Plasma Protein Therapeutics Association

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National Institute of Health
National Library of Medicine
6705 Rockledge Drive, Suite 301
Bethesda, MD 20892

SUBJECT: Public Meeting on Expansion of the Clinical Trial Registry and Results Data Bank [Docket No. NIH-2009-0002]

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) is pleased to provide these comments on National Institutes of Health (NIH) Public Meeting on Expansion of the Clinical Trial Registry and Results Data Bank [hereinafter, "Public Meeting"]. PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies. Our members provide 60 percent of the world's needs for Source Plasma and protein therapies. These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a complex of diseases in persons with immune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency which typically manifests as adult onset emphysema and substantially limits life expectancy, and albumin which is used in emergency room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed life-sustaining therapies.

PPTA understands that NIH held this meeting to meet the requirements delineated in the Food Drug Administration Amendments Act of 2007 (FDAAA). Section 801 of FDAAA requires the development of regulations that would expand the clinical trial registry and results data bank, ClinicalTrials.gov. PPTA appreciates the opportunity to participate in the proposed rulemaking process and has provided comments to the topics delineated in the *Federal Register Notice Vol. 74, No.54, March 23, 2009* below.

Topic 1: Whether to require submission of results information for applicable clinical trials of drugs, biological products, and devices that are not approved under sections 505, 515, or 520 m of the FDC Act, licensed under section 351 of the PHS Act, or cleared under section 510 (k) of the FDC Act.

PPTA supports maintaining the current requirements whereby results posting for unapproved products in development and for which an initial approval is being sought may be delayed 30 days after a positive decision for a marketing application. PPTA has concerns that the reporting for unapproved products could become burdensome. If the disclosure of results for such studies is ultimately required, NIH should carefully consider

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the criteria for determining which studies are affected as well as the implications of the timing and format requirements imposed upon such postings.

If NIH requires disclosure of trial results for other unapproved products in certain cases, e.g. where development has been stopped or approval is no longer being sought, PPTA recommends that a simplified mechanism for providing such results be implemented as an alternative to the current complex data entry model. The results summary format set forth in the *ICH E3 Guideline: Structure and Content of Clinical Study Reports* could readily be used for this purpose as an uploadable PDF document. Use of the *ICH E3* summary format would help to ease the burden on data submitters while still providing important information to patients and health care providers in a format that is familiar to those involved with clinical trials.

Topic 2: Whether narrative summaries of the clinical trial and its results can be included in the data bank without being misleading or promotional.

Narrative summaries should be provided with the "basic results" tables in order to provide context to the data shown. The *ICH E3* summary could serve as the format for the technical summary. PPTA is concerned that the inclusion of such a results summary on ClinicalTrials.gov could be considered prior publication by medical journals. This may prohibit publication of the study in a peer-reviewed journal. In such cases, NIH should permit the sponsor to delay posting the summary, if requested by the editors of the targeted journal.

Topic 3: What additional information, if any, that is written in nontechnical, understandable language for patients should be required to be submitted to the data bank to assist patients in understanding and interpreting the information available in the data bank.

The value of non-technical summaries of individual clinical studies to patients and the general public should be carefully weighed against the resources required of sponsors to create them. PPTA encourages NIH to work with experts and focus groups to address the issue of whether it is feasible to provide information to a patient audience in a manner that is not misleading or promotional before reaching a decision on whether to require such summaries on ClinicalTrials.gov. It may be more appropriate to provide nontechnical summaries for products that are approved by FDA.

Topic 4: Whether to require submission of the full clinical trial protocol or only such information on the protocol as may be necessary to help evaluate the results of the trial.

PPTA does not support the public release of the full study protocol. The summary information currently provided to ClinicalTrials.gov captures the most important information about the trial. This information is sufficient to allow patients and health care providers the ability to assess the study objectives and outcome measures appropriately.

Topic 5: Procedures the agency might consider for quality control, with respect to completeness and content of clinical trial information, to help ensure that data elements are not false or misleading and are nonpromotional.

PPTA does not have any comments on this topic at this time.

Topic 6: Whether the 1-year period for submission of basic results information should be increased to a period not to exceed 18 months.

PPTA strongly recommends that the time period for results posting be based on the study *overall completion date* rather than the *primary completion date*, as currently specified in the FDAAA. The 1-year period for submission of results of approved products is sufficient for posting results from the time of *overall study completion,* i.e. the date of the last study procedure performed on the last subject enrolled. This time period is consistent with European requirements for reporting the results of clinical studies.

If results posting remains tied to the *primary completion date*, i.e. the date of the last primary outcome measure, PPTA supports an increase in the time period from 12 to 18 months. Such an increase may alleviate some of the problems experienced with studies where data continue to be collected for secondary outcomes after the last measure of the primary outcome is made. An 18-month period would also provide sponsors more time to publish study results in a peer-reviewed journal prior to publication in the Clinical Trials.gov database.

