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July 20, 2010

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2009-N-0247, FDA Transparency Initiative: Draft Proposals for Public Comment Regarding Disclosure Policies

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the FDA Transparency Task Force Phase II Draft Proposals regarding the Agency's public disclosure policies.

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.

Our comments below are divided into two parts - Part 1: General Comments and Part 2: Specific Comments on the Draft Proposals.

PART I: GENERAL COMMENTS

BIO applauds FDA's efforts to improve transparency to all stakeholders to promote the Agency's accountability, increase its credibility, and enhance its work of protecting and promoting the public health. We agree that FDA should seek to make Agency activities and processes accessible to patients, physicians, health care providers, and all other stakeholders in a timely manner to improve credibility and public trust of the Agency. A highly credible FDA is in the best interest of both public health and the industries FDA regulates. FDA should be commended for convening the Transparency Task Force and

for evaluating ways to make the Agency's activities and decision-making more transparent, useful, and understandable to the public. Our paramount concern is whether these efforts will appropriately protect confidential information. Additionally, BIO is concerned about: the focus of FDA's initial transparency efforts, in light of limited Agency resources; whether the release of information would benefit the public health and serve FDA's public health mission; what internal review and redaction measures would be employed; and what Sponsor notification measures would be employed.

Efforts to increase transparency must respect the well-established laws and regulations that protect trade secrets and confidential commercial information -- a framework that is critical for the promotion of innovation and protection of incentives for product development. BIO is concerned that FDA's Draft Proposals do not clearly address how FDA intends to protect this information. At a minimum, FDA should describe the process by which redaction of protected information will occur, how the Sponsor will be involved in the redaction of documents proposed for disclosure, and what Agency reviews and approvals will be used to ensure compliance.

The report proposes a number of positive, common-sense recommendations that BIO supports implementing. These proposals can have a significant impact in promoting Agency transparency without placing critical competitive, confidential commercial information at risk and potentially undermining entrepreneurial biomedical discovery.

For example, if appropriately implemented with dedicated resources, BIO would support the following FDA proposals:

#2 - Enhancements to the Docket Management Process
#3 - Publication of FDA Enforcement Reports
#4 - Publication of Office of Regulatory Affairs Work Plans Older than 5 Years
#5 - Disclosure of Third Party Importer Evaluations
#7 - Publication of Summary Information on Commonly Observed Inspectional Violations
#19 - Efforts to Communicate to the Public Which Products are Not Subject to a Recall
#20 - Public Notification When a Recall Has Terminated

Additionally, BIO believes that FDA's transparency efforts should properly begin with enhancing existing processes, before the Agency seeks to expand its mission. Specifically, BIO encourages FDA to provide greater transparency in three longstanding core regulatory functions: Freedom of Information Act (FOIA), Citizen Petitions, and Advisory Committee Meetings.[1] Greater transparency in these core processes as a starting objective – both inside the FDA and between the FDA and regulated entities – would ensure maximum utility and efficiency in FDA's efforts to increase transparency in other areas. With limited resources at FDA, improving the timeliness of FDA's responses to these core functions should be a priority over any new initiatives to increase transparency further.

[1] BIO's recommendations for improving the transparency of the existing Advisory Committee process can be found in the BIO Comments on FDA Transparency towards Regulated Industry, April 12, 2010, http://bio.org/letters/20100412b.pdf

In BIO's experience, FOIA requests can take well over a year to be processed, and by the time a response from FDA has been received, the information requested often arrives too late to be of any realistic use. Such delays effectively can deny citizens the meaningful access that FOIA intended to provide. FDA should focus additional resources improving the FOIA process and reducing the response times for these requests. Such improvements would enhance transparency, without the confidentiality and competitive advantage risks raised by a number of FDA's Draft Proposals. Improvements should include: better training for reviewers to ensure consistent, adequate redaction; consistent verification by the Sponsor to confirm that trade secret and confidential information has been removed; and increased timeliness in response respond to FOIA requests.

In sum, FDA should focus on first improving the FOIA and other core processes already in place to ensure transparency before taking up entirely new and expansive initiatives.

I. Transparency for Transparency's Sake is Not Always in the Interest of the Public Health

While we understand FDA's goal of promoting openness in government, we are concerned that some of the Agency's Draft Proposals may seek transparency for transparency's sake, without any determination that the information to be disclosed would actually promote or protect public health, and despite the fact that such disclosures may exceed FDA's mission or be misleading.

A. Some Draft Proposals Extend FDA Beyond the Agency's Mission

The Federal Food, Drug, and Cosmetic Act (FFDCA) clearly defines FDA's mission and responsibility to promote and protect the public health by assuring the safety, efficacy, and quality of the products it regulates.[2] Yet some of the Draft Proposals have a far reaching effect that may go beyond FDA's statutorily defined role. These proposals could inappropriately position FDA as referee of scientific discussion and the dissemination of scientific information, as an arbiter of making an efficient market place for clinical development or as an overseer of financial transactions. Any Agency transparency efforts must be consistent with its core mission to promote and protect the public health, and not merely provide a conduit for distribution of information for transparency's sake with no public health benefit.

B. Release of Technical Information Not Intended for the Lay Public Can Lead to Confusion

BIO urges FDA to assess whether each type of information identified in the Agency's Draft Proposals would in fact be understandable and useful to healthcare providers, patients, and the general public. Without such determinations, FDA would be acting purely on an assumption that the information disclosure would benefit the public health, when in fact it could result in more confusion than clarity.

[2] 1003 903(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 393(b) ("Mission").

Some of the types of information FDA proposes to disclose may be confusing or even misleading to consumers, either because the language used is highly technical, such as in a Complete Response letter, or because the information is isolated and out of context, such as in a final inspectional classification. As FDA and Congress recognize in other contexts, and as research demonstrates, patients are not helped by being provided with raw data without any context or training to understand the implications of the data.

For example, recent research suggests that public disclosure of risk information before it has been verified may have little effect on improving public trust and may result in patients inappropriately discontinuing therapy. Accordingly, FDA should exercise caution around the disclosure of preliminary or pre-decisional safety information, as this disclosure could negatively impact public health.

Wisely, when Congress enacted the Food and Drug Administration Amendments Act of 2007 (FDAAA) directing the Secretary to expand the www.clinicaltrials.gov registry and results database, and to consider including clinical trial information written in a manner that is non-technical and understandable to patients, it stated that the Secretary should first determine whether it would be feasible to do so without the information being "misleading or promotional" to that intended audience.[3] FDA should employ that same decision-making process here, before disclosing any product-related information.

The complete package insert (PI) for a drug product is not directed towards a lay audience; that is why patient package inserts (PPIs) are developed and distributed. FDA advises that PPIs contain straightforward language, simple command sentences, and other similar features to make them consumer-friendly. Any information that FDA proposes to disclose to consumers under these Draft Proposals should likewise be understandable, straightforward, and non-technical.

FDA has considerable knowledge and expertise in determining whether information is comprehensible and user-friendly, as the Agency oversees the development of labeling intended for patients and consumers in MedGuides, PPIs, over-the-counter drug labeling, as well as direct-to-consumer (DTC) advertising. BIO urges FDA to rely upon this expertise and its health literacy experts to assess whether the information proposed to be disclosed under the Agency's Draft Proposals would be understandable to the public and beneficial to public health.

