BIOTECHNOLOGY INDUSTRY ORGANIZATION

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2009-N-0247, Food and Drug Administration Transparency Task Force, Public Meeting

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the FDA's Transparency Task Force. BIO applauds the FDA for convening this Task Force. Clear, consistent and open communication with the public and regulated industry, conducted in a manner that balances the importance of protecting competitive commercial information, is a critical FDA function and essential for protecting and promoting the public health. BIO's previous comments to the Task Force offer recommendations to enhance transparency in FDA processes for communicating with the general public and interacting with regulated industry.[1]

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.

[1] Biotechnology Industry Organization (BIO), *Comments to the FDA Transparency Task Force*, August 5, 2009, http://bio.org/reg/20090805.pdf

I. Product Applications That Are Abandoned or Withdrawn By the Applicant Before Approval

Regarding *Topic B: Product Applications That Are Abandoned (Which Means That No Work is Being Done or Will Be Undertaken to Have the Application Approved) or Withdrawn By the Applicant Before Approval*, BIO strongly supports efforts to increase transparency and the availability of accurate, scientific evidence to inform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.

However, we are concerned that this issue is being discussed in two separate regulatory tracks which may lead to confusion and lack of coordination. The Food and Drug Administration Amendments Act of 2007 (FDAAA) Title VIII instructs the Secretary of the Department of Health and Human Services (DHHS) to promulgate regulations to expand the federal registry and results data bank by September 27, 2010. FDA and the National Institutes of Health (NIH) have been seeking public comment on how best to implement these provisions in FDAAA, and specifically on whether submission of results information for applicable clinical trials of unapproved products should be included in ClinicalTrials.gov. BIO testified at the Public Meeting on Expansion of the Clinical Trial Registry and Results Data Bank on April 20 and submitted written comments containing more detailed responses to the 11 specific questions posed by NIH in its March 23, 2009 *Federal Register* notice.[2, 3] Before adopting any additional changes to FDA's data protection policies, we encourage FDA to continue to participate in the clinical trial results databank rulemaking process and determine if the expansion of ClinicalTrials.gov achieves the level of transparency envisioned by the Task Force.

If FDA does consider disclosing additional application data for unapproved products, we believe there are several principles and considerations that the agency should apply. As stated in our comments to NIH, BIO supports the goal of FDAAA Title VIII to "provide more complete results information to enhance patient access to and understanding of the results of clinical trials." 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 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.

If this information were to be publically disclosed it would be critical to ensure that data provided has scientific merit because it would be accessed and interpreted outside of FDA's expert review process. In response to FDA (Docket No. FDA-2009-N-0247) and NIH (Docket

[2] BIO, *Comments to NIH on Expansion of the Clinical Trial Registry and Results Data Bank*, April 13, 2009, http://bio.org/healthcare/BIO_Comments_NIH_2009_0002.pdf

[3] BIO, *Comments to NIH on Expansion of the Clinical Trial Registry and Results Data Bank*, June 22, 2009, http://bio.org/reg/20090622.pdf

No. NIH-2009-0002), BIO recommends that results from pivotal confirmatory clinical trials be disclosed on ClinicalTrials.gov once a product has been discontinued in development for all indications when such trials were terminated due to safety reasons. Disclosing results on ClinicalTrials.gov only from *pivotal confirmatory* clinical trials will help ensure that the information provided has scientific merit. Disclosing 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 new therapeutic agent in patients who have the disease or condition to be treated. These trials usually represent the most rigorous demonstration of the therapeutic agent'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,[4] 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.

We note that in the Transparency Task Force meeting notice, FDA defines a product application that has been abandoned as one where "no work is being done or will be undertaken to have the application approved." However, in many instances it is difficult to ascertain if a product development program has been abandoned without an affirmative declaration from the sponsor. As BIO has stated in previous comments with respect to disclosing clinical trial data on ClinicalTrials.gov, we recommend 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.

The above options (definitions) if adopted into the Agency's official 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 changes

[4] The harmonised tripartite guideline entitled *E9: Statistical Principles for Clinical Trials* (ICH E9), developed and adopted by the International Conference on Harmonisation, is available here http://www.ich.org/LOB/media/MEDIA485.pdf.

in FDA policy 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. For example, a small company may receive a Complete Response (CR) letter from the FDA requesting additional clinical data and the company may place the development program on hold while it searches for new sources of capital to fund the trials. In that instance, premature FDA disclosure of the application's highly proprietary study information and intellectual property would undermine the company's ability to generate funding for an active development program and would impede their ability to successfully bring the product to market. Providing clarity as to when a product would be classified as discontinued in development would help meet 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 (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) — 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.

