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June 22, 2009

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

Dear Sir or Madam:

The Biotechnology Industry Organization (BIO) thanks the National Institutes of Health (NIH) for the opportunity to submit comments for the agency to consider as it develops regulations to expand the clinical trial registry and results data bank commonly known as ClinicalTrials.gov in accordance with section 801 (Title VIII) of the Food and Drug Administration Amendments Act of 2007 (FDAAA) [Public Law 110-85].

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

BIO supports the provisions in FDAAA intended to increase the transparency of controlled clinical trials and enhance patient enrollment. Further, BIO strongly supports efforts to increase transparency and the availability of accurate, scientific evidence to inform clinical decision-making. BIO believes that individual patients and their doctors should be armed with the best available information to assess the relative clinical benefits and risks of various treatment alternatives.

ISSUES FOR DISCUSSION

I. Submission of results information for unapproved products.

BIO Members Are Committed to Helping Ensure that Patients and Healthcare Providers Have Access to Key Clinical Trial Results Information

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. However, transparency objectives must be balanced by recognition of feasibility limitations and the need to protect certain highly proprietary study information. Reasonable accommodations should also allow for sufficient time to seek patent protection, as appropriate, before results information is disclosed publicly. Such protections can be critical to preserving resources and incentives for investing in the development of new treatments.

It is critical to ensure that data provided on ClinicalTrials.gov has scientific merit because it will be accessed and interpreted outside of FDA’s expert review process. 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 recommends 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 ensure that the information provided has scientific merit. Posting results from those pivotal confirmatory trials *terminated for safety reasons* ensures that information pertinent to protecting patient safety – our paramount concern when conducting clinical trials – is disseminated through ClinicalTrials.gov.

We are not aware of a formal definition of “pivotal clinical trial”. However that phrase is generally understood to mean a controlled trial to evaluate and confirm the safety and efficacy of a drug in patients who have the disease or condition to be treated. These trials usually represent the most rigorous demonstration of the therapeutic’s efficacy and safety, and are the basis for the new drug application (NDA) or biologics license application (BLA) filing with the FDA.

Drawn from ICH E9, BIO’s definition of “confirmatory clinical trial” is: an adequately controlled trial in which the hypotheses are stated in advance; where the key hypothesis follows directly from the trial’s primary objective, and is the hypothesis that is subsequently tested when the trial is complete. The rationale and design of confirmatory trials nearly always rests on earlier clinical work carried out in a series of exploratory studies (e.g., Phases I and II) in which objectives may not always lead to simple tests of predefined hypotheses.

It is important to note that FDAAA grants statutory authority to the Secretary of Health and Human Services (HHS) to require any sponsor to post clinical trial results “deemed necessary to protect the public health”. Further, 21 CFR § 312.130 requires that the FDA shall disclose upon

request from an individual who has taken an investigational new drug a copy of any investigational new drug application (IND) safety report relating to the use in the individual. We believe that these provisions, in addition to future regulatory requirements that may be established – consistent with our recommendation above – as well as existing requirements to report safety information to FDA and Institutional Review Boards, will protect patients and the public health.

Providing Clarity and Limitations to the “Seeking Approval” Certification Process

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. It will be important for regulations to clarify when approval of a product is no longer being “sought”. BIO interprets this to mean that a product has been “discontinued in development”, and we have developed recommendations regarding the definition of “discontinued in development”, based on FDA’s IND and NDA regulations.

There are provisions currently in place that address public disclosure by FDA of information included in an IND or in an NDA prior to approval. First, 21 CFR § 314.430 (d)(1) states that data and information in an application for marketing approval will not be publicly disclosed prior to issuance of an approval letter. However, all safety and effectiveness data and information in an application that has not previously been disclosed are available to the public, upon request, at any time any one of the following occurs unless extraordinary circumstances are shown: 1) no work is being or will be undertaken to have the application approved; 2) a final determination is made that the application is not approvable and all legal appeals have been exhausted; 3) approval of the application is withdrawn and all legal appeals have been exhausted; and 4) a final determination has been made that the drug is not a new drug. Second, 21 CFR § 314.430(f), provides that FDA can terminate an IND that has remained on inactive status for 5 years or more.

In consideration of the activities and efforts reflected in these existing regulations, BIO recommends that the following actions taken by the sponsor of an application or by the FDA would render a product “discontinued in development”: 1) a sponsor announces publicly that the development of a product has been discontinued for all potential indications; 2) INDs for studies in all potential indications have remained on inactive status for 5 years; 3) the sponsor no longer certifies it is seeking approval; or 4) the sponsor discontinues a drug development program due to safety concerns identified during one or more trials that were part of the sponsor’s development program.

