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Submission of comments on 'Policy 0070 on publication and access to clinical-trial data'

Comments from:

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Please note that these comments and the identity of the sender (not contact details) will be published unless a specific justified objection is received.

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Who We Are

Public Citizen's Health Research Group is a patient advocacy group based in the United States (U.S.). We have worked for over 40 years conducting research and advocacy aimed at ensuring consumer access to safe, effective drugs, medical devices, and other health products. Much of our work involves analysing data from clinical trials and adverse event reports submitted to the Food and Drug Administration (FDA), which we obtain in part by making requests under the Freedom of Information Act (FOIA), the U.S. transparency statute that serves a similar function to EU Regulation 1049/2001. We also rely on data published in the European Union and on European Medicines Agency (EMA) regulatory decisions to inform our research and advocacy work.

Public Citizen's Health Research Group is a stakeholder in the EMA policy on publication and access to clinical trial data because we expect to use the data published under the policy to better understand the safety and effectiveness of drugs approved in Europe and the U.S. All analysis we conduct using data released under the policy will be shared publicly to benefit the public health in the U.S., Europe, and elsewhere in the world.

I. Introduction

Public Citizen generally supports the EMA's proposed policy 0070 on publication and access to clinical trial data,[1] which provides for the publication of clinical-trial data submitted to the EMA in the future including de-identified patient-level data, as well as other documents held by the agency. This policy complements the existing "Policy on access to documents (related to medicinal products for human and veterinary use)" (policy 0043), which provides for access to documents related to data previously submitted to the EMA.[2]

We support draft policy 0070, which will enable independent re-analysis of the benefits and risks of EMA-approved drugs. Draft policy 0070 promotes transparency and the opportunity for independent review, cornerstones of both sound medical research and good regulatory decision-making in a democratic society. The policy will adequately protect patient privacy if clarification is made to ensure appropriate implementation. The policy currently sufficiently protects legitimate commercial interests, preserves incentives to innovate, conforms to appropriate informed consent standards, and guards against data misuse.

We request that the policy be clarified so as not to suggest, misleadingly, that informed consent is required for de-identified data and can be complied with "in spirit." We also propose that the policy be strengthened by enabling access to de-identified patient-level data by research groups based outside of Europe, as research generated by international groups serves to benefit the public health, both internationally and within European member states.

II. Summary of Specific Comments

1. Protecting Patient Privacy

Patient privacy is of great concern when considering use of data from clinical trials enrolling human subjects. Patients participating in clinical trials share sensitive health information, disclosure of which may harm the individuals' privacy interest. Moreover, personal information is protected under Article (4)(2) of EC Regulation 1049/2001, against disclosure that would undermine the privacy and integrity of individuals.[3] With some

[1] European Medicines Agency. Publication and access to clinical-trial data POLICY/0070. June 24, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf. Accessed September 30, 2013.

[2] European Medicines Agency. European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use) POLICY/0043.http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf. Accessed September 23, 2013.

[3] That regulation states that European Community institutions, including the EMA, "shall refuse access to a document where disclosure would undermine the protection of: ... (b) privacy and the integrity of the individual, in particular in accordance with Community legislation regarding the protection of personal data." Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001. http://www.europarl.europa.eu/register/pdf/r1049_en.pdf. Accessed September 30, 2013.

clarifying changes, we believe that policy 0070 could adequately protect the privacy and integrity of individuals.

Data from clinical trials should only be shared after appropriate steps are taken to de-identify any information applicable to specific patients. The EMA has selected a proposed minimum standard for de-identifying patient data, described in Hrynaszkiewicz,[4] and has also required additional de-identification methods where appropriate. Preventing re-identification will ensure that disclosure will not undermine the privacy and integrity of individuals.

When dealing with large data sets, there is sometimes a risk that data may be processed or "mined" in ways that allow individuals to be re-identified. We believe that the risk of re-identification is low, in part because few individuals or organizations with capacity to conduct such a "mining" effort have a financial or other interest in uncovering the identities of the patients who participated in clinical trials research. Nevertheless, the EMA has provided additional safeguards against this practice by requiring that the requester of patient-specific data enter into a legally binding data-sharing agreement, through which the requester agrees to refrain from any attempt to retroactively re-identify patients in clinical trials, including by relying on outside databases. This agreement requirement, if appropriately implemented to cover all data at risk for re-identification, would be sufficient to protect against re-identification.

