BIOTECHNOLOGY INDUSTRY ORGANIZATION
1201 Maryland Avenue SW, Suite 900, Washington, DC 20024
202-962-9200, www.bio.org

April 12, 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 Toward Regulated Industry

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to provide recommendations on how the Agency can be more transparent towards regulated industry. We support the goals of this initiative and we are pleased to see the Agency's commitment to advancing the principles of transparency, consistency, and accountability by leveraging modern communication tools and re-evaluating Agency processes. 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 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.

I. TRAINING AND EDUCATION FOR REGULATED INDUSTRY ABOUT THE FDA REGULATORY PROCESS IN GENERAL AND/OR ABOUT SPECIFIC NEW REQUIREMENTS

A. Earlier and More Frequent Communication with First-time Filers

Because ninety percent of BIO's research and development focused healthcare companies are small businesses, we are concerned by 2006 and 2008 Booz Allen Hamilton (BAH) reports that demonstrated lower first-cycle approval rates for small biotechnology companies without prior U.S. approved products. Based on retrospective and prospective analysis of 185 applications submitted between FY2002 and FY2007, experienced sponsors had first-cycle approval rates of 55% compared to 38% for sponsors with no prior approved products. Additionally, larger companies had a 78% first cycle approval rate for Priority Review products, while small companies had only a 48% approval rate.

The BAH report reflects anecdotal experience of members of BIO's Emerging Companies Section (ECS). To more fully quantify ECS members' views, BIO surveyed 163 companies in 2008 regarding their experience with FDA and potential areas of improvement. The BIO survey identified early, frequent and explicit communications with the FDA as the most important actions FDA could take to better assist first-time filers. Among the BIO emerging companies surveyed, 62% indicated the FDA should provide frequent consultations that are informative and clear on what the FDA expects from the first-time filer. The majority of scientific and regulatory personnel surveyed (65%) put a high value on having the opportunity to conduct informal communications with the FDA throughout the development and review process to resolve issues.

Overall, the areas identified as important by the BIO emerging companies' are corroborated by the Booz Allen Hamilton (BAH) report that showed Sponsors who had positive and effective communications with the FDA both early on and throughout the process had higher first-cycle approval rates. Indeed, the importance of frequent and open FDA-Sponsor communication applies equally for all BIO member companies, regardless of size and experience.

B. Additional Educational Resources for Small Businesses and First-time Filers

BIO members – large and small - understand the importance of recruiting highly qualified regulatory staff to help navigate the FDA drug development and review process, but also believes that FDA could assist businesses by ensuring Sponsors have a clear understanding of FDA's expectations throughout the development and review process, including pre-IND meetings.

The CDER Small Business Assistance website could provide additional information that would assist small businesses in improving their interactions with FDA. The website currently contains a vast of amount of important information. Adding information for small businesses on how to ensure formal meetings with the FDA are productive and how to establish a productive communications strategy with their FDA review team would be valuable to small business Sponsors.

BIO members made the following suggestions as to what information would be beneficial to small businesses:

- What expectations are for key meetings during the development and review process; what types of questions should be asked during those meetings;
- What types of questions the Sponsors should address on their own; how to create a check and follow up list with the FDA review team;
- What information should a Sponsor examine to ensure they are able to take advantage of previous studies for the basis of marketing approval;
- Differences in how a small business Sponsors should approach the approval process based on the type of application (i.e. second generation drug/therapy vs. novel drug/therapy); any new information on how FDA views critical drug development issues (clinical trial design, etc.);
- A compilation of practices small business Sponsors should avoid, and a compilation of best practices.

Additionally, it would be beneficial to expand FDA educational seminars for small businesses. These seminars could be used to address five areas critical to small businesses Sponsors:

- How to submit a high quality application;
- Understanding FDA's expectations throughout the review process;
- How to successfully communicate with FDA prior to and during the review process;
- Educational seminars on Good Review Management Principles and Practices (GRMPs); and
- Educational seminars on key drug development issues.