C. *Disclosure Based on "Selective Transparency" Can Be Misleading*:

FDA must ensure that it does not implement policy disclosures that, in essence, result in "selective transparency." Transparency is only meaningful to the extent that FDA provides full, fair and balanced context for the information to be disclosed. FDA elsewhere recognizes the need for complete, fair and balanced user information, for example, on product labeling and in promotional material. These same principles should govern FDA's disclosures.

[3] Section 801(j)(3)(D)(iii) of FDAAA, codified at section 401(j)(3)(D)(iii) of the Public Health Services Act, 42 U.S.C. § 282(j)(3)(D)(iii).

The release of incomplete and potentially misleading information has the ability to cause more confusion rather than less. For example, the release of an inspectional classification "Voluntary Action Indicated (VAI)," without any accompanying explanation or without also posting the firm's response to the Form 483, may give rise to a misimpression that FDA has observed manufacturing or quality defects at the firm, when in fact FDA has only faulted the firm's procedures - without in any way questioning manufacturing or product quality. FDA should ensure that such Draft Proposals, no matter how well intentioned, do not cause misinformation or misimpressions that achieve the opposite of transparency.

Most of the twenty-one proposals are broadly defined and cover the entire range of products regulated by the FDA. In its reasoning, the Task Force differentiated between the different types of stakeholders, but has not considered the differences in regulatory processes governing these products, the level of detail to be disclosed, the timing of the disclosure, or the context in which the information will be disclosed. The context is critical for FDA to consider as these proposals are refined further for potential implementation.

Additionally, the proposals do not appear to differentiate between disclosures of information related to products under development that are not available to the public compared to currently marketed products that are available to patients. A product's stage in development and public availability significantly alter the implications of disclosure from a public health perspective. For example, if a product is not yet commercially available, it is unclear what if any public health benefits would accrue from releasing safety information to the public as a whole. It is therefore critical for FDA to take product development stage and availability into account when considering implementing these proposals.

II. Some Proposed Disclosures May Not Be Lawful Under Existing Authority

In public statements, FDA has suggested that the legal issues raised by these proposals are to be addressed separately from the current policy discussion. We request that before taking further action on the Draft Proposals, FDA provide the public with more detailed information on that legal analysis to ensure that all applicable legal issues are addressed fully. Before the Task Force makes recommendations to the Commissioner, we suggest that FDA indicate publicly its determinations regarding which of its Draft Proposals will require statutory changes; which will require changes to existing regulations or promulgation of new ones; which will require Level 1 or 2 Guidance,[4] and which, if any, may be implemented without any attendant process. FDA should not only indicate the procedures it intends to follow to address legal issues, but it should also provide a robust opportunity for public comment on these procedures before implementing the Draft Proposals.

As FDA appears to recognize, the Draft Proposals contemplate the release of information that may be protected from disclosure under current statutes and/or regulations. For

[4] 21 CFR § 10.115

example, the disclosure of a Complete Response Letter (Draft Proposal #13), a Refuse to Approve (Draft Proposal # 14), or a Not Approvable Letter (Draft Proposal #15) would violate existing law. Accordingly, for FDA to properly release such information would require statutory changes or, in some cases, duly promulgated regulations.

The main protections implicated and perhaps contravened by the Draft Proposals are found in the FFDCA, the Trade Secrets Act, and FDA regulations. The FFDCA prohibits public disclosure of any method or process that is a trade secret if acquired under certain authority of the FFDCA, such as under an Investigational New Drug (IND) application, a New Drug Application (NDA), or Biologics License Application (BLA).[5] It also prohibits public disclosure of certain device-specific confidential commercial information or trade secrets if obtained under certain statutory provisions, such as through a Premarket Approval (PMA) application or a device inspection.[6] The Trade Secrets Act prohibits officers and employees of federal agencies from publishing or disclosing trade secrets and other confidential business information "to any extent not authorized by law."[7] Finally, FDA regulations at 21 CFR part 20 and other applicable parts[8] prohibit or restrict the release of broad swaths of information, including information about investigational products or pending marketing applications.

These statutory and regulatory protections, individually and collectively, prohibit public disclosure outright or restrict FDA's ability to disclose information including for the purpose of facilitating transparency. BIO recommends that FDA take great care in advancing these Draft Proposals to ensure that the Agency complies with existing law. BIO further requests that FDA forgo or delay implementing Draft Proposals that contradict or conflict with existing law unless and until any warranted statutory and regulatory amendments are in place.

III. FDA Internal Review and Redaction Procedures

BIO notes that much of the information covered by these Draft Proposals is commercial in nature - concerning investigational and marketed products - and a subset of this information is likely proprietary. The Draft Proposals define trade secrets, but do not adequately define the term Confidential Commercial Information (CCI) or recognize that CCI is already defined in relevant statutory and regulatory provisions[9] CCI generally consists of information the disclosure of which would likely result in a competitive disadvantage to the company owning the information. Information in pending product applications and FDA decisions regarding those applications, as memorialized in Action and Complete Response letters, may constitute CCI. Any CCI, like trade secrets, must be protected from unauthorized disclosure.

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[5] Section 301(j) of the FFDCA, 21 U.S.C. § 331(j)
[6] Section 520(c) of the FFDCA, 21 U.S.C. § 360i(c),
[7] 18 U.S.C. § 1905
[8] A list of cross-references to other applicable FDA regulations is found at 21 CFR § 20.100.
[9] FDA regulations at 21 CFR § 20.61(b) define "commercial or financial information that is privileged or confidential" as "valuable data or information which is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs."

BIO is concerned about the lack of any identified process in the Draft Proposals for ensuring that trade secrets and CCI are not released to the public inadvertently and without authorization from the owner of the information. In other contexts, FDA recognizes how essential it is to avoid inadvertent disclosure of CCI or trade secrets in violation of law[10] and can cause substantial competitive harm to the submitter of the information. FDA has dedicated FOIA and information disclosure staff within the Office of the Commissioner and in each product-area Center who are trained to review all materials that are to be disclosed, whether generated by FDA or submitted to FDA by outside parties. These staff are responsible for making the necessary and appropriate redactions and decisions about withholding information that is exempt from disclosure under FOIA and/or protected from disclosure under other applicable laws and regulations.[11] BIO understands that these disclosure staff work under extensive supervision, as needed, to ensure that all procedures are followed and that all necessary and appropriate redactions are made. Yet the Draft Proposals include no discussion or even acknowledgment of the need for any such review process as applied to the new categories of information proposed to be disclosed.

BIO strongly disagrees with FDA's rationale that, because some companies release certain categories of information, such information lacks commercial value for all. Small companies may release information for business reasons to stimulate capital investment; others may withhold the very same type of information to protect investments they have already made. In either case, the competitive value of this type of information is sustained. The decision to make this type of information public belongs to the owner of the information and not to the government. FDA's Draft Proposals provide scant rationale other than vague reference to "the public interest" for usurping this prerogative.

Given the importance of protecting proprietary information and the negative implications of inadvertent disclosure, it is imperative that the Agency impose internal procedures for review and redaction before implementing some or all of the Draft Proposals. Possibilities include extending current review procedures to the new categories of information or developing new review procedures, each of which likely requires hiring more disclosure staff to cope with the increased workload. Whatever the procedures adopted, BIO recommends that the Agency ensure that all information before release is subject to multiple levels of review by those expert in the legal and regulatory protections of proprietary information and trained in proper procedural safeguards.