This policy would provide clarity and establish limitations as to how long a sponsor could continue to certify that it is seeking approval for a product. These recommendations also take into account that sponsors, especially those that are filing with the FDA for the first time, may undergo multiple reviews before their product is approved. In fact, it has been documented that more experienced larger companies have a significantly higher first cycle approval rate than smaller biotechnology companies (86% for large biotechnology companies and 33% for small biotechnology companies). Any rulemaking should seek to assure that small biotechnology companies who are filing for the first time are not at a disadvantage by disclosure of information to the public before a final determination is made by FDA (i.e. after multiple review cycles).

Failure to do so could devalue a small biotechnology's company's only asset, its intellectual property portfolio and drug development data.

Providing clarity as to when a product would be classified as discontinued in development would provide the necessary balance for biotechnology companies' need to be able to plan for public disclosure of information for unapproved products, as that may impact their research and development or fiscal strategies. Again none of these recommendations would prevent the Secretary from requiring results to be posted that are "deemed necessary to protect the public health" – they simply clarify when a sponsor is considered to be seeking approval and which specific actions taken by the FDA or the sponsor would lead to a product being classified as discontinued in development.

Determining if a pivotal confirmatory trial for an 'unapproved' product contains important safety information should be defined by the following actions taken by a sponsor, the FDA or a Data Safety Monitoring Board: 1) the sponsor terminates the study due to safety concerns identified during one or more trials that were part of the sponsor's development program; 2) FDA puts a study on clinical hold due to safety results, and the clinical hold is unresolved; or 3) a Data Safety Monitoring Board terminates a study due to safety results. It is important to note that 'terminated due to safety results' does not necessarily mean a compound is "unsafe" but rather that the safety results were not sufficiently robust or satisfactory in a particular trial to continue development of the drug. However, information from the trial could potentially be instructive to patients, researchers and/or physicians. BIO's recommendations would ensure comprehensive public access to key safety information from clinical trials conducted on products for which development has been discontinued.

Impact on Small Biotechnology Companies: Requirements for Submitting Data Must Be Reasonable and Efficient

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.

Providing clarity on what constitutes "discontinued in development" would afford 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 requirement regarding clinical trial data for unapproved products does not restrain important research on innovative treatments.

Moreover, 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 five products in the research and development stage, meaning it has little experience with ClinicalTrials.gov. Therefore, BIO urges NIH to carefully balance the value of the information against the burden of collecting it, and to ensure that any new requirements for expansion of the public database are

not overly burdensome to small, minimally staffed, biotechnology companies. Accordingly, BIO does not believe that new requirements, enacted as part of the expansion, should apply to clinical trials already reported.

Requirements for submitting clinical trial results of unapproved products must balance the goal of transparency with the goal of ensuring that requirements for submitting 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 distributed a questionnaire and obtained member company responses regarding experiences with ClinicalTrials.gov as well as policies and procedures regarding trial registration and results posting. 52 pharmaceutical and biotechnology company members replied, representing both small and large companies. According to the questionnaire results, BIO is concerned that this reporting burden has been substantially underestimated. Replies 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. Further, 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 BIO believes the range of time for posting results of approved products is far more than the 10-20 hours NIH anticipated.

The Secretary Should Conduct a Study on the Utility and Understandability of Any Information To Be Disclosed If It Is Broader Than BIO's Recommendation

BIO recommends that if any requirements for more expansive submission and dissemination of results – i.e. broader in scope than 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.

II. Technical and Non-Technical 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.

BIO's comments focus on the feasibility of these narratives rather than the potential advantages and disadvantages of such summaries to the interested parties, as a feasibility 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. An evaluation by such experts could also address what format might be useful for communicating results information to a lay audience without being misleading or promotional. That evaluation could in turn inform the regulatory process and enable NIH to establish a model or template for submission of a non-technical summary.

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.

BIO also recommends that the *Guideline E3: Structure and Content of Clinical Study Reports* (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. Additionally, BIO would like to be involved in establishing criteria for whether a third party would meet the objective standard, and what level of training/expertise would be required of these reviewers.

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 since a finding that it is not misleading will provide liability protection.

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.

III. Protocol Information

BIO believes the information required for registration of trials with the NIH including purpose, study design, and eligibility criteria, is sufficient for evaluating the results of the trials. It seems unlikely that submission of the protocol would significantly assist patients or practicing physicians in evaluating the results of a trial or the completeness of the results. In addition, sponsors already make protocols and pre-specified data analysis plans available to journal editors and regulators – the constituencies who are likely to be interested in reviewing such information. Furthermore, when companies submit protocol information to journal editors and regulators, they generally do so under confidentiality agreements to safeguard confidential and proprietary information.

