles (e.g., the types of information that could fall under CCI, including exploratory end-points, method of PK/PD determinations, information about innovative bioassays/analytical methods). According to the Proactive Disclosure Policy, any information that can be found in the public domain cannot be considered to be CCI.

The EMA advises that companies should redact CCI with a black box and a red label.

The court decisions on the Reactive Disclosure Policy may have an impact on what qualifies as CCI under the proactive policy.

Does the clinical data need to be anonymized?

Yes. Marketing authorization applicants/holders should anonymize clinical data to prevent patients and professionals who participated in clinical trials from being identified. The EMA advises that companies should redact personal data with a light blue box and a black "PPD" label and prepare an anonymization report describing the anonymization methods used and their impact on data utility.

What is the process for redacting clinical data?

After submitting a clinical study report to the EMA as part of a marketing authorization application, applicants should submit a redacted version of the report to the EMA together with a justification table explaining the redactions. The EMA then reviews the proposals and provides recommendations. The company subsequently submits a revised redaction proposal and the EMA publishes a redacted version of the clinical data.

If the EMA considers that the applicant's proposed redactions to the clinical study report contain information that should be public, the EMA will consult the applicant. At the end of the redaction consultation process, the EMA enters rejection codes in the justification table to reflect the EMA's final position on the document. The final redacted document package must include a cover letter, including a statement on whether the applicant fully or partially agrees with the EMA's final position on the report. The Proactive Disclosure Policy explains that where an applicant only partially agrees with the EMA, the only means of challenging the final decision is by taking legal action in the EU General Court. There is no known legal challenge yet, but this may change following the decisions on reactive disclosure.

Where is the clinical data published?

On October 20, 2016, the EMA launched its clinical data website.[2] Since the launch of the website, the EMA has uploaded clinical data for a number of medicinal products. Website users must register user accounts with the EMA to view uploaded data and may choose between an on-screen view only or a full download-and-print access depending on the intended purpose of viewing the information.

What are the controls on accessing the published documents?

The controls take the form of "terms of use" ("ToU"), and govern the access to and use of the clinical reports. There are two sets of ToU depending on whether the intended use of the information is for general, non-commercial purposes or academic and non-commercial research purposes. Both sets of ToU incorporate certain conditions, which acknowledge the risk that data could be misused.

When will clinical data be published?

Although there is currently a delay in clinical data being published, the EMA envisages that clinical data in applications for marketing authorizations and variations will be published 60 days after the European Commission decision on the application, and that clinical data from withdrawn applications will be published 150 days after receipt of the withdrawal letter.

Has the EMA provided any additional guidance on the Proactive Disclosure Policy?

Yes, the EMA has published a detailed external guidance document on the Proactive Disclosure Policy that provides further details on the scope of the policy, procedural aspects related to the submission of clinical reports, how to anonymize clinical reports and how to identify and redact CCI, together with various templates. The EMA has also hosted a number of helpful webinars on the topic that can be found on the EMA's website and expects to host future webinars on a quarterly basis.

Transparency under the Clinical Trials Regulation 536/2014 ("CTR")

The CTR was adopted in April 2014 and aims to harmonize the assessment and supervision processes for clinical trials throughout the EU, via an EU portal and database. The portal will be the single entry point for submitting clinical trial information in the EU, which will be stored in the database. The EMA will make information stored in the database publicly available subject to transparency rules.

How does the CTR differ from the Proactive Disclosure Policy?

The Proactive Disclosure Policy concerns clinical studies submitted to the EMA for centrally authorized products in the context of marketing authorization applications and variations regardless of where the study was conducted. Under the Proactive Disclosure Policy, the EMA publishes clinical data (clinical overviews, clinical summaries, clinical study reports) and the anonymization report prepared by the applicant.

The CTR concerns clinical trials conducted in the EU for investigational medicinal products regardless of whether they have a marketing authorization. Pursuant to the CTR, the EMA will publish all clinical-trial related information generated during the life cycle of a clinical trial, such as the protocol, assessment and decision on trial conduct, summary of trial results, study report and inspections, etc.

When will the CTR apply?

Although the Regulation was adopted and entered into force in 2014, the timing of its application depends on confirmation of full functionality of the EU portal and database through an independent audit. The CTR becomes applicable six months after the European Commission publishes notice of this confirmation, which the EMA expects to happen by October 2018.

Will the Court decisions on reactive disclosure affect the CTR transparency rules?

It is possible that the decisions in the pending cases on reactive disclosure will have an impact on the transparency under the CTR. They may require a different interpretation of the CTR rules, and in the interim decisions in *MSD/Intervet* and *PTC Therapeutics*, the President of the General Court suggested the possibility that the transparency provisions in the CTR itself may not be legal under general EU law principles.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Pharma and Biotech practice:

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[2] https://clinicaldata.ema.europa.eu/web/cdp/home