BIO further recommends, as described below, that the Agency obtain input and consent from the entities potentially affected by disclosure in advance of releasing any such information - for example, consulting the NDA applicant before releasing a redacted version of a Complete Response Letter. If FDA decides that a document should be released, the impacted company must be given the opportunity to provide a redacted version of the document to FDA prior to any such release.

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[10] As discussed earlier, the laws that may prohibit such disclosure include the Trade Secrets Act, 18 U.S.C. § 1905, Section 301(j) of the FDCA, 21 U.S.C. § 331(j); and Section 520(c) of the FDCA, 21 U.S.C. § 360i(c). We note that FDA recently settled a long-litigated lawsuit in which the plaintiff alleged wrongful disclosure of proprietary information, in *Jerome Stevens Pharmaceuticals, Inc. v. FDA*.

[11] See above footnote and 21 CFR part 20 (FDA's regulations implementing FOIA). A list of cross-references to other applicable FDA regulations is found at 21 CFR § 20.100.

IV. Sponsor Pre-Notification Procedures

BIO recommends that any procedures the Agency develops to ensure the protection of proprietary information include Sponsor pre-notification and consent. Indeed, such pre-notification is required in other, related contexts. Under FDA regulations, when FDA receives a FOIA request that potentially includes CCI or trade secrets, FDA must make reasonable efforts to notify the submitter of the information and provide the submitter an opportunity to object to disclosure of all or part of the information.[12] FDA must give full consideration to the objections raised and notify the submitter in writing before releasing the information, if it decides not to sustain some or all of the submitter's objections.[13] BIO urges FDA to adopt the same process here, for any information proposed to be released under the Draft Proposals.

Although the Draft Proposals do not provide detail about the process for disclosure, BIO notes that at least three proposals seem to preclude pre-disclosure notification of the Sponsor. Draft Proposals #13, #14, and #15 contemplate publicly releasing letters issued to Sponsors, or possibly summaries of such letters, "at the same time" such letters are issued. The apparent lack of pre-notification in these proposals causes particular concern for BIO because these proposals implicate proprietary information. For example, a Complete Response letter that includes a description of aspects of a company's manufacturing process or statistical analysis likely would include confidential commercial information or trade secrets.

Companies are generally in the best position to identify, in the first instance, what information is proprietary and should be protected from disclosure, as FDA recognizes in the context of FOIA. This is the main reason FDA regulations establish that the Agency seek companies' input *before* disclosing potentially proprietary information in response to FOIA requests.[14] This same pre-notification procedure should apply to the Draft Proposals to the extent implemented and otherwise authorized by law, because inadvertent disclosure of proprietary information could have serious consequences both for the owner of the information and for FDA.[15]

V. Resource Considerations

BIO recognizes that conducting additional activities to promote transparency to the public can be resource intensive and create additional workload for the Agency. Indeed, the Task Force Report states that the "recommendations will consider feasibility and priority, considering other Agency priorities that require resources. *Some of the draft proposals may require extensive resources to implement* and some may require changes to regulations and possibly even legislation. As a result, the Task Force may ultimately recommend some, but not all, of the draft proposals for implementation." (p.3, *italicized*

[12] 21 CFR §20.61(e)(1).
[13] 21 CFR § 20.61(e)(3).
[14] 21 CFR § 20.61.
[15] Such disclosure may constitute a violation of law and may result in substantial competitive harm to the entity affected, for example allowing competitors to understand and adapt proprietary manufacturing methods. See footnote 9.

for emphasis). Many of the Draft Proposals will require extensive rulemaking processes; full time equivalents to identify, redact, and publicly post disclosed documents; and significant staff training on new policies. These resource implications must be seriously considered, particularly in cases where the information FDA is proposing to disclose is already in the public domain by other mechanisms and therefore FDA disclosure would be redundant and without benefit.

The lack of resources at the FDA and the impact this has on FDA's ability to carry out its mission is well documented. BIO recognizes that over the last 20 years, FDA resources have eroded while new responsibilities and mandates have been placed on the Agency. As a strong proponent for a fully funded FDA and active member of the *Alliance for a Stronger FDA*, BIO has advocated successfully for significant new appropriated funding for the Agency. However, FDA has not achieved adequate levels of appropriated funding necessary to meet its current responsibilities, keep pace with evolving science, and achieve its core mission.[16] If additional resources are necessary to implement the Draft Proposals made in this report, BIO strongly urges the Agency not to divert existing funding from current activities and priorities, but rather to request new appropriations from Congress.

In summary, if the Task Force determines that there is public health value in disclosing additional information about FDA's activities, it would be counterproductive to weaken those very same programs by diverting limited resources to the disclosure process.

VI. FDA Activities Should Not Duplicate Existing Government Activities or Expend Limited Resources Releasing Information Already in the Public Domain

In light of these resource considerations, BIO believes FDA should not focus its scarce resources on activities that would be duplicative of existing programs administered by sister public health agencies or other regulatory bodies. For example, several of the proposals relating to the disclosure of clinical trial information (Draft Proposals #8, #9, #10, #16, #17) appear to be duplicative of or even inconsistent with the www.ClinicalTrials.gov registry and results database administered by the National Institutes of Health (NIH).

Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA), instructs the Secretary of HHS to promulgate regulations to expand the ClinicalTrials.gov federal registry and results data bank by September 27, 2010. NIH is still working on this rulemaking. We are concerned that clinical trial disclosure is being discussed in two separate regulatory tracks within HHS - NIH and FDA -which may lead to confusion, lack of coordination, and significant implementation burden for the Agency and Sponsors. Before FDA adopts any additional changes to its data protection policies, we encourage the Agency 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. Indeed, many of the concerns cited

[16] See, for example, remarks of Commissioner Hamburg, "Protecting Health: FDA's Global Challenge" (Jan. 28, 2010), *available at* http://www.fda.gov/NewsEvents/Speeches/ucm199422.htm.

by the Task Force could be potentially addressed through disclosure on clinicaltrials.gov, while maintaining the integrity and confidentiality of the review and approval process and ensuring a coherent and unified government approach.

PART II: SPECIFIC COMMENTS ON DRAFT PROPOSALS

(In order of importance)

Draft Proposal #13: FDA should disclose the fact that the Agency has issued a refuse-to-file or complete response letter in response to an original NDA, BLA, or an efficacy supplement for an NDA or BLA at the time the refuse-to-file or complete response letter is issued, and should, at the same time, disclose the refuse-to-file or complete response letter, which contains the reasons for issuing the letter.

A. Disclosure of Confidential Commercial Information and Trade Secrets Would Undermine a Company's Competitive Position and Hinder New Drug Development:

In the absence of established processes to protect trade secrets and CCI as discussed above, BIO cannot agree with the Draft Proposal to disclose Complete Response (CR) letters and Refuse-to-File (RTF) letters and believes that it would be detrimental to future development of new medicines and therapies. As discussed throughout these comments, FDA transparency efforts must continue to protect commercial confidential and trade secret information from disclosure. FDA CR letters often include confidential commercial information and 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 likely discussed in RTF or CR letters.