IV. Quality Control

To ensure greater standardization and objective quality assurance review, NIH should develop for public comment frequently asked questions, glossaries of common terms, a central database of standard outcome measures and scales (and possibly interventions when appropriate) and quality evaluation criteria that would help compliance prior to sponsors posting registry and results data. This information would provide consistency in feedback from NIH's quality assurance teams as well objective measures for ensuring data accuracy.

The NLM administrators should develop and publish standard operating procedures similar to FDA's Manuals of Policies and Procedures (MAPPs). Additionally, BIO urges that any substantive change to these procedures be made public at least 30 days prior to implementation.

NLM has recently suggested they will outsource review of clinical trial results to academic medical centers to assist in quality control. We strongly urge that standardized quality evaluation criteria be developed by the agency and properly vetted by stakeholders for public comment, prior to implementing such as process and releasing results to third parties. The academic medical centers would also need appropriate training to ensure consistency and adherence to statutory requirements.

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

BIO believes one year is currently sufficient for submission of basic results. However, in some instances there may be a delay in posting of complete trial information due to the need to seek intellectual-property protection, in the U.S. or other countries, or to comply with confidentiality provisions in agreements with other parties. In such cases, an extension should be granted. Additionally, given that NIH will be addressing the expansion of the results database in forthcoming regulations, it is not known at this time exactly what the burden and timing issues will be in the future. Accordingly, timing issues—such as the need for more than 12 months—may be more appropriate to address in the future, perhaps in response to the proposed rulemaking.

Notwithstanding the above, trial results pertinent to protecting the safety of the public should be made publicly available expeditiously.

BIO urges NIH to develop guidance for public comment on the extension process. Guidance should address when extensions are feasible, including:

- New indication for approved product. There are timeline differences for whether a new indication is pursued as a supplement or a new IND/NDA. In many cases, a two year timeline is difficult to meet (particularly when based on the Primary Completion Date).
- Please clarify that companies can then apply for a "good cause" extension.
- When there is a significant gap in time between the final collection of the primary outcome measures and the actual completion date for the study as a whole (e.g., secondary outcome measures). Please clarify that companies can then apply for and receive a "good cause" extension?

VI. **Format of Data**

The “ICH E3 summary” Should Serve as the Format for Posting Results of Unapproved Products and Voluntary Posting of Results Submissions and for the Technical Summary.

As noted earlier, BIO recommends that the ICH E3 summary serve as the format for posting results of unapproved products, for voluntary posting of results submissions (i.e. for studies that are not “applicable clinical trials” but may require results postings under other regulation due to sponsor company policy and 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 (EMA) implements its requirements for results posting.

We do not believe that NIH should establish additional standards unique to the NIH database, without coordinating with FDA, other regulators, the World Health Organization, biomedical journal editors, and industry.

VII. Reporting Adverse Events

Replace “Other (Not Including Serious) Adverse Events,” with “All Adverse Events” (both serious and non-serious) that exceed a frequency threshold within any arm of the clinical trial.

BIO understands that the NLM proposes that two types of adverse event data are to be reported in www.ClinicalTrials.gov for each clinical trial. The first type, “Serious Adverse Events”, is well defined by the regulatory authorities (e.g. FDA) for biopharmaceutical sponsors and therefore, is appropriate for inclusion in ClinicalTrials.gov. The second type, “Other (Not Including Serious) Adverse Events”, is understood to be adverse events that exceed a frequency threshold within any arm of the clinical trial, grouped by organ system, and presented by the adverse event term (e.g. MedDRA preferred term). Further, when determining the number of affected participants and applying the frequency threshold for a particular event term, participants reporting serious adverse events for that term should be excluded.

BIO recommends replacing “Other (Not Including Serious) Adverse Events,” with “All Adverse Events” (both serious and non-serious) that exceed a frequency threshold within any arm of the clinical trial. BIO also recommends that only “treatment emergent” adverse events be reported.

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. Specifically Section 12.2.2, “Display of Adverse Events,” of the ICH Guideline E3 states:

“All adverse events occurring after initiation of study treatments (including events likely to be related to the underlying disease or likely to represent concomitant illness, unless there is a prior agreement with the regulatory authority to consider specified events as disease related) should be displayed in summary tables (section 14.3.1). The tables should include changes in vital signs and any laboratory changes that were considered serious adverse events or other significant adverse events.”