However, it remains unclear how this aspect of the policy will be implemented. Under the policy, some types of de-identified patient-level data will be classified as Category 2 and made available "open access" without a data-sharing agreement, while other de-identified patient data are classified as Category 3 and require an agreement. We think it is reasonable to require different levels of protection depending on the risk of re-identification. However, we do not believe the policy makes clear when and how de-identified data will receive the higher level of protection. One way to make this clearer would be to define what it means for data to be "adequately de-identified" under Category 2 (page 4, line 143), and how this differs from "appropriate de-identification" under Category 3 (page 5, lines 165-175). With clarification in place, we believe that policy 0070 can be implemented to adequately protect patient privacy.

2. Disclosure of Clinical Trials Personnel Data

In addition to patient data, information submitted to the EMA will include personal data related to the personnel involved in clinical trials (clinical investigators and other health care providers). These data, which generally relate to the identity and professional activities of the individual in the context of the clinical trial, do not implicate the same privacy interests as the health information collected from clinical trial participants.

[4] Hrynaszkiewicz, I., M. L. Norton, et al. (2010). "Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers." *BMJ* 340:c181.

The protections for personal data in EC Regulation 1049/2001 are not absolute, but rather bar disclosure only where "disclosure would undermine the protection of: . . . (b) privacy and the integrity of the individual."[5] Asking an investigator or health care provider to identify his or her professional involvement in a clinical trial does not undermine the privacy or integrity of that person, any more than an author's attribution on an academic publication undermines the privacy or integrity of the author. Moreover, such information is essential in order to identify potential conflicts of interest held by the investigators and understand how potential biases might have affected the integrity of the clinical trial results. The EMA therefore correctly determined that the personal data of clinical trials personnel is not protected against disclosure under EC Regulation 1049/2001, and should be made openly available to the public without restriction.

3. Legitimate Commercial Interests

The EMA is required, under Article (4)(2) of Regulation 1049/2001, to refuse access to documents where disclosure would undermine the protection of "commercial interests . . . unless there is an overriding public interest in disclosure."[6] We believe that policy 0070 appropriately protects commercial interests by preventing disclosure of commercially confidential information (CCI), which is defined under the policy 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."[7]

Some information submitted to the EMA may be proprietary in nature, including trade secrets and information from preclinical biopharmaceutical studies that could be used by other companies to identify proprietary compounds and create potential competing products. Such data are adequately protected under policy 0070, which protects pre-clinical reports from publication (except by specific request under the agency's policy 0043 on access documents).

We agree with the EMA that data disclosing the methodology and results from human clinical trials cannot, as a general matter, be considered CCI.

Most safety and efficacy trials rely on standard, validated techniques that are non-proprietary and well known to industry competitors. Information on the methodology from clinical trials should therefore be made widely available.

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[5] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001. http://www.europarl.europa.eu/register/pdf/r1049_en.pdf. Accessed September 30, 2013.

[6] Official Journal of the European Communities. Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001. http://www.europarl.europa.eu/register/pdf/r1049_en.pdf. Accessed September 30, 2013.

[7] European Medicines Agency. Publication and access to clinical-trial data POLICY/0070. June 24, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf. Accessed September 30, 2013.

Under rare circumstances, it is possible that a novel, previously undisclosed method used to established safety and efficacy during human clinical testing might be of some value to competitors. Examples offered during the EMA's recent workshop series included:[8]

- Methods to pursue newly validated/devised endpoints that are persuasive to regulators: e.g., the suite of validated measurements for assessing the effects of migraine on the whole body in support of the approval of a drug
- A novel trial design, streamlining and making more economical the proof of efficacy for a novel compound
- A new assay methodology for biomarkers
- A new validation methodology for a Patient Reported Outcome

We recognize that some of these methods may qualify as "commercial interests" under Regulation 1049/2001. However, to the extent that these methods are submitted to justify a regulatory submission, there is an overriding public health interest in disclosure, both so that the data and rationale underlying the regulatory decision can be independently evaluated and so members of the medical community can understand the evidence supporting safety and efficacy and use the product appropriately.

