Biotechnology Industry Organization

December 4, 2014

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

Re: Docket No. FDA–2014–N–1698: Food and Drug Administration Activities for Patient Participation in Medical Product Discussions; Establishment of a Public Docket

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on potential strategies to enhance patient participation in drug and biologic development discussions. The future of drug development will require active collaboration and cooperation between FDA, drug Sponsors, and, most importantly, patients to better understand patient perspectives and views on study designs, meaningful clinical outcomes, and benefit/risk determinations. Methods for soliciting the views of patients, as well as their caregivers and healthcare providers, should be further evolved into data-driven mechanisms for conveying the patient perspective and preferences at all stages of the drug development process.

BIO represents nearly 1,000 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.

While BIO understands that the scope of this *Federal Register* notice is primarily focused on the use of patient representatives as Special Government Employees (SGEs), our comments focus more broadly on the evolving science of assessments of patient preference and other health outcomes, as well as a framework for integrating the patient voice into all stages of drug development. An important advantage of the current process of relying upon a single patient representative is a streamlined and simple process that eases implementation. However, the drawback is that a single patient chosen at random may be unable to provide the views of large, often heterogeneous patient populations. New methodologies should be adopted in order to assess the views of broad patient constituencies in a timely, systematic, and structured fashion and to integrate the feedback into drug development and FDA regulatory decision-making.

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I. Background

Patient perspectives can provide valuable input to drug development on how to develop clinical trial programs that can improve the efficiency and effectiveness of clinical research and address other issues that are important and relevant to patients. We encourage FDA to work with patients, patient advocates, and industry to ensure that patient views are considered during medical product development and post-marketing so that the products will address the needs and preferences of patients to the extent possible, and to ensure the necessary information for patients about what they should expect from medical products is available once products are marketed.

Patient views on benefit/risk can be sophisticated and nuanced. Their views may be influenced by a number of factors, including the context of the patient's prior experiences with therapies, disease severity, progression, and available therapeutic options, life circumstances, as well as individual risk tolerances. Patients may express either a higher threshold for tolerating potential risks or scientific uncertainty in exchange for benefit, or conversely, a lower threshold if there is no perceived benefit. Such quantitative and qualitative patient feedback should be captured in a systematic process to help inform drug development, the review process, and the selection of risks and perceived benefits. However, there is a lack of guidance or general consensus from a regulatory perspective regarding the process, and further development of tools and methodologies for assessing patient preferences and documenting patient experiences in a manner that efficiently produces high quality data.

To address the need for a framework to incorporating patient perspectives and the information needs of patients into medical product development, the FDA Centers for Drug Evaluation and Research (CDER) and Biologics Evaluation and Research (CBER) initiated, as part of PDUFA V, a Patient-Focused Drug Development Program (PFDD). As part of PFDD, FDA is conducting a series of public workshops to solicit from patients what it is like to live with and undergo treatment for one of 20 diseases selected by FDA, capturing their perspectives on the disease, its severity, its impact on daily life, the desired effect of treatment, benefit/risk and other issues that are beyond what is traditionally captured by clinical trials. To date, FDA has conducted more than ten PFDD workshops and has posted or is preparing a summary of each workshop in a "Voice of the Patient" report that summarizes the input provided by patients and patient representatives. The next step is a reflection of the patient feedback into the requirements for the degree of evidence required for approval, and incorporation of the feedback as part of the structured benefit/risk framework.

CDER and CBER's Structured Benefit/Risk Framework may play an important role in ensuring that patient feedback is considered when FDA is making approval decisions and communicating how reviewers weighed a product's benefits and risks so that FDA staff and external stakeholders can understand how any potential benefit/risk value judgments were incorporated into the broader decision, based upon the body of scientific evidence.

CDER and CBER's PFDD meetings and Voice of the Patient reports are valuable and potentially a necessary first step, yet these reports do not address how FDA has or will use the information gleaned from PFDD meetings in revising policy, establishing

guidance, or ensuring that patient views are considered during regulatory review of individual product development programs. It is critical that patients, industry, and the FDA advance the PFDD program. In its current form, the feedback from PFDD meetings is periodic, anecdotal, and not scalable to the thousands of diseases afflicting patients and the ever changing healthcare environment. To truly incorporate the patients' perspective throughout medical product development, FDA needs ongoing processes to solicit patient perspectives at each stage of development in a manner that is structured, systematic, and scalable with a more apparent link to informing FDA's regulatory decision-making.

In parallel with CDER and CBER's PFDD effort, the FDA Center for Devices and Radiological Health (CDRH) initiated a Patient Preference Initiative[i], intended to consider the roles of formal measurements of patient preferences in medical device development and regulatory review. To support this initiative, CDRH actively participates in and provides funds for a public private partnership, the Medical Device Innovation Consortium (MDIC)[ii], which includes a project to develop a framework for the assessment and use of patient preferences in device regulatory review. While BIO's focus is not on medical devices, the framework being developed by MDIC may have considerable applicability to drugs and biologics.