Topic 7: Whether the clinical trial information required by the regulation should be required to be submitted for applicable clinical trials for which "basic results" information is submitted before the effective date of the regulation.

Any retrospective posting of information eventually included under the "expanded results" requirements should be voluntary. Records for which an expanded results posting is not required under FDAAA should be clearly labeled as such on the ClinicalTrials.gov "Results" page.

Topic 8: The appropriate timing and requirements for updates of clinical trial information Timing and Tracking of Record Updates.

Six months is a reasonable time frame for regular review of records for active studies. Updates to the record within 30 days of any change in the *overall recruitment status* and completion of the study are also reasonable. It is not feasible to continuously update the recruitment status for *individual study sites*, especially in large multi-center studies, especially for those sponsor that have no automated means to transfer this information to ClinicalTrials.gov.

Topic 9: The standard format for the submission of clinical trial information required by regulation, including adverse event information, and additions or modifications to

the manner of reporting of the data elements established under the basic results reporting provisions of the FDAAA.

PPTA recommends that the *ICH E3 Guideline: Structure and Content of Clinical Study Reports* summary format be used as the technical summary for applicable clinical trials of approved products. This format should also be adopted as the primary presentation of results for certain unapproved products (if ultimately required) and for voluntary results submissions (e.g. for any study that is not an "applicable clinical trial"). Providing study results in the existing ClinicalTrials.gov format is a time intensive endeavor. Use of the *ICH E3* format would increase the likelihood that results are submitted for studies registered on ClinicalTrials.gov voluntarily, since this document is generally already created as part of the standard clinical study report.

If the *ICH E3* format is adopted, it should be possible to upload the document as a PDF file rather than being required to manually re-enter the information into ClinicalTrials.gov data fields.

Topic 10: A statement to accompany the entry for applicable clinical trial when the primary and secondary outcome measures for such clinical trial are submitted as a "voluntary submission" after the date specified in the FDAAA for submission of such information.

According to information presented by Dr. Zarin at the April 20 Public Meeting, approximately one-third of studies registered on ClinicalTrials.gov are "applicable clinical trials." Therefore, the disclosure of results is not required under FDAAA for the majority of studies registered on the site. For those sponsors providing results on a voluntary basis with respect to FDAAA, a clear distinction between voluntary and required submissions would be beneficial and should be apparent on the "Results" page associated with the record.

The ClinicalTrials.gov "Results" page currently contains only a generic statement with possible reasons for why study results may not yet be posted. Sponsors should be given the possibility to indicate the specific reason why results are not yet posted for a study that has been completed, including whether such a posting would be voluntary under FDAAA.

Topic 11: Other issues associated with Section 801 of the FDAAA that will inform rulemaking.

- **Primary data source for results records**

Differences in statistical calculations between authorities and sponsors may lead to different interpretations of clinical study data during the review of a licensing application. PPTA recommends that the results posting on ClinicalTrials.gov reflect data as analyzed in the sponsor's clinical study report (CSR) and that the field "Overall Limitations and Caveats" be expanded to incorporate a general statement that the results presented on ClinicalTrials.gov reflect the data as evaluated by the sponsor and may deviate from information provided in the product labeling. Due to the timing requirements for posting study results of products for which approval is being sought (i.e., within 30 days of approval decision), many results

records will have to be prepared based on the content of the CSR, well in advance of any review of the data by an authority. The sponsor should not be required to modify a results record within this time period in the case where FDA may propose a different interpretation/analysis of the data.

- **Mechanism for early review of specific results records with delayed publishing**

We recommend that ClinicalTrials.gov implement a mechanism by which sponsors may release results records to ClinicalTrials.gov in order to initiate the ClinicalTrials.gov quality review process, but be given the option to determine the timing of publication of the record once the review has been completed. Such a mechanism should be available for products where an initial approval is being sought and the sponsor is permitted to delay results posting until 30 days after the approval is given.

The ability to delay publication of results records in this situation could encourage sponsors to release study results earlier for ClinicalTrials.gov review, subsequently relieving some of the burden on ClinicalTrials.gov staff for record review. ClinicalTrials.gov currently takes up to 4 weeks to provide an initial review of a results record once it is released. If the results for all clinical studies used to support a licensing application are released to ClinicalTrials.gov only upon the date of product approval, it is unlikely that results for all studies will be posted within the specified 30-day time period.

- **Reporting adverse events**

PPTA recommends replacing the requirement for reporting “Other (Not Including Serious) Adverse Events," with "All Adverse Events" (both serious and non-serious). The reporting of "Other (Not Including Serious) Adverse Events" is not consistent with harmonized worldwide regulatory reporting (e.g. *ICH Guideline E3*) as it pertains to the summarization of adverse event data. The reporting of “All Adverse Events” (both serious and non-serious) is consistent with this guideline.

If you have any questions, please contact me at the Association.

Respectfully submitted,

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Plasma Protein Therapeutics Association