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EMA Draft Policy on Publication and Access to Clinical Trials Data Provides Broad Researcher Access to Participant-Level Data




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I. Introduction

On June 24, 2013, the European Medicines Agency (EMA) released a draft policy titled *Publication and Access to Clinical-Trial Data*, which provides for wide researcher access to many types of clinical trials (CT) data that are submitted to the EMA in support of marketing authorization applications. Information released under the policy would include both summary and participant-level data. The policy, or some version of it, likely will become effective on Jan. 1, 2014, and is the result of deliberations between January and April 2013 of five separate advisory groups to the EMA, which were composed of experts from the pharmaceutical industry, academia, public health groups, and patient advocacy organizations. This article provides an overview of the new EMA draft policy and its likely im-

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pact on the planning and conduct of clinical research and discusses areas in which the draft policy has left some significant unanswered questions.

II. Overview of Draft EMA Policy

a. Scope of Data Sharing Policy

The draft policy defines CT data by reference to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD), which provides specifications for dossiers submitted for the registration of medicines in the United States, the European Union (EU), and Japan.[1] Specifically, the draft policy requires the sharing of data submitted to the EMA after the effective date of the policy that are contained in the following CTD modules: Module 2.5, which consists of a clinical overview, Module 2.7, which contains a clinical summary, and Module 5, which contains the clinical study report (CSR).[2] The draft policy applies not only to conventional randomized controlled trials, but also to other types of interventional or observational research such as large simple trials, cohort studies, case control studies, and registry data.[3]

Under the new policy, data would be made available for sharing at the time of publication of a European Public Assessment Report (EPAR) for a given medication's marketing authorization application.[4] The EPAR contains the scientific conclusion reached by the EMA's Committee for Medicinal Products for Human Use and provides a summary of the grounds for the committee's decision either to grant or refuse a marketing authorization for a specific medicinal product.[5] Under the proposed policy, data would be released regardless of whether the EPAR issued contains a positive or negative decision on the marketing authorization application, and data also would be released in cases in which an application for marketing authorization has been withdrawn, regardless of whether a withdrawal EPAR is issued.[6]

b. Process of Data Sharing

During the advisory group process that preceded release of the draft policy, much of the discussion focused on three issues: (1) whether commercially confidential information (CCI) of pharmaceutical companies contained in CSRs would be protected; (2) whether data would be made available freely over the internet or subject to a gatekeeping process; and (3) the extent to which participant-level data listings would be anonymized prior to release. This discussion was motivated by concerns that data sharing could reveal trade secrets or otherwise compromise the intellectual property rights of pharmaceutical companies, that those accessing shared data would lack an adequate research protocol or knowledge of statistical analysis to make meaningful use of the data, and, perhaps most importantly, that CT participant privacy would be undermined by the release of participant-level data. In its draft policy, the EMA has accommodated some of these concerns by proposing a regime in which the degree of availability of data differs based on the type of data at issue.

The draft policy creates three broad classifications of data:[7]

- Category 1 Data: Data containing CCI,[8]
- Category 2 Data: Data without protection of personal data (PPD) concerns, and
- Category 3 Data: Data with PPD concerns.

Category 1 data would not be made available under the new policy.[9] The draft indicates that examples of such data include details of the investigational product itself, some in vitro studies, and bioanalytical data characterizing the product.[10] The EMA has suggested, however, that it does not consider CCI to be a major concern, noting that only a ''small number of CT data/documents'' contain CCI, and that even for the categories of data that it has identified as potentially containing CCI, it would deem such data to contain CCI only ''in duly justified cases.''[11] The draft policy also states a broad presumption that ''interests of public health outweigh considerations of CCI,'' but it does not provide a definition of ''interests of public health.''[12] The draft policy thus affords the EMA significant discretion to determine when data would be classified as Category 1 data.

Category 2 data would be the most freely available data under the new policy, with the draft indicating that such data would be made freely available for download via the EMA website.[13] The EMA defines ''personal data'' for the purpose of this category as any data related to an identified or identifiable natural person,

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[1] *See* EMA, *Publication and Access to Clinical-Trial Data: Draft for Public Consultation*, Policy/0070, at 3 (2013), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf [hereinafter EMA, *Draft Policy*]; *see also,* Food and Drug Administration, *Guidance for Industry: Submitting Marketing Applications According to the ICH-CTD Format—General Considerations* (August 2001) (Draft Guidance), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129720.pdf.