While PDUFA V has made major strides in providing FDA with access to the patient voice, it is unclear how the feedback from PFDD meetings will be incorporated into individual product development programs. Ideally, representative patient input would be considered when clinical trials are being designed and throughout drug development. To do so, BIO offers several recommendations on how we together can advance the integration of the experiences, preferences, and values of patients into medical product regulation through FDA's direct engagement with patients throughout drug development.

II. A Partnership to Advance the Science of Patient Preference Assessment in Support of FDA Regulatory Decision-Making

To more fully integrate patient perspectives in medical product regulation, BIO recommends the establishment of public-private partnerships (PPP) to provide ongoing forums for dialog between patients, industry, clinicians, the scientific community and FDA. The PPP would also develop methodologies and study protocols for surveying patients for their views of their conditions and benefit-risk assessment and would serve as a shared infrastructure for conducting these studies on a voluntary basis. The overarching goal of the PPP would be to move away from the public meetings and anecdotes as a primary source of patient input to a standardized, repeatable, and representative pre-competitive data collection model that could be used across FDA divisions.

The approach taken by CDRH in using MDIC to collaborate with industry, academics and patient groups for developing a patient preference focused benefit-risk framework is an example of one such PPP. Other existing forums, such as the C-PATH Patient-Reported Outcome (PRO) Consortium, other C-PATH Consortia, the Patient-Centered Outcomes Research Institute (PCORI) or other disease-focused consortia could be expanded to include patients as key participants and to embrace dialogue between patients, industry,

and FDA; or a new PPP could be developed. We encourage CDER and CBER to build on experience with such existing PPPs, including consulting with CDRH about their work with MDIC.

The data developed through the partnership forum or patient preference assessments would be viewed as representative of a patient population and incorporated into the benefit-risk framework in a visible way and actively considered by FDA reviewers in the overall regulatory decision making process. In situations where the balance of benefit-risk associated with a medicinal product may not be apparent, and views may vary among different stakeholders (*e.g.*, FDA reviewers, key opinion leaders, and sponsors), then such a framework would be desirable to describe and incorporate patient preferences into the decision-making process, with the advantage of transparency and consistency as compared with a simple qualitative conclusion.

In order to further advance the science of patient preference assessment, the PPP could be tasked with leading the following activities:

- *Evolve the Methods and Tools for Patient Outcomes Assessments*: The partnership would engage with academia, government, patient groups, and Sponsors to catalogue and further develop the scientific methodologies, survey tools, and supporting information technologies for conducting patient preference studies in a manner that is scalable across multiple therapeutic areas. These methods may include both quantitative and less structured, more flexible qualitative approaches.

- *Establish a Shared Infrastructure to Conduct Patient Outcomes Assessments:* The partnership would serve as a common, shared infrastructure to pool funds from multiple stakeholders to conduct larger scale and higher quality patient preference studies than can reasonably be conducted by a single Sponsor or patient advocacy group. With the use of world-class experts to help design, conduct, and analyze the results, many of the limitations of currently conducted preference studies could be overcome. These studies also could be integrated into new versions of PFDD meetings that make use of structured data in the preparation for and conduct of the meetings. The results of the program could serve the needs of regulators, patients, Sponsors, payers, and physicians.

- *Best Practice Guidelines for Patient Preference Assessment Studies*: The PPP would develop recommendations to FDA on best practices for conducting patient outcomes studies to help guide regulatory decision-making. Based on those recommendations, we suggest that FDA CDER/CBER issue guidance within two years on best practices for studies to gain insight from patients about outcomes and preferences, the process and timeframe for submitting that data, and how the data resulting from the studies will be used to inform individual product development programs and FDA's marketing approval decisions. This CDER/CBER guidance could in part be based on a similar guidance planned by CDRH for early 2015. We also suggest that the guidance describe how PROs will be evaluated against other clinical endpoints, either in the context of important clinical benefits or in the context of benefit-risk tradeoffs, should other clinical endpoints be considered important by FDA or key opinion leaders.

- *Evolution of the PFDD Meetings Process*: Per the criteria outlined below in Section VIII, the PPP could work with patient advocacy groups with experience in benefit/risk (*e.g.*, National Health Council, FasterCures, National Organization for Rare Disorders (NORD), Parent Project Muscular Dystrophy, diaTribe) to develop a draft guidance for FDA consideration on how patient-focused drug development meetings run by patient organizations or other external groups can be conducted most effectively, as well as what deliverables would be of greatest value in each stage of drug development to inform FDA's regulatory decision-making. Precedent in this area includes the Parent Project on Muscular Dystrophy draft guidance on clinical trials for Duchenne Muscular Dystrophy. Since the meetings will be run by non-FDA organizations, there is the opportunity to extend and improve the meetings in a fashion that is currently not feasible for the FDA, such as incorporating structured data gathering before the meeting and using those results within the meeting. Special attention must be taken by non-FDA organizations in planning such meetings or in the development of disease-specific guidance to ensure all relevant stakeholders have an opportunity to participate in a balanced, transparent, and open discussion.