We also suggest FDA provide more training for both large and small companies around specific new requirements or important changes to policy or processes via webinars that allow for open public participation.

C. Online Access to Scientific-basis for Decision-Making

We are pleased that the Task Force is assessing how information technology can help to facilitate transparency towards regulated industry. FDA's website already represents a vast repository of regulatory information and we believe that additional user-friendly online tools can promote a better understanding of FDA's decision-making and requirements, especially in areas where the science is rapidly evolving. For example, the posting of FDA reviews of approved original applications on the Drug@FDA website is very useful. Timely posting of efficacy supplement approval reviews would also be helpful. To further advance understanding of the regulatory system and Agency decision-making, FDA could consider establishing a free and easily accessible database containing the current regulatory basis for all publicly-available decisions and actions (approvals, citizen petitions, guidances, etc.) from a specific time point forward. Building such a public library may be a cornerstone of ensuring Agency consistency, transparency, and

quality decision-making for the present and future. Not only is such a resource of value to the public and industry, but also to FDA staff.

D. FDA Website Enhancements

We suggest that FDA continue to work towards improving its website to make it an effective resource and tool for education. Many frequent users of its website tend to agree that the web architecture that was mandated across FDA in the last few years has not achieved its goal of increasing user friendliness. For example, many useful documents continue to be embedded deep within the website, other documents and pages are duplicative or outdated, organizational information below the Office level is no longer available, and related information and data can be dispersed across several different pages.

We also suggest that FDA update the website on changes in organizational structure, contact information, and personnel in a timely fashion - no more than 30 days after an official change is made.

Finally, FDA should make a concerted effort to ensure its own posting of presentation slides or transcriptions of scientific policy presentations by FDA staff to outside groups in order to ensure fair, open, and equitable access.

II. THE GUIDANCE DEVELOPMENT PROCESS

E. FDA Should Re-Evaluate the Guidance Development Process

Regulatory transparency and clear articulation of FDA's policies and expectations through development and timely publication of guidance documents can help to foster innovation. Yet it takes the Agency long periods of time—often several years—to finalize policy under FDA's guidance development process. The time-consuming and burdensome process also creates a disincentive for FDA to develop guidance in key areas where FDA direction is sorely needed. This creates significant uncertainty for Sponsors, leaving companies to ascertain FDA policy by interpreting agency's regulatory decisions and enforcement actions, which is a less efficient way for industry to understand and meet the Agency's expectations.

To optimize the use of guidances to educate stakeholders on the agency's policies, we ask FDA to review its guidance development process to ensure that adequate resources are provided to facilitate the timely issuance and finalization of guidance documents. In addition, we ask FDA to review its utilization of its guidance process to ensure that there is regulatory transparency, consistency, and predictability to help stakeholders better understand the agency's expectations. To advance public health, FDA should target high-priority disease areas that may be lagging in medical product development and commit to production of guidances following workshop or public meeting sessions to further understand hurdles and concerns.

F. Proposed, Draft, and Obsolete Guidances Should be Revisited on a Regular Basis

To enhance the guidance development process, we suggest that FDA more consistently utilize the Guidance Agenda discussed in the "Transparency in Guidance Development" section of MaPP 4000.2: *Developing and Issuing Guidance,* and include a similar process in CBER SOPP 8002: *Procedures for the Preparation, Routing, and Issuance of Guidances*. The Guidance Agenda issued annually is a very useful tool when employed strategically by the Agency. Unfortunately, it appears that many guidance documents do not develop beyond the agenda listing (e.g. draft guidance regarding requirements for post-approval change in a risk-based environment). As discussed in the following section, additional public consultation regarding the guidance development process may help to prioritize which guidances should be developed.