[2] *See* EMA, *Draft Policy*, *supra* note 1, at 3.

[3] *See id*. at 3.

[4] *See id*. at 4, 6. The marketing authorization application serves a similar function to a new drug application (NDA) submitted to the U.S. Food and Drug Administration. *See* EMA/FDA, *Report on the Pilot EMA-FDA GCP Initiative, September 2009-March 2011* (2011), *available at* http://www.fda.gov/downloads/InternationalPrograms/FDABeyondOurBordersForeignOffices/EuropeanUnion/EuropeanUnion/EuropeanCommission/UCM266259.pdf.

[5] *See* EMA, European Public Assessment Reports, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000433.jsp&mid (last visited July 7, 2013).

[6] *See* EMA, *Draft Policy*, *supra* note 1, at 4, 6.

[7] *See id*. at 4-7.

[8] The draft policy defines CCI as ''any information that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the owner of the information.'' CCI includes both trade secrets and commercial confidences. *See id*. at 3.

[9] *See id*. at 4.

[10] *See id*.

[11] *See id*. The draft policy indicates that documents/data containing CCI would remain available under the EMA's Policy on Access to Documents, which has been in place since 2010 and allows for the disclosure of documents upon request on a case-by-case basis. *See European Medicines Agency Policy on Access to Documents (Related to Medicinal Products for Human and Veterinary Use)* (EC) No. 1049/2001, *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf.

[12] *See* EMA, *Draft Policy*, *supra* note 1, at 2.

[13] *See id*. at 4.

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meaning a person who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his or her physical, physiological, mental, economic, cultural, or social identity.[14]

The EMA draft policy indicates that Category 2 includes documents that have never contained personal data (*e.g.*, summary tables presenting only aggregate data), documents in which any personal data have been ''adequately de-identified,'' and those for which a ''public-health reason'' overrides any PPD concerns.[15] A definition of ''public-health reason'' is not provided, nor does the draft policy indicate the factors that will be taken into account when determining whether a ''public-health reason'' overrides PPD concerns. The draft policy does, however, provide that the ''public-health reason'' override justifies the release of personal data about CT personnel that are contained in the CSR, including the identities of investigators and of those who collect and analyze CT data, such as nurses and biostatisticians.[16] Category 2 data submitted in support of a marketing authorization on or after March 1, 2014, would be subject to the new data sharing policy.[17]

Unlike Category 2 documents, which are subject to an open access policy, Category 3 data would be made available only through a gatekeeping process. The EMA indicates that Category 3 data consist primarily of ''raw CT data,'' defined to include individual patient data sets, individual patient line-listings, individual case report forms, and documentation explaining the structure and content of data sets.[18] Before being granted access to such data, the requester must identify himself or herself and the EMA must verify the requester's identity, the requester must be a natural or legal person ''established'' in the EU, and the requester must enter a ''legally binding'' data-sharing agreement.[19] The data-sharing agreement requires data requesters to adhere to several conditions, including that:[20]

- data be accessed solely for the purpose of addressing a question or conducting analyses that are in the interest of public health;
- a detailed list of the aims of accessing the data be submitted;
- no attempt be made to identify retroactively the participants in the CT;
- no use of the data falls ''outside the boundaries of patients' informed consent'';
- the data not be used to gain a marketing authorization outside the EU;
- data accessed from the EMA not be shared with any other party;
- studies performed with the data receive ethics committee approval;
- the identity of the requester may be shared by the EMA;
- all results of secondary analyses be made public after a ''reasonable period of time,'' usually no more than one year; and
- any CT data accessed be destroyed once the secondary analysis is complete.

While all requesters of Category 3 data would be required to enter a data-sharing agreement, the EMA has not specified any sanctions for those who violate the agreement; there is no mention of specific civil penalties, let alone possible criminal sanctions. Accordingly, it appears that those violating a data-sharing agreement would be subject to simple breach of contract liability.