The identities of clinical trials investigators who "recruit well" may also be financially valuable, especially for rare diseases or difficult patient populations.[9] Again, the public health interest in understanding potential conflicts of interest and bias outweighs the potential commercial interest.

We also recognize that disclosing results from clinical trials, including patient-level data, may help to identify previously undisclosed safety or efficacy concerns, thereby harming pharmaceutical sales, a "commercial interest." Yet we do not consider the company's interest in preventing the discovery of safety and efficacy information in order to promote sales to be a "legitimate commercial interest," or the type of interest meant to be protected under Regulation 1049/2001.

Likewise, we fail to see a legitimate interest in maintaining a cloak of secrecy around withdrawn or denied applications. While some have argued that disclosing such data would "undermine the future commercial viability" of the withdrawn or denied product, we believe additional scrutiny for such products is appropriate.[10] If anything, it is especially important for the EMA to publish data from withdrawn or denied applications, as in many cases

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[8] European Medicines Agency. Advice to the European Medicines Agency on rules of engagement for accessing clinical trial data. April 4, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142859.pdf. Accessed September 27, 2013.

[9] *Ibid.*

[10] European Medicines Agency. Comments on Policy 0070 submitted by the European Federation of Pharmaceutical Industries and Associations. September 5, 2013. http://www.efpia.eu/uploads/EFPIA_comments_on_EMA_draft_policy_access_to_CT_data_FINAL.pdf. Accessed September 20, 2013.

the withdrawal or denial implicates a safety risk that should be fully considered upon re-submission.

The mere fact that information from clinical trials may be frequently requested by competitors is not sufficient to conclude that disclosure will undermine a legitimate commercial interest. Competitors are strongly motivated to uncover and disclose potential health risks. Blocking such disclosure – regardless of whether the disclosure is financially motivated – is not a legitimate commercial interest.

Moreover, we respectfully disagree with the suggestion, made in recent comments on this policy, that the mere fact that a clinical report is voluminous, or contains the "intellectual analysis and know-how" of sponsors, indicates that disclosure would undermine a legitimate commercial interest.[11] Having reviewed tens of thousands of pages of regulatory submissions for FDA new drug approval in the course of our 40 years of research, we can assert that although this information is highly technical in nature, its form is non-innovative and its substance is of limited commercial value except to the extent that it provides valuable public health information on the safety and efficacy profile of a lucrative commercial product.

Participants at the EMA's recent workshop series raised the concern that clinical-trial data may be used inappropriately to circumvent existing regulatory data protection rules or take advantage of the absence of such rules in other countries.[12] (For example, workshop participants asserted that data exclusivity in Australia, China, and Mexico is undermined by publication of the relevant data elsewhere in the world.)[13]

We believe that such concerns are adequately addressed by the policy. First, the EMA has required data requesters to agree not to use patient-level data to gain marketing authorisation outside the EU, or share such raw data with other individuals who have not agreed to the same terms. Second, summaries of the main findings supporting a product's safety and efficacy are already made available upon request under policy 0040, and are generally also made public in many ways, including through medical review documents published on the website of the U.S. Food and Drug Administration. [14] We fail to see how the post-hoc analysis enabled through disclosure of patient-level data would provide additional value in obtaining regulatory approval. Third, even assuming that data exclusivity in Australia, China, and Mexico can be undermined with EMA data (which

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[11] *Ibid.*

[12] Advice to the European Medicines Agency on rules of engagement for accessing clinical trial data. April 4, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142859.pdf. Accessed September 30, 2013.

[13] *Ibid.*

[14] Summaries of the methodology and results of clinical trials supporting safety and efficacy are published by the FDA following a product approval. These summaries, provided in a "medical review," are published on the FDA's website. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed September 30, 2013.

has not been established), we think the number of foreign markets that would be so affected is small (most countries either lack a premarket approval system or have data exclusivity provisions that would not be affected by the publication of EMA data). Any commercial interest in bolstering data exclusivity protection among a subset of foreign markets is outweighed by the public health interest in ensuring transparency of clinical trial results.