The “Other (Not Including Serious) Adverse Events” requirement, along with the “Serious Adverse Events” requirement, would not be consistent with ICH E3 principles unless the threshold requirement was eliminated.

Furthermore, no information would be lost by this change. The information in the current "Other AE" presentation can easily be derived from an “All AE” presentation by subtracting the counts in the “SAE” section from the counts in the "All AE" section. As proposed by NLM, in many situations one could derive "All Adverse Events" by adding the counts in the “Serious Adverse Events” section with the counts in the "Other Adverse Events" section. However, the use of thresholds to determine which terms are included leads to differences in the selection of events and thus, it is not always possible to derive “All Adverse Events”. As an example, the table below illustrates that if a 5% threshold is used to determine what events are included in the second type of adverse event data reported, term 2 (e.g. Chest Pain), would be included in the "All AE" definition, but would not be included using the current "Other AE" definition.

Type of AE Data Presentation	Adverse Event Term	Group (N=100) n (%)
SAE	Term 1 (e.g. Bronchitis)	1 (1%)
SAE	Term 2 (e.g. Chest Pain)	2 (2%)
Other (not Including Serious) AEs	Term 1 (e.g. Bronchitis)	5 (5%)*
Other (not Including Serious) AEs	Term 2 (e.g. Chest Pain)	4 (4%)
All AEs (serious and non-serious)	Term 1 (e.g. Bronchitis)	6 (6%)*
All AEs (serious and non-serious)	Term 2 (e.g. Chest Pain)	6 (6%)*

*Indicates that the 5% threshold was met and the term would be included.

To be consistent with the previously offered comment, BIO recommends moving from the current requirement to report the "Total Number Affected by any Other (Not Including Serious) Adverse Event above the Frequency Threshold" to "Total Number Affected by All Adverse Events (serious and non-serious)." The summary row should show only the number of subjects with at least one AE calculated over all adverse events.

Remove the Specified Frequency Threshold for Reporting the Overall Number of Participants Affected by One or More Adverse Events

The current requirement is to only include the number of participants affected by one of the events that meets a defined threshold. The specific requirement is "Overall Number of

Participants Affected by One or More Other (Not Including Serious) Adverse Events above the specified Frequency Threshold (e.g., 5%)” as reported in the table.

BIO recommends reporting the “Overall Number of Participants Affected by Any Adverse Event,” regardless if the events were serious or non-serious. Make the frequency threshold as an option rather than requirement.

For smaller studies we may want to include ‘All Adverse Events’ (serious and non-serious) rather than those which exceed a certain frequency threshold. However, for large studies we would want to use a frequency threshold since eliminating the frequency threshold could result in many pages of adverse events being reported which would not be useful to the lay person. (Note: All serious adverse events would still be reported).

Include a text field, “Adverse Event Reporting Criteria,” in the AE results reporting section of ClinicalTrials.gov

Each study may have unique AE reporting criteria that are driven by study-specific requirements. These reporting criteria may differ for drugs vs. devices, therapeutic area, and study phase (e.g. pivotal phase 3 study vs. post-marketing study).

BIO recommends including a text field, “Adverse Event Reporting Criteria,” to permit a study sponsor to explain the criteria by which AEs were reported for a particular trial. Such a text field should be limited to no more than 500 characters.

The addition of a text element will assist with the interpretation and understanding of the AE data. Providing the context of the study-specific reporting criteria should assist the reader to compare reported adverse events across studies. Respondents to the BIO questionnaire consistently noted that the existing data fields did not provide sufficient opportunity to provide contextual information.

The current requirement is to provide the "number of participants at risk" for each adverse event term reported. BIO recommends a single number be provided for each study arm/group overall for the "number of participants at risk," with an option to provide different values for the "number of participants at risk" for each adverse event term only when applicable.

The “number of participants at risk” is determined at the study arm/group level, and often does not vary across the specific adverse events being reported. For example, the “number of participants at risk” is often taken to be the number of participants who received at least one dose of study drug. If the “number of participants at risk” is reported once, for each study arm/group, and the “number of affected participants” is reported for each adverse event term, the incidence rate for any specific adverse event term can be calculated by taking the “number of affected participants” for that adverse event term and dividing by the “number of participants at risk” in the study arm/group. However, in some cases (such as laboratory or systematic adverse events) the "number of participants at risk" can be lower than the number who received at least

one dose. In such cases, the appropriate "number of participants at risk" can be provided for those specific event types where it differs from the overall "number of participants at risk".