During the advisory group process, one of the main debates centered on whether those requesting data would have to put forth a research protocol, and/or demonstrate competence in statistical analysis prior to receiving participant-level CT data. The draft policy provides that requesters of Category 3 data would have the ''opportunity'' to upload a statistical analysis plan and/or other relevant documents pertaining to their proposed analysis; however, the granting of access to Category 3 data would not be affected by a requester's failure to upload an analysis plan.[21] Furthermore, the EMA has indicated that it would not judge the qualifications of those submitting requests for access to the data, and that if a statistical analysis plan is submitted with the request, the EMA would not evaluate the quality of that plan.[22]

In addition to minimizing the possibility of re-identification of Category 3 data through the use of a gatekeeping process, the EMA also requires ''appropriate de-identification'' of Category 3 data.[23] As a ''minimum standard'' for de-identification, the draft policy refers to a *BMJ* article that sets forth standards for de-identification of patient data in scientific journal articles.[24] The cited article advocates for the removal of all ''direct identifiers,'' which is essentially the list of 18 identifiers that must be removed to satisfy the Health Insurance Portability and Accountability Act of 1996 (HIPAA) de-identification safe harbor,[25] with the exception that rather than providing for the removal of *all* geographic subdivisions smaller than a state, it only requires the removal of the participant's address.[26] Beyond discussion of direct identifiers, the cited article also indicates that data sets containing three or more indirect identifiers, such as sex, place of treatment, rare disease or treatment, or ethnicity, should be evaluated by an independent researcher or ethics committee to evaluate the risk that individuals might be identifiable.[27]

Due to the need to develop the mechanics of the data request process, the EMA has indicated that Category 3

[14] *See id*. at 3. Those familiar with the 18 identifiers that must be removed to meet the de-identification safe harbor under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), *see* 45 C.F.R. § 164.514(b)(2), will note that the EMA's definition of ''personal data'' does not map to the HIPAA identifiers. Indeed, factors such as cultural and social identity that are included in the EMA definition of ''personal data'' are not taken into account under HIPAA.

[15] *See* EMA, *Draft Policy*, *supra* note 1, at 4.

[16] *See id*. at 4, 9.

[17] *See id*. at 7.

[18] *See id*. at 4-5.

[19] *See id*. at 5.

[20] *See id*. at 5-6.

[21] *See id*. at 6.

[22] *See id*.

[23] *See id*. at 5.

[24] *See* Iain Hrynaszkiewicz et al., *Preparing Raw Clinical Data for Publication: Guidance for Journal Editors, Authors, and Peer Reviewers*, 340 *BMJ* 304 (2010).

[25] *See* 45 C.F.R. § 164.514(b)(2).

[26] *See* Hrynaszkiewicz et al., *supra* note 24, at 305.

[27] *See id*.

data would not be available for request until at least Jan. 1, 2015. Additional guidance on the release of Category 3 data is expected by the end of October 2014.[28]

III. Questions Left Unanswered by the EMA Draft Policy

The EMA's draft policy leaves several important questions unanswered, including the treatment of CCI; the level of de-identification required for Category 2 data as compared to Category 3 data; the method and nature of evaluation of informed consent from studies for which data are being shared; the extent to which secondary analyses produced with released CT data would be placed in the public domain; the impact the draft policy would have on regulatory decisionmaking; and the extent to which the new policy would lead to high-quality secondary analyses.

While as discussed above the draft policy excludes from release data deemed to contain CCI, the EMA has indicated that such data would continue to be available on a case-by-case basis under the agency's Policy on Access to Documents.[29] The Policy on Access to Documents, however, currently is the subject of two lawsuits in the European General Court brought by the pharmaceutical companies AbbVie and InterMune challenging the release of CT documents containing CCI.[30] Given the EMA's view that documents subject to release under the new policy would only be considered to contain CCI in ''duly justified cases,'' a phrase the draft policy leaves undefined, it is quite likely that pharmaceutical companies would wish to challenge the EMA's decision that a given document does not contain CCI. The draft policy, however, lacks clarity regarding whether an administrative avenue would exist for review of this determination. It also fails to discuss the process the EMA would use to notify CT sponsors once the EMA has determined that a given document lacks CCI, and it does not indicate whether sponsors will be able to redact information they consider to be CCI. Given this lack of clarity, the draft policy's treatment of CCI likely would spawn litigation by pharmaceutical companies contending that the information contained in their reports is a ''duly justified'' instance of CCI, thus barring release of the documents. The outcome of the ongoing *AbbVie* and *InterMune* cases also may affect the EMA's implementation of this new policy if the court decisions discuss the scope of CCI.