Second, the guidance development process should include clear timelines and accountabilities. For example, stakeholders should be able to determine the status of a guidance under development. If guidance is in draft longer than 12 months after the close of the comment period, FDA should reopen the comment period so that the final draft reflects the most current knowledge of the subject matter and continues to be relevant. Although not specified as a topic for comment, the same concept should apply to the rulemaking process.

Finally, to address the current backlog, we suggest that FDA formally track Draft Guidance documents. At a fixed period not to exceed 5 years, each Draft Guidance should be re-issued for public comment and either finalized, modified, or withdrawn after the period for public comment.

G. FDA Should Incorporate Additional Public Participation into the Guidance Development Process

Early consultations with industry and other stakeholders are critical to developing successful Guidance. We suggest that FDA open dialogues with industry before beginning to draft new policy to understand the underlying science and technology and practical impacts of potential Agency actions. We support the Agency's increased practice of holding public workshops to discuss and/or present a draft of a guidance document to an Advisory Committee when highly controversial or unusually complex new scientific issues exist. We strongly suggest that FDA should continue and build upon this type of public dialogue.

H. Education and Training on New Guidances

We also suggest that training and education should be part of the guidance implementation process. Training on new guidelines should not only restricted to Industry, but also include regulators. It is also important that there be an opportunity for Industry to ask questions regarding new guidelines or expected regulatory practices. Responses to Industry questions should be addressed through an appropriate forum that

engages all relevant stakeholders and provides a consolidated, universal response within an acceptable time frame.

III. MAINTAINING OPEN CHANNELS OF COMMUNICATION WITH INDUSTRY ROUTINELY AND DURING CRISES

Given the critical importance of communication throughout product life cycle, we would like to better understand the interactions between OND and the Office of Surveillance and Epidemiology (OSE) and how differing pre and post approval safety interpretations are resolved both internally and with external stakeholders. We recommend that FDA utilize a clear and efficient escalation and decision making process with a well articulated and transparent method for individuals who have differing opinions to voice their concerns so that FDA managers can make a decision based on the available scientific data. We also request that prior to a public communication, FDA share confirmatory analyses and study methodologies with the Sponsor so that the company can fully understand the scientific context of the safety signal, and further evaluate it if necessary.

I. FDA Should Coordinate with Sponsors Prior to a Public Safety Notification

Adequate communication among FDA, regulated industry, and the public is a critical component of an FDA public health intervention. In the event of a safety issue or enforcement action, 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. We suggest FDA engage with Sponsors at least 48-72 hours in advance of communicating emerging safety information or results of manufacturing site inspections (Form 483) to the public. Companies need to prepare to respond to inquiries from media, international health authorities, advocacy groups, and consumers that will be triggered by FDA public announcements.

For example, although MAPP 6700.4 states the Office of New Drugs (OND) safety regulatory project manager will notify the Sponsor once a DARRTS Tracked Safety Issue (TSI) has been created, it does not state that FDA will communicate to the Sponsor regarding FDA web posting of alerts or communication on this topic. In addition, MAPP 4151.6 on the Drug Safety Newsletter states that Sponsors of products discussed in the newsletter will be notified by fax only 24 hours before posting of the newsletter. There is need for more communication and coordination between FDA and Sponsors to minimize the potential for conflicting information and provide multiple channels of communication to better inform patients and physicians.

J. Changes in Policy Should be Communicated Before Implementation

As a regulatory agency in the possession of confidential and trade secret Industry information and with the authority to take enforcement action, it is of paramount

importance to Industry that the FDA clearly communicate policy changes before implementing them. BIO members have noted instances in recent months when the Agency has implemented new policies without first communicating them to Industry or the public. For example, the Agency has made a company response to a Warning Letter publicly available in a manner contrary to prior Agency policy as described in the Regulatory Procedures Manual, Section 4-1-8 (March 2010). Additionally, FDA's issuance of 14 Untitled Letters to biopharmaceutical manufacturers in March 2009, citing sponsored links on Internet search engines, has led to considerable confusion in the area of internet and social media promotion and has reduced the helpfulness of sponsored links for patients and healthcare providers. This confusion could have been avoided through clear articulation of FDA policy in this area.