Inappropriate disclosure of confidential commercial or trade secret information would be a clear detriment to public health by chilling product development and innovation. Such disclosure could confer an unfair advantage on a competitor by providing insights into a rival compound's development process. Providing competitors with this sensitive product, manufacturing, and business information would enable them to misappropriate the innovator's discoveries and unfairly use this information in its business strategies. Over time this practice would disincentivize investment in biopharmaceutical discovery and ultimately result in fewer new drugs being brought to market, a consequence that would be contrary to protecting and promoting public health.

B. If Refuse-to-File or Complete Response Letters Are Disclosed, FDA Should Coordinate with the Sponsor to Redact Sensitive Information:

If Congress were to provide FDA with statutory authority to disclose CR or RTF letters, it would be our strong preference that any version of the letter that potentially would be released publicly would be reviewed by the Sponsor to determine what sensitive competitive information should be redacted. Given the importance of protecting confidential information and the negative implications of inadvertent disclosure, the Agency's default position should be that, at a minimum, no information will be released unless it has been cleared through multiple-levels of internal FDA review and serves an important public health goal. In addition, the affected parties should have an opportunity to provide input into the information that should be redacted from a document that will be released and should approve any publication of the material.

We would like to work with the Agency to determine if sensitive competitive information could potentially be redacted to create a publicly releasable version of the Complete Response letter. BIO would like to engage in a dialogue with FDA on the types of information included in CR or RTF letters might be useful for public dissemination, as well as what types of information would be considered trade secret, confidential commercial information, or sensitive competitive information. As previously discussed, FDA also should evaluate what type of technical information disclosed in a CR or RTF letter would be comprehensible to the average layperson and would provide meaningful benefit to the general public and use that evaluation to help determine what, if any, such information should be released.

C. Timing of Disclosure is an Important Consideration:

The timing of any disclosure is also important. The proposal seems to suggest that FDA would disclose this information (the content of the letter) publicly at the same time it sends the letter to the manufacturer. Releasing this information in the middle of a conversation about drug development can lead to confusion, misinterpretation, and misuse. At a minimum, if this information is to be released, it should not be released until after the Sponsor has reviewed the Agency's letter for protection of trade secret/confidential commercial information, and has submitted an initial response to the CR or RTF letter so that both the FDA and Sponsor letters are disclosed in tandem with appropriate redactions. This would provide a more complete, balanced context, presenting the issues from both the FDA's and the Sponsor's perspectives.

Draft Proposal #16: FDA should disclose relevant summary safety and effectiveness information from an investigational application, or from a pending marketing application, if the Agency concludes that disclosure is in the interest of the public health, which includes when FDA believes it is necessary to correct misleading information about the product that is the subject of the application.

BIO disagrees with this proposal and questions the expansion of FDA's role into the scientific peer review process. Current FDA practice is that summary safety and efficacy information for pending applications is not publicly available, except when the unapproved product is subject to discussion at a public FDA Advisory Committee meeting. However, FDA does make such information available for approved products in a timely manner on the FDA website by posting review packages or in response to FOIA requests. Particularly important information also would be included in the approved product label. This proposal would allow FDA to disclose summary safety and efficacy information for a product that is still under regulatory review if FDA believes it is in the interest of public health, including when FDA believes it is necessary to correct what it believes is misleading information.

A. FDA's Role is Not That of an Arbiter of the Scientific Peer Review Process:

This proposal has broad implications that would greatly expand the role of the FDA beyond its statutorily defined mission of protecting and promoting the public health and provide product information prior to a complete FDA review and prior to product availability. For example, one possible scenario is for FDA to conclude that information published in a scientific journal is misleading. Articles submitted to scientific journals are peer reviewed by scientific experts and, as appropriate, the published information should be reflective of the safety and efficacy information about a product as it relates to the published study. Were FDA to disclose "relevant" safety and efficacy information to correct information it believes is misleading, FDA would be positioning itself as an arbiter or backstop for the scientific peer review process employed by scientific journal editors. FDA commenting or taking a position on information that has been published in a peer reviewed journal could put FDA at odds with the journal editorial review process, potentially placing FDA in a contradiction or dispute with journal editors and/or scientific reviewers. This is not the role of the FDA and could have the opposite of the intended effect by undermining FDA's credibility with the public. Similarly, it is not the role of the FDA to regulate or correct non-promotional disclosures a Sponsor makes under its obligations to the investment community.

If FDA believes inaccurate information is being disseminated about an investigational product or a product that is under regulatory review, and that information is deemed to be promotional, FDA has enforcement mechanisms to stop further dissemination of the information and, where warranted, require the information to be corrected. If the information FDA is attempting to correct is scientific exchange or otherwise not promotional, it is not the role of the FDA to regulate or "correct" this information.

B. What Constitutes "Misleading Information"?

It is unclear how this proposal would be implemented in practice. There is a lack of clarity regarding what criteria FDA will use to determine whether disclosure is warranted and, if so, what information should be disclosed. On what basis would FDA make the determination that it "believes it is necessary to correct misleading information about the product that is the subject of the application"? Indeed, in the pre-approval period it is unclear how FDA would determine that information in the public domain is misleading until it has analyzed all of the relevant data and completed the review of the product. Further, "misleading information" is a subjective standard that is determined by individual opinion. There may be disagreements within FDA as to whether certain information is misleading and the proposal does not state who at FDA would make the final determination to disclose. The standards employed by FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) in reviewing advertising and promotional materials for marketed products to assess whether materials are "misleading" would not be appropriate or applicable to clinical development information, which is often still undergoing review and analysis and is subject to differing interpretations and scientific debate. If the information FDA is seeking to correct is not promotional in nature but rather is scientific exchange or information a Sponsor is communicating to the investment community, it is not the role of the FDA to regulate or "correct" what it may view as misleading.

C. How is "The Interest of the Public Health" Defined?

Additionally, we encourage the Task Force to define specific criteria for what would constitute "the interest of public health" and how that determination would be made in concert with the relevant product Sponsor. The criteria and instances where the FDA would disclose safety and effectiveness data from pending marketing applications should be clarified in a guidance document on which the public can provide comment.[17] Disclosure should occur only after dialogue between FDA and the Sponsor.

In defining "the interest of the public health," FDA should pay careful attention to the development stage and public availability of products. For example, while FDA may feel the need to disclose safety information from a NDA or IND pertaining to a drug which is approved in one indication but is being studied in another, there seems to be little value in disclosing to the public at large information for a product that is not yet marketed for any indication. In the latter scenario, or if potential class-based effects are discovered, there are already mechanisms for informing participants in clinical trials, such as the Investigator Brochure, Informed Consent form, and letter to investigators. For pending marketing applications, FDA advisory committees are venues for public discussion where the FDA, Sponsor, public and stakeholders can provide their perspectives. FDA should consider these other mechanisms already available for disclosing information about products under review when assessing whether this Draft Proposal is warranted.