Finally, critics of draft policy 0070 have suggested that the policy will harm the public health by undermining incentives to innovate.[15] Ensuring investment into future biomedical research is an important public health aim. Yet investment by the pharmaceutical industry is already amply protected by an aggressive system of intellectual property rights in place in the United States, Europe, and the world's other most lucrative pharmaceutical markets. Moreover, even assuming pharmaceutical companies could gain a hypothetical benefit from reviewing the clinical trials information submitted by competitors during the regulatory review process, this increased understanding will confer its own public health benefit by making drug development more efficient.

4. Policy 0070 Protects Against Inappropriate Secondary Analysis

As noted in the draft policy itself, the agency cannot guarantee that all secondary data analyses made possible through policy 0070 will be conducted and reported to the highest possible scientific standard (lines 58-59). The policy will appropriately encourage good analysis practice by making available a document communicating the agency's views on the subject, requiring publication of results within a reasonable period, and providing an opportunity for requesters to upload a statistical analysis plan, which will be made publicly available. Requesters are also required to report their identities and provide a detailed and exhaustive list of goals for accessing the data. We think all of these requirements serve the interest of transparency and provide appropriate safeguards against misuse.

Critics have claimed that the risk of misinterpretation and misuses of clinical data will "undermine the trust" in the regulatory approval system.[16] We disagree. The current lack of transparency regarding clinical-trial data itself has engendered mistrust in the regulatory approval system. Transparency is the best mechanism for restoring that trust and ensuing reliability within the regulatory system. We note that data originators are also capable of misusing data to mislead the public, and agree with EMA officials that "in an open society, trial sponsors and regulators do not have a monopoly on analysing and assessing drug trial results."[17] Moreover, well-established mechanisms for peer review and further independent validation will help to ensure that only analyses based on high scientific

[15] European Medicines Agency. Comments on Policy 0070 submitted by the European Federation of Pharmaceutical Industries and Associations. September 5, 2013. http://www.efpia.eu/uploads/EFPIA_comments_on_EMA_draft_policy_access_to_CT_data_FINAL.pdf. Accessed September 30, 2013.

[16] *Ibid.*

[17] Eichler H-G, Abadie E, Breckenridge A, Leufkens H, Rasi G (2012) Open clinical trial data for all? A view from regulators. *PLoS Med* 9(4): e1001202.

standards gain widespread acceptance within the medical community. Open access to the underlying data sets will further facilitate this process of peer review.

The agency has appropriately declined to insert itself as judge of data requesters' professional competence or plan for statistical analysis. Such a role would be logistically challenging, resource intensive, and unnecessarily restrictive of access to data. We do not believe, as some have argued, that requests for re-analysis of clinical-trials data should be subject to the same level of "proportionate review" [18] to avoid a "double standard"[19] between the original data sponsor and subsequent requesting parties. This is because the potential consequences of granting the data request are much less severe than the consequences of granting a market authorisation: An inappropriate market authorisation exposes millions of patients to a potentially harmful medical product. A poorly conducted re-analysis results in a poor quality paper that will be read and assessed on its merits by the scientific community and subject to academic debate. Though bad analysis should still be avoided, we think the safeguards recommended by the EMA take the right approach by encouraging high-quality analysis. We do not believe the public would benefit if the EMA were to restrict scientific debate by imposing a pre-approval requirement on requests for data.

5. Informed Consent

Policy 0070 requires data requesters to agree that analysis will be conducted "in the interest of public health, in line with the spirit of informed consent (line 183)." We agree that requesters should be required to declare their goals in requesting data and that these goals should be in the interest of public health. Such a requirement is appropriate in that it furthers the public health objective of the policy and helps to ensure transparency. We think this requirement will be easily satisfied by requesters seeking to engage in the type of research envisioned under the policy.

However, we believe it is unnecessary and misleading to suggest that informed consent may be satisfied "in spirit." Informed consent must always be obtained prospectively, and it is generally not possible to obtain informed consent for post-hoc data re-analysis, as such analysis is designed and implemented after the research subjects have already agreed to and completed participation in the trial. In the U.S., informed consent is not required for research that involves only de-identified data sets, as such

[18] European Medicines Agency. Comments on Policy 0070 submitted by the EFPIA. September 5, 2013. http://www.efpia.eu/uploads/EFPIA_comments_on_EMA_draft_policy_access_to_CT_data_FINAL.pdf. Accessed September 30, 2013.