IV. PROVIDING USEFUL AND TIMELY ANSWERS TO INDUSTRY QUESTIONS ABOUT SPECIFIC REGULATORY ISSUES

K. Meetings and Scientific Dialogue with Sponsors Promote Transparency

As noted previously, a critical area that deserves greater transparency and consistency is FDA's interaction with drug and biologics manufacturers at various stages across a product's life-cycle. To promote the advancement of new cures, we must reiterate the importance of technical expert-to-expert meetings between FDA and Sponsors early and often in the development and review process. However, we are concerned that in a recent survey of BIO's membership, half of respondents suggested that requested meetings are not being granted on a consistent basis and responses to questions are delayed in some instances for several months. We hope to work with FDA to identify and minimize barriers to granting meeting requests.

Moreover, in meetings with Sponsors we encourage FDA to communicate recommendations clearly and precisely so that Sponsors can more effectively consider the issues raised or act upon them. It is also just as important for Sponsors to clearly communicate and track issues raised in meetings.

L. A Common Understanding of the Basis for Special Protocol Assessment (SPA) Agreements will Enhance the Value of the Process

Additionally, Sponsors would also appreciate greater understanding of the SPA process and improved consistency across review divisions regarding the level of granularity and detail needed to reach agreement on a protocol. For example, will the division agree upon the general protocol framework or do the reviewers need to approve all of the study tools, such as the case report forms and Statistical Analysis Plan? Transparency, consistency, and predictability in the SPA review would maximize the value of the process to Sponsors and minimize the potential for multiple SPA review cycles.

V. COMMUNICATING WITH SPONSORS DURING REVIEW OF APPLICATIONS

M. Implementation of GRMPs Can Enhance Consistency Across Review Divisions

We also note that FDA drug and biologics review processes can be inconsistent across different review divisions. For example, many review divisions appear to have differing informal criteria for meeting with Sponsors, requesting clinical data, and interacting with Sponsors during the review process. This can lead to difficulty anticipating FDA regulatory expectations and uncertainty for Sponsors. We are pleased to see FDA managers implementing the Agency's Good Review Management Practices and Principles through the *21st Century Review Program* and establishing timelines and milestones for certain Sponsor-FDA interactions. We encourage FDA to continue to fully implement and adhere to the 21st Century Review Program, which will encourage greater consistency and predictability in the review process as part of a clear and transparent regulatory decision making process.

N. Inconsistencies in Regulatory Practices Persist

Transparency is promoted through both consistent adherence to review milestones and consistent application of regulatory practices. For example, BIO's members report that FDA reviewers occasionally provide different and seemingly inconsistent comments on the same or related issues, and the reason for those differences or inconsistencies in answers is not always apparent. We understand that if a specific company experiences such inconsistencies, the company can always ask FDA to provide a reason for its comments and it may be possible to address the issue at the project level. However, we would welcome and we encourage FDA to provide companies more information about the process FDA uses to assure review consistency.

O. Enhanced Communication Tools Should Be Sought for Simple or Clarifying Questions

BIO members fully understand that questions asked to a review division in the context of a formal meeting request are likely to be answered in a predictable timeframe due to the PDUFA goals associated with Type A, B, and C formal meetings. However, in the course of drug development and during application review, a Sponsor might have a relatively simple or clarifying question that could have significant impact on the development program or information provided in response to an Information Request, but is not sufficient in itself to warrant a formal meeting request. Currently, no system exists to track or incentivize timely responses to such questions posed to review divisions. Response time varies significantly across review divisions and among review teams, from hours to even years. We recommend that the Agency partner with Industry to develop an avenue for such informal communications, including a two-way dialogue in the resolution of more complex or controversial issues, to reduce the impact on development programs, provide more predictability and transparency in communications, and provide incentives to Industry to use a less burdensome route than requesting a formal meeting.