D. The Proposed Content of the Disclosure is Unclear:

The proposal is also unclear on exactly what information is to be disclosed. Exactly what summary information will be released and who is responsible for preparing it? To what extent would the company be consulted or allowed to participate in the preparation and disclosure of information? An investigational application alone does not contain a consolidated summary or sufficient safety and effectiveness information to make a determination on the product's safety and effectiveness. Indeed, it would be premature to release safety and efficacy data for investigational products early in development, since the safety profile and benefit/risk information could evolve once the Sponsor conducts Phase 3 trials. Even in a marketing submission, the summary statement could change during the review process and is not appropriate to disclose until the application has been approved. It is unclear what disclosure of unapproved safety labelling prior to approval would achieve - certainly not fair balance or clarity. For example a drug may be approved only on secondary efficacy data that was not part of the original summary. We ask FDA to identify, precisely, the information it proposes to disclose and to provide a detailed supporting rationale.

Additionally, we request that FDA clarify and provide evidence to justify its assertions in support of this Draft Proposal: namely, that, "blanket protection of all information in pending applications has not been shown by industry to be economically necessary" and "the impact on a company's competitive position may cut both ways." These statements seem ill-founded or at least poorly articulated, and cause BIO concern.

[17] 21 CFR § 10.115(f)(4)

In summary, we urge FDA not to disclose summary safety and efficacy from INDs or pending NDAs. There needs to be a more defined, evidence-based explanation of when the FDA would disclose information and what information FDA would disclose. FDA should work with Sponsors in this regard if FDA determines it is necessary to disclose any such information.

E. FDA Advisory Committee discussion of safety and effectiveness information in unapproved products needs to be addressed in the context of this proposal:

The Task Force notes that FDA Advisory Committee meetings provide a public forum for airing important matters concerning products FDA regulates. FDA frequently discusses issues related to marketing applications for drug products at Advisory Committee meetings. Indeed, the Food and Drug Administration Amendments Act of 2007 establishes a preference for FDA to discuss applications for all new molecular entities with the relevant Advisory Committee prior to approval. Advisory Committee meetings include public discussion of summary safety and efficacy data from the perspective of both the Agency and the applicant, and provide an opportunity for FDA to raise "misleading product information" or other information for discussion in the interest of public health. The Agency's proposal to release summary data for unapproved products overlaps with its use of Advisory Committees and needs to be clarified in the context of Advisory Committee meetings. At a minimum, the Agency needs to describe its considerations with regard to disclosing summary safety and efficacy data under this proposal versus public discussion at an Advisory Committee meeting.

Draft Proposal #17: FDA should convene a group of internal and external stakeholders to discuss the possible uses of non-summary safety and effectiveness data from product applications, the circumstances under which it would be appropriate for Sponsors to disclose non-summary safety and effectiveness data from applications submitted to FDA, and if appropriate, the format and the method by which disclosure should occur.

While the details of the proposal are vague, for the same reasons as identified in Draft Proposal #16, we do not agree with the underlying premise of this proposal and could not support the disclosure of non-summary safety and effectiveness data.

The proposal is specific to disclosure by Sponsors but not by FDA. It is not clear whether or not there would be FDA review of information to be disclosed, or even what the purpose of disclosure would be. From a proprietary asset perspective, after patents themselves, raw data is a biopharmaceutical companies' life blood. Global data package exclusivity holds significant commercial value to Sponsors and potentially making raw data from submissions publicly available would provide an opportunity for competitors to misappropriate data to support their submissions for marketing approval. We firmly believe that there is no regulatory basis for mandating a Sponsor to disclose raw data to the public.

If the goal of the proposal is to set standards for Sponsors to follow, rather than addressing disclosure on a case-by-case basis, this could raise concerns. Clearly, any

goals of the disclosure could not seek to require companies to disclose information that would not be consistent with the approved product label.

First, we note that the proposal does not explain what is meant by "non-summary data." If this terminology refers to individual case reports, the proposal could have implications for patient privacy, as the information disclosed may be sufficiently identifying to breach the patient's privacy authorization provided as part of informed consent.

Second, the proposal is not clear as to the timing of the disclosure. An approved product label should discuss any non-summary safety and efficacy information relevant to the prescriber. This proposal could create another channel of communication that could be discrepant from the label eventually approved, leading to confusion among prescribers and a potential compromise in patient care. Further, as with summary information, FDA reviews non-summary safety and efficacy information to assess whether the data contained in the application have demonstrated substantial evidence of safety and efficacy. It is imperative that the FDA reviewers have the opportunity to review such data without any biases imposed. Making such non-summary information available prior to the completion of the Agency's review has great potential for imputing reviewer biases and, though unintended, will likely have negative consequences on the review cycle.

Additionally, it is unclear how the proposal would be implemented. For example, it is unclear what constitutes "relevant" information and what criteria and process FDA would adopt to determine what information must be disclosed. FDA should further clarify whether this proposal for disclosure of non-summary safety and effectiveness data would be limited to prospective use or may also apply retroactively to applications already approved. Given the legal issues raised by retroactive disclosure, coupled with the limited utility of and potential confusion caused by retroactive application, we assume that any such disclosure would apply prospectively only. Nevertheless, FDA should clarify as much.

While BIO does not support this proposal, if the Agency does implement this provision, the group of stakeholders that FDA convenes should include adequate representation from industry. All members, including industry participants, should be given equal standing and participatory rights.

As discussed previously, FDA also needs to clarify this proposal in the context of public Advisory Committee meetings, where safety and efficacy data may be discussed.

We note in closing that product applications do not contain "effectiveness" data. This term should be changed to "efficacy" data.

<u>Draft Proposal #8:</u> FDA should disclose the existence and, when asked, confirm the existence or non-existence of investigational applications. For investigational applications, the disclosure should include the name of the application Sponsor, the date the application was received, the proposed indication(s) or intended use(s) of the product, and the proposed proper and/or trade name of the product, if available.

A. This Provision is Duplicative of FDAAA, Goes Beyond Congressional Intent, and Raises Competitive Issues

BIO cannot support this proposal as it would overturn the long-held policy of maintaining as confidential the existence of an IND. For many emerging and fledgling companies, the early step of initiating Phase 1 clinical trials is a critical business decision, and exposing that previously confidential information would alter the competitive landscape.

BIO can appreciate FDA's interest in offering information to the public that may increase enrollment in clinical trials. However, that purpose is already being achieved through the existence and expansion of ClinicalTrials.gov, as mandated by FDAAA. FDAAA clearly communicates what clinical trial information Congress believes should appropriately be considered for disclosure. Enacted in September 2007, FDAAA directs that the Secretary, acting through the Director of NIH, to promulgate a regulation within three years of enactment to expand the clinical trials database, a deadline that is two months from the present date. BIO believes that this regulation is a necessary first step in clinical trial transparency, and that FDA should work with NIH to achieve that goal before seeking to expand disclosure and transparency for investigational drugs and in other areas. The NIH rulemaking process should be resolved, in other words, before FDA makes any recommendations about clinical trial transparency.

In enacting FDAAA, Congress carefully considered the balance between public transparency in clinical trial registration and results reporting versus preserving incentives for private sector biomedical research and innovation. However, many of the Draft Proposals appear to disregard this balance and go well beyond the Congressional intent reflected in FDAAA. Specifically, this Draft Proposal could result in disclosure of a broader set of trials than under ClinicalTrials.gov, such as disclosure of all Phase I trials, well beyond what Congress intended through FDAAA. This discrepant scope is all the more reason for FDA to wait until the NIH rulemaking process is complete before issuing its own recommendations.

