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National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892

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

Introduction

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO thanks the National Institutes of Health (NIH) for the opportunity to offer these comments as NIH develops regulations to expand ClinicalTrials.gov in accordance with Title VIII of the Food and Drug Administration Amendments Act (FDAAA). We welcome the opportunity to provide testimony at this meeting, and in addition to our comments today BIO will submit written comments containing more detailed responses to the 11 specific questions posed by NIH in its March 23, 2009 *Federal Register* notice for this meeting.

As part of our preparation for this public meeting, BIO conducted a questionnaire on member company experiences with ClinicalTrials.gov as well as policies and procedures regarding trial registration and results posting. 59 pharmaceutical and biotechnology company members replied, representing both small and large companies. Some of these results will be presented today and more will be included in our additional written comments.

BIO appreciates the National Library of Medicine's (NLM's) work toward and commitment to improving the transparency of clinical trials through the ClinicalTrials.gov website. We recognize the tremendous amount of effort required to implement Title VIII of FDAAA.

We would like to make the following points.

1) BIO and its member companies are committed to helping assure that patients and healthcare providers have access to key clinical trial results information. It is critical that information subject to dissemination meet established scientific standards and that ClinicalTrials.gov requirements do not restrain our member companies' ability to conduct research into new treatments that will help patients in the future.
2) BIO recommends the "ICH E3 summary" (described below) to serve as the format for posting results of unapproved products and for the technical summary.
3) BIO believes that the question of whether clinical trial information can be presented in a manner that would not be misleading or promotional should be based on research that determines what information is understandable to each of two distinct audiences – non-technical (patients) and technical (clinicians and researchers).

BIO members are committed to helping assure that patients and healthcare providers have access to key clinical trial results information.

BIO supports efforts to increase the availability of accurate, scientific evidence to inform clinical decision-making. We believe that individual patients, clinical decision makers and scientific researchers should be armed with the best available information to help assess the relative clinical benefits and risks of various treatment alternatives.

FDAAA provides that the Secretary shall, by regulation, expand the registry and results data bank by September 2010 to "provide more complete results information and to enhance patient access to and understanding of the results of clinical trials". We support this goal and believe that disseminating certain additional trial result information may reduce duplicative studies which divert industry resources that could be used to undertake innovative research, and could also alleviate pressures on the Food and Drug Administration's (FDA's) review resources.

Established scientific standards must be met for clinical trial results information that is to be submitted for public disclosure, and critical research must not be restrained.

It is critical to ensure that data provided on ClinicalTrials.gov, which will be interpreted outside of FDA's expert review process, is information that has scientific merit and can enhance the treatment and safety of patients. Therefore, in response to the question posed by NIH regarding whether submission of results information for applicable clinical trials of unapproved products should be included in ClinicalTrials.gov, BIO makes two recommendations.

First, we recommend that results from pivotal confirmatory clinical trials be submitted once a product has been discontinued in development for all indications, when such trials were terminated due to safety reasons. Posting results only from *pivotal confirmatory* clinical trials

will help to assure that the information provided has scientific merit that can augment the clinical decision-making process. Posting results from those pivotal confirmatory trials *terminated for safety reasons* ensures that information pertinent to protecting patient safety – which is our paramount concern when conducting clinical trials – is disseminated through ClinicalTrials.gov (although it is important to note that when a trial is 'terminated due to safety results' that does not necessarily mean the tested compound is "unsafe" but rather that the safety results were not satisfactory in a particular trial).

Second, we recommend if any requirements for more expansive dissemination of results – i.e. beyond BIO's recommendation – are to be considered, the Secretary should a) conduct a study to evaluate the utility of different types of results information for stakeholders, and b) develop and implement a process (for example a process involving review by an FDA expert panel) that ensures only results that have clear and significant utility for stakeholders are released.

We recommend these steps because there are some circumstances where wide dissemination of clinical trial results relating to unapproved products may restrain our member companies' ability to conduct research into new treatments that will help patients in the future, for example, by releasing information that undermines a company's competitive position and ability to raise capital to fund its research. Therefore, it is important that any new requirements for dissemination be very carefully considered.