P. FDA-Sponsor Communication Regarding Product Review Status Should Be Improved

We also believe that FDA can be more responsive to communications and inquiries regarding application review status. The FDA project management staff are responsible for managing communication with the applicant, but are sometimes not responsive to calls or emails, or are unwilling to engage an applicant during the review until an FDA action is taken. We request that FDA provide review staff, especially project management staff, with training in communication during review of applications, and provide applicants with a better understanding of what information to expect – and when – during the review. Also, an ongoing pre-established timeframe should be instituted to provide timely scientific discipline clarifications as part of the review process, such as a regular weekly or biweekly call which can be cancelled when not needed.

We also suggest that FDA provide modern communications tools to enable routine communication between applicants and project management staff. For example, we note that other industry groups have proposed the development of an electronic, real time application tracking system.[1] We believe that this capability may provide value to Sponsors if the tracking system is set up in such a way that it allows companies to monitor the status of the review as it moves through the GRMP milestones established under the *21st Century Review Program.* However, given the importance of protecting competitive and confidential commercial information, it is imperative that such a system provide access only to the Sponsor and be operated under strict security guidelines. The implementation of any such system could be conditioned on (1) the existence, and FDA's acquisition of, appropriate technology with all necessary firewalls; (2) an extensive public workshop and comment process; (3) the execution of a thorough and well-designed pilot program; and/or (4) FDA agreeing to assist in bringing all available sanctions in the case of any such breach.

While FDA is currently in the process of developing a capacity for electronic two-way regulatory correspondence, many FDA regulatory actions are currently being conducted via paper. However, the Agency is not consistently providing rapid communication of action letters to applicants. In certain review areas, FDA staff is not willing to fax or email a copy of a signed action letter to the applicant before processing the letter through regular mail, and additionally refuse to inform the applicant of the outcome until the letter arrives in the mail. It can often take one week or more for the applicant to receive the action letter through regular mail. Technology exists to avoid these delays in communication and the time and effort required to provide this rapid notification via email or fax is minimal and seems justified.

Q. Advisory Committee Meetings

In recent years, FDA has increasingly turned to Advisory Committees for guidance regarding key safety concerns, yet FDA conclusions over safety findings or interpretations that differ significantly from those of the Sponsor are not consistently

[1] Plasma Protein Therapeutics Association (PPTA), Comments to the FDA Transparency Task Force Public Meeting, August 9, 2009, www.pptaglobal.org/UserFiles/file/FDAA09011_Transparency%20task%20force.pdf

being shared with the Sponsor in a timely fashion prior to the meeting. This can be especially problematic if the agency determines a REMS is necessary yet there has been no or little dialog about what would be appropriate measures until or at the action date.

We suggest that FDA communicate to the Sponsor well in advance the issues, concerns, arguments it will raise with the Committee, so the Sponsor can be prepared to address those issues and the Committee Members can provide well-informed advice. We ask that the questions to be asked of the Committee be formulated and presented to the Sponsor, with the briefing materials, at least two weeks in advance of the Advisory Committee meeting. Also, we suggest a policy that FDA review division management and review staff meet with the Sponsor before any Advisory Committee meeting to iron out differences regarding data and methodology, so the Committee can focus where their advice is most needed instead of on trying to figure out which analyses are reliable. In addition, we ask FDA to share its presentation in advance with the Sponsor. Access to these materials fosters the opportunity for meaningful company analysis and preparation, without which a well-organized, thoughtful, and targeted presentation becomes difficult at best. By allowing for informed presentations, access to these materials maximizes the benefits of the Advisory Committee process.

CONCLUSION:

BIO appreciates this opportunity to comment to the Transparency Task Force. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Andrew J. Emmett, MPH
Director for Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)