B. Most Trade Names Do Not Yet Exist at the Time of IND Filing and Disclosure would be Premature:

We are concerned by the provision that the Agency would disclose the proposed proper or trade name of the product, if available. The proper or trade names of the product during early development are likely unavailable but, if a name has been granted, it should not be disclosed. Disclosure of a name at this early point, before FDA approval, could have potential confidentiality, intellectual property, and competitive intelligence implications. In addition, disclosure may cause confusion if a trade name has been sought but is ultimately not approved. Likewise, compelling disclosure of the proper name at this early stage could put the Sponsor at a competitive intelligence or intellectual property disadvantage without benefiting the public. For example, the World Health Organization (WHO) publishes International Nonproprietary Names (INNs) together with chemical information about the drug substance as early as the proposal stage, long before such names are actually granted. With the nonproprietary name in hand, competitors can also readily access detailed information about the chemical structure of the active ingredient, its molecular formula, the identity of the manufacturer, the manufacturer's

internal code designation, and the Chemical Abstracts Service (CAS) registry number from public records of the U.S. Adopted Name (USAN) Council. If this proposal were adopted, we would suggest using the internal reference number or another identifier which cannot as easily be linked to such competitive information.

C. Indications May Change or Become More Refined During Drug Development:

As a Sponsor continues the drug development process for a given investigational product, the indication(s) for that product become more refined. There are instances where Sponsors may stop development for a particular indication yet continue or begin development for other indications. The FDA may not be aware of these adjustments to product indications under development, unless the indications are discussed during milestone meetings. Therefore, the information that the FDA proposes to disclose may not be consistent with the Sponsors' current plan.

Additionally, disclosure would inform competitors of early-stage investigations, indication by indication, before the investigations have started or been otherwise disclosed. Disclosure could therefore lead to potential competitive disadvantages with no corresponding benefits to public health. Indeed, there could be *harm* to public health. Disclosure of new proposed indications of marketed products before any safety data are available for such indications could lead to off-label use without an understanding of the risks of such use, potentially compromising patient safety.

Furthermore, this proposal may be problematic with regard to patent filing, particularly for use patents. Releasing this protected information to the public early in the drug development process could preclude significant patent rights based on the data subsequently generated in the clinical trial and could force manufacturers to file their patents earlier and with less supporting information in order to secure some patent protection. Doing so, however, could put such early filed patents at risk for lack of sufficient support. The result of these patent issues would have a detrimental effect on public health by reducing the incentives for innovation and diminishing research and development into important new medicines.

Draft Proposal #9: FDA should disclose: (1) whether an investigational new drug application (IND) has been placed on hold, terminated, or withdrawn, whether an investigational device exemption (IDE) has been terminated or withdrawn, or whether an investigational exemption for a new animal drug has been terminated and (2) if an IND has previously been placed on hold, whether and when the hold is lifted. A statement should be included that such actions may be taken for various reasons, only some of which relate to safety or effectiveness.

A. This Information is Already Disclosed and Communicated through other Mechanisms:

BIO agrees that the public has an interest in the status of clinical trials, but clinical trial holds, terminations or withdrawals are better communicated through ClinicalTrials.gov than released directly from FDA. Again, this is an area where FDA is proposing to

expend limited funding to duplicate an existing government function. Currently ClinicalTrials.gov provides limited information with regard to enrollment status of a trial. If this information were to be modified to reflect that an IND is on hold, terminated, or withdrawn, caution must be exercised in how this information is communicated to the public to preserve the ability for enrollment in future trials.

The interest in disclosing the existence of an IND hold is strongest when a hold was imposed due to a bona fide safety concern. If the IND has been placed on hold because there are concerns about the safety and/or efficacy of the drug, there are existing mechanisms in place for the appropriate parties to be notified. For an investigational product, a Sponsor is obligated to inform investigators and clinical trial participants via investigator mailings, clinical investigator brochures, and informed consent. For a marketed product under investigation for a new indication, the label can or event must be updated to reflect concerns about safety and/or efficacy. A publicly owned Sponsor also has obligations to disclose material information to the investment community. If, on the other hand, the trial has not yet begun or FDA has placed an IND on hold for reasons other than safety and/or efficacy - reasons that may not be otherwise disclosed - it is unclear why FDA would be disclosing the information to the public.

B. Clinical Holds Occur for a Variety of Reasons and Should be Communicated in Context:

Caution must be exercised here, as there is a great potential for misinterpretation of this information that could undermine patient enrollment in future clinical trials. Clinical holds can happen for many reasons, and a disclaimer or statement may not adequately mitigate the potential for misinterpretations. Disclosure by the FDA that an IND has been placed on hold requires an appreciation for the regulatory context in which such determinations are made. Without that context, such disclosure could have negative public health consequences owing to the potential inability to recruit future clinical trial participants.

Disclosure of withdrawn or "on hold" INDs may compromise patient care. For example, if patients are currently on therapy, physicians may be unwilling to engage in compassionate use in the face of disclosure that such use could not meet the standard of care.

Further, disclosure could have a chilling effect on future development. If the reason for the withdrawal or hold is overcome with time, the stigma of withdrawal could be misconstrued and implications misinterpreted, leading to an unwillingness or inability to pursue further development of the compound.

For these reasons, BIO does not agree that release of this information promotes public health in many instances. If FDA nonetheless decides this information should be released, disclosure of this information should occur through ClinicalTrials.gov. BIO also recommends that FDA convene a group of internal and external stakeholders to review information already disclosed by companies through financial disclosures and ClinicalTrials.gov, in efforts to facilitate a common standard for minimal disclosure, to carefully assess the depth of information to be publicly disclosed, to assess the value of

this information to the public (*i.e.*, is it for the sake of transparency or for intrinsic safety purposes), and to discuss how to assure that such disclosure would not impede future enrollment in clinical trials. Finally, if this proposal were implemented, appropriate resources would need to be assigned to keep the databases updated with the most current information, because disclosure of out-of-date information could lead to public confusion.

<u>Draft Proposal #6:</u> FDA should disclose the name and address of the entity inspected, the date(s) of inspection, type(s) of FDA-regulated product involved, and the final inspectional classification—Official Action Indicated (OAI), Voluntary Action Indicated (VAI), or No Action Indicated (NAI)—for inspections conducted of clinical trial investigators, Institutional Review Boards (IRB), and facilities that manufacture, process, pack, or hold an FDA-regulated product that is currently marketed. The disclosure of this information should be timed so as not to interfere with planned enforcement actions.

A. Disclosure of Location Address Creates a Security Concern:

We are pleased that the Task Force is assessing how disclosure of FDA's inspectional findings can help facilitate transparency within regulated industry, make firms more accountable to the FDA and public at large, and provide an incentive to correct violations.

However, we also believe that certain pieces of information must be redacted to maintain the integrity of the supply chain and to minimize risks of theft and diversion, especially for manufacturers and distributors of controlled substances. Hence, we propose that the FDA redact any information that would publicly disclose, directly or indirectly, site addresses or locations in an effort to safeguard product manufactured or stored at any sites referenced in the report. Such redaction is particularly important in the context of national security and protection against domestic and foreign terrorist activities.