One of the scenarios presented for the panel discussion during the November 3, 2009 Task Force meeting concerns whether FDA should disclose information about a product discontinued from development, the reason for discontinuation, or disclose information about the product if the application was withdrawn for apparent safety-related reasons (FDA hypothetical case study 2).We note that even in situations where a safety issue has been identified, FDA may not be aware of all the reasons behind the sponsor's decision to discontinue development of the product. Such decisions are often multi-factorial, taking into account considerations such as the product's emerging safety profile, preliminary efficacy data, overall benefit-risk assessment, research portfolio analysis, status of competitor's products, business priorities, etc. The decision is often based on a combination of these factors, and if the sponsor elects not to continue development of the product it does not necessarily mean that the identified safety issue could not have been

overcome or resolved if further analysis or research were conducted. If the FDA were to divulge that a pending application was withdrawn due to apparent safety reasons, it could provide a distorted or incomplete picture especially in cases such as that described in the hypothetical case study when the linkage between the safety concern and the product was not firmly established.

Furthermore, 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.

Again, 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.

Moreover, it is our view that the majority of applicants disclose to the public — usually via press releases and annual financial reports — when an application for a new product or significant new indication has been submitted, approved or withdrawn. This is especially common practice for products that are new molecular entities. It is therefore highly questionable what the added value would be if FDA were to issue its own public communications about applications submitted or withdrawn. One exceptional situation where agency communication would be warranted is the situation in which an application is withdrawn or discontinued from development due to a clear association with a serious and unexpected adverse event, and if other related products in the same chemical class or with closely related molecular structures are under development for the same indication, and there is evidence indicating that other products within the same class might have the same serious side effect. In that case, the agency should inform the applicants and sponsors of the related products about the significant safety finding, but should first contact the initial applicant whose product was implicated to coordinate the content and interpretation of the information to be communicated. This would ensure the applicants and sponsors for the related products are informed about an important safety finding that is potentially relevant to their products and enable them to increase their monitoring, revise their study protocols, or take other actions that might be appropriate based on the circumstances to protect the subjects participating in clinical trials.

II. Communicating Agency Decisions about Pending Product Applications

FDA can and should do more to clearly communicate the scientific basis for its regulatory actions in a manner that is understandable to the layperson. The greatest single change that FDA

can make to enhance transparency is to more clearly articulate the Agency's deliberative processes and to educate the public on how the agency conducts its work — including being forthright about the way it works with industry, how it balances risk and benefit, where protection of confidential and/or undeveloped information is appropriate, and how this information might benefit the layperson.

The Transparency Task Force meeting notice asks several specific questions regarding public notification of certain regulatory milestones. For example, "should the agency inform the public when a marketing application seeking approval of a drug or biologic is submitted to the agency for review?" In fact for a number of reasons, drug and biologics companies will often issue press releases to notify the public when a New Drug application (NDA) or a Biologics License Application (BLA) has been submitted. In light of the current high-level of public disclosure of submission of marketing applications, BIO does not view this as a policy concern that needs to be addressed. In the rare instance when a company declines to announce the submission of a marketing application, it is generally due to a strategic business decision and has little impact on the public health since the product is not yet publically available.

FDA also asks "should the agency disclose to the public a determination not to approve a marketing application for a drug or biologic? What, if any, information should the agency disclose about the determination not to approve the application?" In BIO's previous comments to the Transparency Task Force, we underscored the importance of protecting trade secrets and confidential commercial information from public disclosure due to competitive considerations. FDA Complete Response letters (CR) will often include sensitive information about a product's manufacturing processes and formulations that could put a company at a competitive disadvantage if disclosed. This is particularly true for biologics, which use complex, highly proprietary manufacturing processes that may be discussed in the CR letter. However, BIO does not necessarily believe that an absolute prohibition on the disclosure of CR letters is the only mechanism to protect this information. BIO welcomes a dialogue with FDA to determine what type of information included in CR letters would be considered trade secret, confidential commercial information, or sensitive competitive information and whether that information could be potentially redacted in a publicly released version of the CR letter. FDA should also evaluate what type of technical information disclosed in a CR would be comprehensible to the average layperson and would provide meaningful benefit to the general public. However, given the importance of protecting confidential information and the negative implications of inadvertent disclosure, the agency's default position should be that no information will be released unless it has been cleared through multiple-levels of internal FDA review and the company has agreed to the release.