A second unanswered question introduced by the EMA draft concerns the demarcation between Category 2 and Category 3 data in terms of de-identification. The draft policy indicates that documents may be classified as Category 2 documents, available for ''open access,'' if all of the personal data contained in the document have been ''adequately de-identified.''[31] The draft does not indicate, however, what is meant by the term ''adequately de-identified,'' nor does it indicate how this de-identification differs from the de-identification required for Category 3 data released via the controlled access process. Logically, the level of de-identification required for Category 3 data cannot be the same as that required for Category 2 data, or else all Category 3 data would be classified as Category 2 data. Given the vastly different data release policies available for Category 2 and Category 3 data, it will be important for the EMA to refine these definitions prior to the effective date of the new policy.

Another question unanswered by the EMA draft policy is the extent to which considerations of informed consent would be taken into account when data are made available for release. Because clinical trials used to support marketing authorizations often last several months or even years, much CT data used to support marketing authorizations at the time the new EMA policy comes into effect will have been gathered before researchers were aware of the new EMA data sharing requirements, and thus the possibility of data sharing could not have been included in the informed consent used for the study. The draft policy makes several vague references to informed consent, noting that because patients participate in clinical trials with the hope of advancing science and public health, any other uses of data would be inconsistent with the ''boundaries'' of informed consent.[32] The EMA also notes that for Category 3 data subject to a data-sharing agreement, any uses of data should respect the ''spirit'' of the informed consent and that requesters must refrain from using CT data for any purposes that are ''deemed'' outside the boundaries of patients' informed consents.[33]

It is not clear from the draft policy's statements regarding informed consent which types of data uses would be considered to fall within the boundaries of informed consent, or who would be responsible for ''deeming'' certain uses as beyond the boundaries of the patient's informed consent. Given the EMA's emphasis on respecting the ''spirit'' of informed consent, would all uses of CT data that can be conceivably categorized as advancing science or public health be deemed to fall within the boundaries of a patient's informed consent? What if the consent form specifically forbade secondary uses of data? These questions must be further addressed in the final EMA policy, or else they undoubtedly will spawn litigation from patients objecting to uses of their data that were not mentioned in their consent forms or consent discussions.

Prospectively, consent forms for trials that may be used to support a marketing authorization with the EMA should be modified to indicate that all of an individual's results and other information collected as part of a CT may be made available for secondary research uses. The prospect of such data sharing may chill vol-

[28] *See* EMA, *Draft Policy*, *supra* note 1, at 7.

[29] *See European Medicines Agency Policy on Access to Documents (Related to Medicinal Products for Human and Veterinary Use)*, *supra* note 11.

[30] The European General Court has issued interlocutory injunctions in both the *AbbVie* and *InterMune* cases barring release of the documents at issue prior to the issuance of the court's final opinions in the cases. *See* Case T-44/13, *AbbVie Inc. v. European Medicines Agency*, Order of the President of the General Court (April 25, 2013), *available at* http://curia.europa.eu/juris/document/document.jsf?text=&docid=137241&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=630272; Case T-73/13, *InterMune UK Ltd. v. European Medicines Agency*, Order of the President of the General Court (April 25, 2013), *available at* http://curia.europa.eu/juris/document/document.jsf?text=&docid=137242&pageIndex=0&doclang=en&mode=lst&dir=&occ=first&part=1&cid=630272.

[31] *See* EMA, *Draft Policy*, *supra* note 1, at 4.

[32] *See id.* at 2.

[33] *See id.* at 5.

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unteerism among potential CT participants who are leery about having their information shared with researchers whom they do not know. If certain types of prospective participants are more likely to be deterred from participating than others, this chilling process could potentially lead to sampling bias.