[19] Advice to the European Medicines Agency on rules of engagement for accessing clinical trial data. April 4, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142859.pdf. Accessed September 30, 2013.

research is not considered "human subjects" research.[20] Under this approach, informed consent is not required. Yet the draft policy suggests that informed consent is required even for de-identified data and that this requirement could be satisfied by requests made in line with the "spirit" of informed consent. We do not think this is the correct approach to informed consent and believe that the phrase should be eliminated to avoid confusion.

6. *Policy 0070 Should Not Restrict Access to Requesters "Established in the EU"*

The proposed policy 0070 currently requires that requesters of patient-level data be "established in the EU" (line 180).[21] We request that this requirement be eliminated, as we believe it to hinder the public health objectives of the policy. Highly qualified researchers exist in the U.S., Canada, Japan, Australia, and other countries, and EU members are therefore likely to benefit from research conducted and published in foreign states. Foreign researchers are no more likely to violate patient privacy than researchers established in the EU. Moreover, it is unfair to restrict access to data to foreign populations when data supporting EU market authorization is often obtained through trials conducted outside of Europe.

In addition, researchers based in the EU may wish to work in collaborative teams with foreign researchers, and it is not clear that such collaboration would be possible if all members of the team would be required to "individually commit themselves to the conditions for access," as required by the draft policy (lines 196-197).

We therefore ask to eliminate the requirement that requesters be "established in the EU."

III. Conclusion

We support policy 0070 because it will enable independent re-analysis of the benefits and risks of EMA-approved drugs through the publication of full clinical trial reports and, where appropriate, patient-level data. Transparency and the opportunity for independent review are cornerstones of both sound medical research and good regulatory decision-making in a democratic society. We believe that draft policy 0070 will benefit the public health by promoting greater transparency while adequately protecting important privacy and commercial interests.

Our chief suggestion is that the policy be modified to remove the requirement that requesters of patient-level data be based in Europe. This requirement does not serve an important public health purpose and will unnecessarily restrict access to clinical-trial data.

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[20] OHRP – Guidance on research involving coded private information or biological specimens. October 16, 2008. http://www.hhs.gov/ohrp/policy/cdebiol.html. Accessed September 30, 2013.

[21] European Medicines Agency. Publication and access to clinical-trial data POLICY/0070. June 24, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf. Accessed September 30, 2013.

IV. Specific Comments on Text

Line number(s) *(e.g. 20-23)*	Comment	Proposed changes, if any *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
138-218	The current language fails to make clear which types of de-identified patient data will be made available open access (Category 2), and which will require a data sharing agreement (Category 3). We think the policy should clarify to require a data sharing agreement in cases where such an agreement is necessary to prevent re-identification.	One way to make this section clearer would be to define what it means for data to be "adequately de-identified" under Category 2 (line 143), and how this differs from "appropriate de-identification" under Category 3 (lines 165-175).
174-175	There appears to be a typo in this sentence.	The methods of de-identification should be such that adherence will preclude subject rd~~d~~e-identification, even when applying linkages with other data carriers (e.g. social media).
180, 196-197	The current language inappropriately restricts access to requesters "established in the EU." We suggest that this provision be eliminated. If it is not eliminated, we recommend that the EMA craft language clarifying that an EU requester may share the data with other members of a research team even if all members of the team cannot individually commit to the requirement of being "established in the EU."	• requester has identified themselves, and the Agency has verified the identity of the requester; ~~• requester, whether a natural or legal person, is established in the EU;~~ • requester has agreed, by way of legally binding data-sharing agreement, to:
182-187	We support requiring data requesters to agree to access the data for a purpose of addressing a question or conducting analyses that are in the interest of public health. However, we disagree that language should be included suggesting	access controlled data for the sole purpose of addressing a question or conducting analyses that are in the interest of public health~~, in line with the~~

Line number(s) *(e.g. 20-23)*	Comment	Proposed changes, if any *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	that requirements of informed consent may be met by taking actions "in line with the spirit of informed consent." We propose removing this language.	~~spirit of informed consent~~; this may include, inter-alia, meta-analyses, re-analysis, or exploratory analyses for additional hypothesis generation. An exhaustive and detailed list of the aims of accessing the data shall be submitted at the time of the request (though not necessarily a statistical analysis plan; see below),

Please add more rows if needed.