VIII. The appropriate timing and requirements for updates of clinical trial information and procedures for tracking such updates

The schedule of updating clinical trial information at least annually and tracking changes in the databank with an audit trail seems reasonable and appropriate.

IX. A statement to accompany the entry for an 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

NIH should not treat voluntary submissions of early stage research, including Phase I studies, bioequivalence or observational studies, as if they were "required" or refuse to post information if one or more of the "mandatory" data elements is not submitted by the responsible person. Many such voluntary submissions involve very early stage research, including Phase I studies, in which some of the mandatory data elements may be considered highly sensitive, confidential commercial information.

In the interest of transparency, many sponsors wish to provide information about early stage studies, but they are not willing to prematurely disclose confidential information that could put them at a competitive disadvantage and/or threaten the viability of future research. As a result, many companies appear to have made the decision to post information about early stage research on other publicly accessible websites, such as company-sponsored websites or PhRMA's ClinicalStudyResults.org databank, given the inflexibility of ClinicalTrials.gov. This, however, seems contrary to one of the main purposes of ClinicalTrials.gov, which is to provide a comprehensive "one-stop-shop" for clinical trial information. BIO thus requests that NIH specifically permit sponsors to voluntarily submit information about early stage studies in a manner that preserves the confidentiality of sensitive information.

X. Other issues associated with Section 801 of the FDAAA that will inform rulemaking

Operational Issues

NIH should allow for data tables to be uploaded, utilizing existing CDISC standards.

Currently NIH does not provide for the uploading of data tables when posting study results to clinicaltrials.gov. This makes the posting of study results (and the quality assurance review of individually entered study endpoints), difficult, time consuming and inefficient. We strongly recommend that NIH allow for data tables to be uploaded; utilizing existing Clinical Data Interchange Standards, established by CDISC, so that

sponsors can focus resources on the quality of the submissions and minimize the use of limited resources for the reentry of data.

The field ‘Overall Limitations and Caveats’ is limited therefore hindering the ability to explain any negative or noted variances and significant limitations of a trial for any such FDAAA posting.

The field ‘Overall Limitations and Caveats’ is limited to 250 characters in the database resulting in a company being unable to attach a disclaimer to the FDAAA posting, as is currently the case in Maine. Therefore, BIO proposes inserting the following language:

“The Posting is intended to disclose accurate and current information pertaining to Company clinical studies. Company uses its best efforts to conform and comply with content requirements for this posting. However, the status of clinical studies often changes and company makes no warranties or representations of any kind as the currency or completeness of the posting, express or implied, including warranties of merchantability and fitness for a particular purpose. Company shall not be liable for any damages, including without limitation, direct, incidental, consequential, indirect special or punitive damages, arising out of access to, use of, or inability to use information posted by company herein, or any errors or omissions in the content thereof. Nothing in this posting is intended to be medical advice or a claim for any particular approved or unapproved product. Accordingly, access to and/or use of information posted on this website is at the user’s own risk and does not replace researcher clinical decision-making or medical opinion. Patients should consult their health care professional for advice and healthcare professionals, before prescribing, should refer to the full prescribing information approved for each product in their country, as clinical studies may include information not contained in the approved product package insert.”

NIH should offer more “Study Status” options to mark the migration from initial entry of results.

We would like to see a transparency regarding initial reporting of primary results vs. later updates to results to add secondary/tertiary results. It should be apparent to all users when results are first reported and if there is a subsequent update to the results reporting screens to add more recent data. This is particularly necessary with trials running over a period of many years as new data endpoints are reached.

One way to do this is for NIH to offer more "Study Status" options to mark the migration from initial entry of results, whether this is the complete story, or when additional results are anticipated. The results screen should clearly mark additions over time.

NIH should include a standard disclaimer to the database entry screen or to each results record, in order to discourage patients from making their own medical decisions based on results postings of a single study.

BIO offers two examples below:

GENERAL DATABASE DISCLAIMER: “Patients should not adjust or discontinue medications based on this information. Contact your doctor if you have questions about how this information relates to your treatment.”

RECORD SPECIFIC DISCLAIMER: “The contents of results postings should not be construed as medical advice, and should not be relied upon as the basis for any decision or action. You should rely only on your health care professional for advice on your specific situation. Health care professionals seeking information about approved uses for this product should refer to the current approved labeling for this product in their country.

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.

If you have any questions, please do not hesitate to contact me at 202-962-6677 or Katie McCarthy, BIO’s Director of Science and Regulatory Affairs, at 202-962-6647.

Sincerely,

/s/

John Taylor
Executive Vice President, Health
BIO