B. Inspectional Classifications Should Be Updated Regularly:

If this provision were to be implemented, it is unclear what process would be used for updating and revising the classifications. If this provision were to be implemented, FDA should establish processes for updating and revising the classifications that would prevent continued posting of out-of-date and therefore misleading information. For example, postings should be removed once the inspectional issue has been resolved, including any potential narrative information provided with the classification.

Additionally, this information has the potential to be misleading and misinterpreted if it is posted too soon. The information should be released only after the Agency has made a final determination and the company has been provided the opportunity to respond to the inspectional findings. The company's response to the inspectional findings should be made public as part of this disclosure.

C. Pre-Market Inspections Should Not be Disclosed:

We note that the proposal covers both pre-approval and post-approval inspections, which are associated with unique considerations. For example, there is a problem with disclosing pre-approval inspection information because of the potential for disclosing confidential information, with the result of placing the sponsor at a competitive disadvantage. The arguments already presented about disclosing information prior to a product's approval, as regards providing advantage to competitors, would apply in this case as well.

Draft Proposal #10: FDA should disclose the fact that an NDA, NADA, ANDA, ANADA, BLA, PMA, or 510(k) application or supplement was submitted (or resubmitted) to the Agency at the time the application is received by FDA. The disclosure should include the name of the application Sponsor, the date the application was received, the proposed indications or intended use of the product, and the proposed proper and/or trade name of the product, if available.

While BIO does not believe this provision provides substantial public health benefit, because this information is regularly disclosed by the company, BIO does not object to disclosure of the existence of marketing applications. However, it would be most beneficial if the disclosure were limited to products for life-threatening conditions.

As with Draft Proposal #8, BIO is concerned about the provision that FDA disclose the proposed or proper trade name of the product, because the proprietary name may not be approved by FDA until late in the review period. Additionally, this disclosure could have potential confidentiality, intellectual property, and competitive intelligence concerns.

Finally, please clarify if this and other Draft Proposals would apply to biosimilar applications filed under Section 351(k) of the FFDCA.

Draft Proposal #11: FDA should disclose that an unapproved NDA, ANDA, NADA, ANADA, BLA, or PMA, or uncleared 510(k) has been withdrawn or, if FDA determines that the application was abandoned, abandoned by the Sponsor. If the drug, biological product, or device is associated with a significant safety concern, FDA should provide a brief description of the product, the use for which approval was sought or obtained, and the identified safety concern.

A. It is Unclear How FDA Determines that a Product has been "Abandoned"

This proposal would enable FDA to disclose publicly when an application has been withdrawn or has been abandoned by the Sponsor. It appears to be at FDA's discretion to determine when a Sponsor has "abandoned" a product application. It is unclear whether FDA will use the criteria in 21 CFR § 814.9(g) to determine if a product application has been "abandoned," or whether the Agency will use some other criteria. Whatever the criteria used, 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.[18, 19]

The above options defining "abandoned," 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 Draft Proposals 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 versus 33% for small biotechnology companies).[20] Any FDA policy aiming for transparency should seek to assure that small biotechnology companies who are filing for the first time are not placed at a disadvantage by the public disclosure of information before a final determination is made by FDA (i.e., after multiple review cycles but review is still on-going).

FDA's failure to adopt appropriate safeguards in defining "abandoned applications" could devalue a small biotechnology's company's only assets, its intellectual property portfolio and drug development data. For example, a small company may receive a Complete Response 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 its ability to successfully bring the product to market.

Finally, providing clarity as to when a product would be classified as discontinued in development would help meet the need of biotechnology companies to plan for public disclosure of information about unapproved products. The ability to plan in this context is essential because this information, once disclosed, may impact research and development and/or fiscal strategies.

B. What Constitutes a "Significant Safety Concern"?

Additionally, we request that FDA clarify what constitutes a "significant safety concern." We encourage FDA to communicate with the Sponsor when making that determination.

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[18] BIO comments on NIH Public Meeting on Expansion of the Clinical Trial Registry and Results Data Bank , April 13, 2009, http://bio.org/healthcare/BIO_Comments_NIH_2009_0002.pdf

[19] NIH Public Meeting on Expansion of the Clinical Trial Registry and Results Data Bank, June 22, 2009, http://bio.org/reg/20090622.pdf

[20] Booz Allen Hamilton, "*Independent Evaluation of FDA's First Cycle Review Performance*", July 2008, http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm127117.htm

<u>Draft Proposal #12:</u> When an application for a designated orphan drug or a designated minor use/minor species animal drug has been withdrawn, terminated, or abandoned, FDA should disclose, if it determines, based on its review, that the application *was not* withdrawn, terminated, or abandoned for safety reasons and the product, if approved, could represent a significant therapeutic advance for a rare disease or for a minor animal species. A disclaimer that provides that FDA's expressed views about the product do not reflect whether a subsequent application involving the product will be accepted for filing or will be approved by FDA should accompany the disclosure of this information.

The biotechnology industry has made a significant contribution to orphan drug research and development over the years. Indeed, the mission of many biotechnology companies is to bring hope to the patients who suffer from rare diseases. Despite our successes over the years, though, there are still estimated 6,000-7,000 rare diseases for which there are no treatments. These diseases affect about 25 million people in the US, as well as another 25-30 million in the EU. Many of these diseases are serious or life threatening. In recent comments to FDA, BIO outlined a number of steps that FDA can take to incentivize further and to facilitate the development of therapies for rare diseases.[21]

The Agency Task Force's Proposal may be another promising mechanism to promote orphan drug development, but as noted under Draft Proposal #11, it is imperative for FDA to clarify how it defines an "abandoned" product application and what constitute "safety reasons."

<u>Draft Proposal #1:</u> FDA should expand the areas in which it provides the public with online access to public information from adverse event reports about FDA-regulated products submitted to FDA, in a format that is searchable and allows users to generate summary reports of this information, including, if known and as applicable, the trade name and/or established name of the product, dosage, route of administration, description of the adverse event, and the health outcome. Adverse event report information should continue to be disclosed with a clear disclaimer about the limits of the information.

BIO recognizes that under current practice spontaneous adverse event data submitted to the Agency are already made publicly available, but the website on which the information is available is difficult to navigate. This proposal would make it easier to search for and obtain information about adverse event reports submitted to FDA. However, increased transparency is only meaningful to the extent that FDA provides full, fair and balanced context for the information to be disclosed. Additionally, we are concerned that there may be the potential to misuse this information, particularly in the absence of established epidemiological standards and best practices.

Information about the safety profile of a product or class of products comes from many different sources, of which spontaneous adverse event reports submitted to the FDA are

[21] BIO comments on Considerations Regarding Food and Drug Administration Review and Regulation of Articles for the Treatment of Rare Diseases, May 31, 2010, http://bio.org/letters/20100531.pdf

only one - and not necessarily reliable at that. Adverse event information can be used to create misleading impressions about the safety profile of a treatment or class of treatments. Interpretation of this information requires particular attention to the regulatory context in which the information is obtained. Spontaneous reporting of adverse events can be highly variable and does not constitute appropriately controlled clinical information on which to base an assessment of whether a particular drug product caused an event. Spontaneous reporting is also limited in usage due to bias in reporting, including incomplete information concerning the patient (that is, unknown medical history), unknown concomitant medications, co-morbid disease states, and under-reporting.