It is important to note that FDAAA grants statutory authority to the Secretary of HHS to require any sponsor to post clinical trial results "deemed necessary to protect the public health". We believe that this statutory authority, in addition to regulatory requirements consistent with our two recommendations above, and existing requirements to report safety information to FDA and to Institutional Review Boards, will serve to protect patients as well as provide ample access to relevant clinical trial results.

Finally, FDAAA provides that if initial approval of a product is being sought then a sponsor may delay submission of results to the data bank until 30 days after approval. We note that it will be important for regulations to clarify when approval of a product is no longer being "sought", which we interpret to mean when a product has been "discontinued in development". BIO has developed recommendations regarding the definition of "discontinued in development", and will provide these recommendations in our additional written comments. It is important that there is clarity as to when a product would be so classified, to provide companies the ability to evaluate proprietary research and development or business strategies that may be impacted by a public disclosure requirement. Clarity on this point is critical to ensuring that any new regulatory process regarding clinical trial data for unapproved products does not restrain important research on innovative treatments.

Requirements For Posting Data Must Be Reasonable And Efficient

Requirements for publicly posting clinical trial results of unapproved products must balance the goal of providing meaningful information for patients, clinical decision makers and scientific researchers and the goal of ensuring that requirements for posting data are reasonable and

efficient. NIH estimates that results reporting will be required for 1,645 trials of drugs and biologics and 375 trials of medical devices each year. Initial submission of results information is estimated to require 10 hours, and each result submission is expected to require two updates that take 5 hours each.

BIO believes this reporting burden has been substantially underestimated. Replies to BIO's questionnaire to members regarding ClinicalTrials.gov showed that depending on the complexity and size of the trial, reporting results for the initial submission averages 17 hours; revisions prior to publishing on the results database averages 7 hours; and revisions subsequent to publishing on the results database averages 14 hours. On average, companies responding to the questionnaire spent 22 hours gathering information per trial prior to submitting to the ClinicalTrials.gov database and obtained the first set of comments from NLM staff in 5 weeks. Furthermore NIH time estimates do not take into account the time-consuming data entry process and the hours spent as a company new to ClinicalTrials.gov learns how to navigate the site. Thus the range of time for posting results of approved products is far more than the 10-20 hours NIH anticipated.

The majority of BIO's members are small companies with fewer than 50 employees. The average small biotechnology company has no product on the market and 5 products in the research and development stage, meaning it has little experience with ClinicalTrials.gov. BIO urges NIH to carefully balance the value of the information against the burden of collecting it, and ensure any new requirements for expansion of the public database are not overly burdensome to small, minimally staffed, biotechnology companies.

Format of Data

BIO recommends that the *ICH Guideline E3: Structure and Content of Clinical Study Reports* summary format ("ICH E3 summary") serve as the format for posting results of unapproved products and for the technical summary.

The ICH E3 format is the internationally accepted standard for reporting clinical research findings to regulatory authorities. Results are already reported in this format on ClinicalStudyResults.org and will be used for reporting pediatric clinical trial results in Europe when the European Medicines Agency (EMEA) implements its requirements for results posting.

Narrative Summaries

FDAAA states that the expanded registry and results data bank should include summaries of clinical trials and their results *if* this can be accomplished without such information being misleading or promotional. The Secretary is charged with addressing first, whether it would be feasible for a summary to be written in language that is non-technical and understandable for patients without being misleading or promotional, and second, whether it would be feasible for a summary to be written that is technical in nature, without being misleading or promotional. If these questions of feasibility are answered in the affirmative, then the Secretary shall require such summaries by regulation.

Therefore, BIO's comments will focus on the feasibility of these narratives rather than the potential advantages and disadvantages of such summaries to the interested parties, as this determination by the Secretary is what can then trigger a regulatory requirement that summaries of clinical trials and results be submitted for inclusion in the databank.