Another question raised by the Task Force pertains to the publication of a study for a product in development, and in the hypothetical example (FDA hypothetical case study 3) the publication lacked sufficient detail to allow a full understanding of the trial design and totality of existing data for the product. In the background material for the case study, FDA asks if the agency should release information about other clinical trials that have not yet been published, and whether it should disclose whether a marketing application has been submitted. In general, we believe it would not be the best use of FDA's resources to routinely expend staff effort to develop public commentary on clinical trials published in the scientific literature. The nature of

product development is inherently variable and it is not unusual that multiple clinical trials with the same product will not always produce completely consistent results. Ultimately, FDA's review of the NDA or BLA, when submitted, will determine whether the product is considered safe and effective, and one of the great strengths of FDA's review process is that it takes into account the totality of the clinical trial data submitted for review. Providing commentary on individual clinical trials during product development, whether published or not, would not only be extremely labor intensive, but could also result in confusing and conflicting information being released before the development program has been completed.

Given FDA's stature as the ultimate authority on the safety and efficacy of medicinal products, we urge FDA to consider the potential unintended consequences if preliminary communications resulted in external stakeholders making premature and possibly erroneous judgments about the future approvability or health value of a product before all the data generated during product development have been evaluated by FDA. If, however, FDA sees a publication of a clinical trial in the scientific literature and the conclusions within the publication differ substantially from FDA's views based on the clinical studies the agency has reviewed, we do recommend that FDA contact the sponsor in that instance to discuss the differences of interpretation. This is important to assure a common understanding of the emerging benefits and risks, and to ensure any important unanswered questions are addressed in future studies as development of the product proceeds.

III. Emerging Safety Issues Concerning FDA Regulated Products

BIO is pleased that FDA continues to refine and enhance its procedures for crisis communication and for benefit-risk communication. We believe that FDA should strengthen the capabilities of its public affairs function to better communicate during times of crises and confusion, so that FDA can adequately explain the steps it is taking to evaluate conflicting or incomplete data to the media and the public. Indeed, FDA, industry, and the public benefit when FDA takes a proactive stance, anticipates the public's concerns, and stays ahead of an emerging safety issue. BIO was encouraged to see FDA develop a Strategic Framework for Risk Communication,[5] and we encourage FDA to translate this high-level document into standard operating procedures that articulate clear expectations, defined practices, and established timelines for FDA communication of new safety information.

For example, in the event of a safety issue or recall, we recommend that FDA notify the company involved well in advance of any external FDA communication so that the company may develop complementary communications to the public and healthcare providers, or work collaboratively with FDA to establish a joint communication plan. This type of coordination between FDA and sponsors will help to minimize the potential for conflicting information and provide multiple channels of communication to better inform patients and physicians.

[5] *FDA Strategic Plan for Risk Communication*, Fall 2009, http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM183683.pdf

It is also important for FDA to determine in advance what risk threshold will trigger a public safety communication. This threshold will vary depending on many factors, including the product, disease indication, risk factor, and confidence in the safety analysis. FDA should decide in advance what criteria will be used to decide if risks will or will not publicly communicated, because certain risks may be so infrequent or minor as to be clinically irrelevant or can be mitigated through other means. To inundate the public with possible safety signals without proper context and regulatory oversight would undermine public confidence in the FDA and appropriate use of necessary medical therapies.

Additionally, BIO believes that FDA communications should be outcomes-focused with clear advice for patients and healthcare providers on how to manage a risk, rather than just focusing on dissemination of facts or conclusions. It is important to balance public health and transparency with the potential for undue public concern that is not commensurate with the strength of the data, which may cause patients to abandon needed therapies without consulting a physician. We think that the first communication of a new signal should be accompanied by an analysis of the signal, and when appropriate, and a sensible recommendation to patients and physicians on next steps. In other words, FDA should not communicate risks of unknown validity with the actual meaning — and important information on how patients should be managed — coming months or years later. Rather we urge FDA to design policies, processes, and pharmacovigilance systems that allow signal identification to be immediately and robustly followed by confirmatory analysis and subsequent public communication, if necessary. In addition to addressing practices for communicating findings that confirm a safety signal, FDA's risk communication framework should also articulate a process for communicating findings that negate a previously communicated safety finding.

We also note that transparency alone will not enhance patient understanding of a product's benefit/risk profile or enhance medical outcomes unless the information is framed in meaningful context. For example, the public health is not necessarily advanced by communication of drug risks in the absence of a discussion of known benefits or the context of other commonly accepted risks, or by publication of analyses that have not been verified by quality systems to ensure accuracy of conclusions. We recognize that providing sufficient contextual information and corroboration as an element of the Agency's commitment to transparency will require adequate internal processes, resources, and infrastructure.

Finally, we suggest that the Agency coordinate more closely with media in order to reduce the potential for sensationalism and to ensure that the media provides the public with balanced, scientifically accurate interpretations of the available data.

IV. Conclusion:

We thank you again for the opportunity to provide comments to the Transparency Task Force. The biotechnology industry looks forward to working with the Agency and other stakeholders to realize greater transparency in FDA communications with the general public and in interactions with regulated industry.

Sincerely,

/S/

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/S/

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