While the EMA policy is motivated by a belief in the positive effects of data transparency, it is questionable to what extent the EMA would be able to ensure transparency among the secondary analyses conducted on released data. The draft policy indicates that the EMA believes that ''transparency is a two-way street'' and that secondary analyses performed on participant-level data should be in the public domain.[34] However, while the Category 3 data-sharing agreement requires data requesters, as a condition of receipt, to agree that all secondary analyses would be placed in the public domain, given the relatively hands-off approach the EMA has indicated it would take with regard to enforcing other aspects of the draft policy, such as evaluating statistical analysis plans and the qualifications of researchers, it is questionable whether the EMA would take steps to ensure that secondary analyses actually are made available. Furthermore, the draft policy limits the requirement of releasing secondary analyses to researchers utilizing participant-level data,[35] and it thus provides no guarantee that analyses performed on other types of data, such as the majority of data contained in Category 2, would be made publicly available.

Because the availability of secondary analyses is a key rationale behind data sharing, the failure of such analyses to be made publicly available undermines the purpose of the new EMA policy. To encourage data requesters to make secondary analyses available, the EMA may wish to impose sanctions on those who fail to share their analyses after a given period of time (*e.g.*, a year) has passed since receiving data. The EMA also may consider making publicly available any statistical analysis plan uploaded by those who fail to share secondary analyses.

Secondary analyses from required data transparency, as proposed in the draft policy, also undoubtedly would lead to challenges to the decisionmaking process of the EMA and other regulatory agencies charged with approving medications for human use, such as the U.S. Food and Drug Administration (FDA). Such challenges may come from many sources. For example, patients suffering from serious diseases may question why the EMA denied a marketing authorization for a new drug treating their disease, whereas insurance companies that do not wish to pay for a costly new drug may use the data released to argue that the drug is no more effective than existing treatments, and thus deny coverage for it. The EMA has indicated that it welcomes such challenges, noting that while the agency needs insulation from external pressures when evaluating marketing authorizations, the need for such insulation disappears once a decision on a marketing authorization has been reached.[36]

It is unclear if agencies in other parts of the world would share the EMA's optimism regarding challenges to their regulatory decisions stemming from shared data given the fact that responding to such challenges likely would impose new and significant resource requirements on such agencies. Furthermore, in instances in which a product receives EMA approval before receiving approval in the United States or other jurisdictions, challenges to an EMA regulatory decision as a result of the new data-sharing policy could impact pending review by the FDA or other national regulatory agencies. The FDA's recent request for comments regarding its own possible future data-sharing efforts indicates that any data sharing undertaken by the FDA would avoid challenges to regulatory decisions by masking data (*i.e.*, removing information that could link the data to a specific product or application) such that those who receive data could not use them to challenge the regulatory decision made on a specific drug.[37]

A final unanswered question about the new policy is the extent to which it will lead to secondary analyses that will be useful to patients and physicians seeking to make informed decisions amongst various medicines. While the EMA has indicated that it will require those requesting Category 3 data to specify their aims in accessing data, it also has indicated that it will not judge the professional competence of the data requesters, nor will it judge the quality of any statistical plan they choose to provide. To receive Category 2 data, requesters need not even divulge their aims in accessing the data. These release mechanisms provide little assurance that those receiving data under the new policy will possess the skills needed to conduct useful analyses with those data. This introduces the possibility of a proliferation of low-quality analyses that could potentially confuse patients and physicians rather than assisting them.

IV. Conclusion

The EMA will be accepting comments on its draft policy through Sept. 30, 2013, with a final policy due out in late 2013. Those pursuing marketing authorizations with the EMA or conducting clinical trials that may be used to support marketing authorizations in the EMA would be well advised to follow these developments closely to understand how data submitted to the agency would be made available to secondary researchers and to prepare to revise their data policies and clinical trial consent forms accordingly.

[34] *See id.* at 2.
[35] *See id.*
[36] *See id.*
[37] *See* Food and Drug Administration, ''Availability of Masked and De-identified Non-Summary Safety and Efficacy Data: Request for Comments,'' 78 Fed. Reg. 33,421, 33,422 (June 4, 2013).