FDA has an important role in protecting public health by disseminating responsible and balanced communications to the public about potential or emerging risks. Balance in communication is achieved by discussing the potential risks in the context of the drug's benefits and also by helping the intended audience understand the context for and limitations of what is known. Public disclosure of risk information before it has been determined to be a real risk may have little effect on improving public trust and may even lead to patients inappropriately discontinuing therapy.

To this end, and as suggested by the Task Force, if this provision is implemented, it is important to have a strong, clear, and understandable disclaimer on these reports. Such a disclaimer would need to explain that: (1) conclusions should not be drawn about the product based on the information in the database because there is no certainty that the reported event was actually caused by the product; (2) limitations exist in calculating the rate of adverse events due to issues related to both the nominator (number or reports received) and the denominator (prevalence of use and exposure); (3) the posting of the information should not lead to any conclusions with regard to FDA's assessment of the reports; and (4) follow-up questions and concerns should be discussed with a patient's healthcare provider. However, BIO remains concerned that even such a strong disclaimer will likely not mitigate the impact of the misperceptions that the adverse event information may cause. The public should not be left with a misinterpretation of product safety based on preliminary adverse event reports.

While it is important to mitigate these concerns, we recognize that there may be a public health benefit to increased transparency surrounding adverse events. In order to enhance pharmacovigilance efforts, the manufacturer name, product ID, and lot number should be included in the database in searchable form to provide capability to trace the adverse events to the manufacturer and the lot number. FDA should continue to review adverse event reports for quality control purposes and to remove personal information prior to posting.

<u>Draft Proposal #3</u>: FDA should disclose when the Department of Justice (DOJ) files a case seeking enforcement on FDA's behalf in the weekly publication, FDA Enforcement Report.

BIO supports the Agency's proposal to include in its FDA Enforcement Report publication notification that the DOJ has filed a case seeking enforcement on the FDA's

behalf. In its implementation of this proposal, however, FDA should ensure that the subject of the enforcement action has received notice of the action before publication in the FDA Enforcement Report.

Draft Proposal #4: FDA should post all Agency Work Plans that are older than 5 years.

BIO supports the Agency's intentions to disclose Work Plans as a means to increase the public's knowledge of FDA, its operations, and how it allocates resources to protect the public health. Disclosure of Agency Work Plans can also serve to improve industry compliance and act as a deterrent to illegal actions. In its analysis regarding this proposal, the Agency noted that Work Plans should be disclosed only after a certain amount of time has passed so individuals could not use the information in the Work Plan to more easily circumvent the law. However, the Agency provided little support for a 5-year delay. If Work Plans are disclosed only when they are so old that the information within is irrelevant, the utility in disclosure is significantly reduced; Agency operations, resource allocations, and priorities are subject to change significantly during a 5-year period. As a result, BIO recommends the Agency disclose Work Plans that are older than 2 years. Agency operations and priorities should remain similar enough over a 2-year period to provide information that is of interest to the public, but at the same time should not provide current details that would be damaging to current enforcement activities. In addition, the deterrent effect of the information would be stronger with more relevant, 2-year information.

Draft Proposal #5: FDA should disclose the outcome of the filer evaluation for importers or third parties working on behalf of importers.

BIO supports this effort to bring more transparency to import and export documentation to provide further assurance of quality and safety of products coming into the country. This information may be useful, especially if third-party prior history were included, but with the important caveat that appropriate protections for trade secret and CCI are in place. We look forward to more clarification regarding the details of the information that is to be made public, such as reasons for denial of importation or the overall outcome of the evaluation.

Draft Proposal #7: FDA should generate, and share with the public, information about the most common inspectional observations of objectionable conditions or practices that are made during inspections of FDA-regulated establishments and post that information online on a regular basis.

In the spirit of continuous improvement to our processes and the quality of our products, we appreciate that summary information provided by the FDA will assist industry in long-term quality improvement and provide insight into potential areas to concentrate additional compliance efforts. We believe it would benefit companies to be aware, in a timely and transparent manner, of the most common inspectional observations of

objectionable conditions or practices that FDA notes during inspections. We believe disclosure would have the most benefit were FDA to provide additional information about its findings, including inspection trends and what particular FDA concerns underlie inspectional observations and other citations.

However, we note that it would be easy to misinterpret the data without appropriate context and without being presented in an impartial manner. BIO suggests that specific information, such as firm names, dates of inspection and other information specific to a company, should not be included in the summary of inspectional observations. Additionally, the information should be separated by type of FDA regulated product (*e.g.*, drug, device, biologic), should be based on trends, and should be presented in proper context, *i.e.*, by providing denominator data in terms of the number of facilities inspected or the percentage of the industry receiving these common violations.

Draft Proposal #18: When a system is set up that provides FDA with authority to require companies to submit certain information to the Agency when they initiate an action to recover or correct a product that is in the chain of distribution, FDA should disclose this information as soon as practicable after receiving this information from the firm.

Since FDA does not currently have mandatory recall authority over drugs and biologics, we remain neutral on this proposal. However, we would like clarification on what kind of information would be disclosed. Typically there are communications between a company and FDA to coordinate activities before a recall is announced and it is unclear if these communications are subject to the disclosure. In light of the potential for "recall fatigue," it is important that only the most important recall information is communicated to the public. We question whether disclosure of FDA-Sponsor communication may detract from key public health messaging.

Draft Proposal #19: If FDA is aware of confusion in the marketplace about products that may be implicated in a food outbreak, and information gathered by industry or other sources may serve to alleviate that confusion, FDA should support efforts by industry and others to communicate information to the public about products that are not subject to the recall when sufficiently reliable information about products not connected with the recall exist, if FDA concludes that disclosure of this information is in the interest of public health.

The potential for confusion about which product or class is subject to a recall or safety concern exists across all FDA regulated products, not just foods. Indeed, poor compliance with FDA regulations by a bad actor can have negative implications for an entire industry or class of products. Therefore, we encourage FDA to include drugs, biologics, and devices in this proposal.

Draft Proposal #20: If FDA determines that a recall is terminated, that information should be disclosed to the public. A recall is considered terminated when FDA

determines that all reasonable efforts have been made to remove or correct the product in accordance with the recall strategy and when it is reasonable to assume that the recalled product has been recovered, corrected, reconditioned, or destroyed.

BIO agrees with this proposal. It seems reasonable that if information is posted about recalls, then information should also be posted in a timely manner regarding termination of a recall.

Draft Proposal #21: FDA should post untitled letters on the FDA Web site, and, if requested by the recipient of the letter, the response to the untitled letter, as appropriate.

Untitled Letters already are often posted in various divisions or centers within the Agency (e.g., DDMAC), but not in other divisions or centers. This proposal would unify Agency practice and might be a useful way to clarify publicly certain issues raised in the letter. We note, however, that the public may not appreciate the distinction between Warning Letters and Untitled Letters. FDA should clearly disclaim that Untitled Letters are far less serious than Warning Letters and do not necessarily demand corrective action or other such responses from recipients.

CONCLUSION:

BIO appreciates this opportunity to comment on the *FDA Transparency Initiative: Draft Proposals for Public Comment Regarding Disclosure Policies*. We would be pleased to provide further input or clarification of our comments, as needed.

Respectfully Submitted,

/S/

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