BIO believes that the question of whether clinical trial information can be presented in a manner that would not be misleading or promotional should be based on research that determines what information is understandable to each of the two distinct audiences – non-technical (patients) and technical (clinicians and researchers). This assessment is clearly more challenging for the non-technical category, where scientific information would need to be translated into patient-friendly language, because consumer or patient-friendly language is by nature less precise than scientific language, and therefore has the potential to be misleading.

BIO encourages NIH to work with experts and focus groups to address the issue of whether it is feasible to provide information – particularly to a patient audience – in a manner that is not misleading or promotional. FDAAA directs NIH to consult with experts in risk communication for the purpose of providing additional information on the data bank website to help ensure that the registry and results information will not mislead patients or the public. Such risk communication experts would be beneficial for the task at hand as well – to help evaluate the ability of patients and consumers to comprehend information that could be presented in non-technical narrative summaries.

BIO also encourages NIH to work with FDA, which has significant expertise in guiding the preparation and evaluation of labeling that is intended for consumers. FDA's experience includes the development of medication guides ("MedGuides") and patient package inserts (PPIs) for prescription drugs, as well as direct-to-consumer (DTC) advertising for prescription drugs, and labeling for over-the-counter (OTC) drugs, including the "Drug Facts" format. BIO believes that the expertise and methods for evaluating consumer comprehension that have been employed by FDA would be extremely valuable in assessing patient comprehension of non-technical summaries of clinical trial results. The goal would be to determine whether the presentation of such information would be inherently misleading and/or promotional, or whether certain formats could be used to avoid those risks.

As discussed earlier, BIO also recommends that the ICH E3 summary serve as the format for the technical summary. While NIH may wish to confirm through use of experts/focus groups that this vehicle would not be misleading or promotional, the relevant scientific community would already be accustomed to this format for presentation of data. Further, to meet other FDAAA requirements, such summaries would be searchable.

We note that both of the terms "misleading" and "promotional" involve some degree of subjectivity. Therefore, it would be useful to involve an objective third party in review of results information prior to posting on the website, to confirm that the information is not misleading or promotional.

While the term ”misleading” is a regulatory term used in the Federal Food, Drug, and Cosmetic Act (FFDCA) and FDA regulations, we do not know of precedent for evaluating whether a summary of a clinical trial would be misleading to clinical decision makers, scientific researchers or patients. The term “promotional” is not used in the FFDCA, but it is incorporated into FDA’s investigational drug regulations, which state that a sponsor of an investigational drug may not state in a promotional context that an investigational drug or biologic is safe or effective for the use for which it is being investigated or otherwise promote the drug.

Significantly, any information disseminated by the manufacturer regarding an investigational product can potentially be considered promotional, and/or misleading, a violation of the FFDCA, FDA’s regulations, and these specific FDAAA provisions as well. This risk highlights the need for objective third party review to assure that information posted on the ClinicalTrials.gov website is not misleading or promotional. Such review would serve the public health interest and also protect the interests of sponsors who submit this information in good faith.

BIO believes that review of information to be posted on ClinicalTrials.gov could appropriately be conducted by FDA, following approval of a product, as the submission would be required to be submitted within 30 days of product approval. FDA review staff would be familiar with the data, and would have worked with the sponsor on labeling, including any patient-directed labeling, enabling efficient review and assessment of a study narrative.

BIO also recommends that information be included on the ClinicalTrials.gov website to help patients understand how to best use the website, the nature of information regarding clinical investigations, and the limitations of such information. The risk communication experts referred to in FDAAA could provide useful expertise here as well.

Conclusion

BIO believes that our recommendations will help NIH achieve the goals of FDAAA, by enabling the disclosure of clinical trial information on unapproved products that is reliable, useful and not harmful to development of new therapies, and by providing such information in a useful format and in a manner that is understandable to the various target audiences.

BIO welcomes the opportunity to work closely with NIH and FDA as they develop regulations to expand ClinicalTrials.gov in accordance with Title VIII of FDAAA.