III. A Framework for Patient Engagement during Drug Development

In addition to patient preference assessment, we encourage FDA, industry and patient groups to develop a process for patient organizations to provide input relevant to drug development to industry and FDA that is representative of a patient population. This could include information about their condition in general and on clinical trial design and operation. FDA's efforts to engage with patients must ensure that information about the impact of treatments on symptoms (disease- and treatment-related), on broader concepts of relevance in individual diseases (*e.g.,* functioning, and on patient preferences) are identified and provided to patients in product labeling or patient educational materials.

The recommendations for these processes would build upon similar work already being conducted by the National Health Council, NORD, FasterCures[iii], and MDIC.[iv,v] Such a framework could help facilitate patient involvement earlier in drug development and inform key decisions about a particular development program, such as more effective study recruitment and enrollment strategies, the development of surrogate or intermediate clinical endpoints, and the establishment of qualified patient-reported outcomes.

FDA should continue to improve upon mechanisms for accessing external patient perspectives during the FDA review phase while integrating a revised framework for systematically incorporating patient views into the development process. As described below, appropriate safeguards would be established to protect confidential commercial information and intellectual property prior to FDA approval.

The information FDA collects from patients during drug development should be shared with sponsors as the recommendations may be incorporated in ongoing development programs. We recommend FDA institute a process to share the collected information within 60 days of FDA receipt of the information.

Similarly, the patient perspective data collection mechanism and a description of how the data was used should be included as a specific section in the FDA review document.

IV. Earlier Use of the Structured Benefit/Risk Framework during Drug Development

Such a process for early patient engagement in drug development could also harness FDA's existing Structured Benefit/Risk Framework. FDA has made considerable progress in implementing its structured Benefit/Risk Framework and is expected to include completed frameworks with NME approval decisions in the coming year. The framework serves as a simple tool to communicate the nature of benefit-risk decisions, and establish a common understanding of a product's benefit-risk profile across the continuum of drug development. As FDA continues to gain experience applying the framework at the time of approval, we welcome an ongoing dialogue around opportunities to use the framework at earlier stages of the review process, including Advisory Committee and late-cycle meetings.

Sponsors should also consider proactively reaching out to patient groups to populate the "Analysis of Condition" and "Current Treatment Options" domains of the structured benefit/risk framework during drug development, and where possible and appropriate, incorporate data from patient preference assessments, including patient views on overall benefit/risk.

Ultimately, Sponsors and FDA should consider comprehensively incorporating these steps into the process, both during drug development and at key development meetings—such as Pre-IND, EOP2, and Pre-NDA/BLA—to align on key issues on the analysis of the condition, current treatment options, benefits, and risks. Best practices or a common process should also be established for Sponsors to submit completed frameworks to FDA as part of the NDA/BLA submission in an appropriate section of the electronic Common Technical Document (eCTD), a topic that is in part being considered by an ICH expert working group in 2014-2015.

V. Clarify Federal Policy on Patient Engagement

One perceived barrier to industry engagement with patient groups during drug development is that FDA may interpret such dialogue as promotion of an investigational product. We request that FDA clarify its policies on Sponsor outreach to patient groups in order to better understand the Agency's perspectives on the design and conduct of a particular clinical development program and/or its perspectives on whether outreach on benefit-risk and meaningful clinical outcomes do or do not constitute promotion or marketing of an unapproved investigational product or indication subject to enforcement. Further, we request that FDA issue guidance describing the appropriate parameters and regulatory/legal safe-harbor for Sponsor engagement with patient groups during drug development.

VI. PROs and Labeling

We urge an ongoing dialogue between FDA and stakeholders to ensure that important patient information about medical products is available to patients, their families, and healthcare providers.

FDA's PRO guidance encourages medical product developers to focus PRO assessment on outcomes important to patients, however much of the PRO data collected in clinical trials is not incorporated in product labeling. Consequently, a disconnect persists between important information for patients and what sponsors can share with patients and medical care providers about treatment alternatives based on their studies. This raises concerns about clinical trial transparency as well as about FDA's willingness to provide important information to patients in approved medical product labeling. Additionally, avenues for communication of these data either within, or independently of, product label should be transparent. FDA's processes test whether patient-directed information is understandable to patients, but not whether the information patients seek is available for their health care decision-making.

We therefore suggest that the PPP and patient groups identify whether currently available patient-directed information in approved product labelling and patient packaging information provides the information patients need, and develop a document for FDA consideration that includes proposed FDA policies and practices to ensure that necessary information for patients about what they should expect from medical products is available once products are marketed.

VII. Expand the Use of SGEs to Solicit Patient Views during Drug Development, FDA Review and After Products are Marketed

While BIO believes that broad, data-driven surveys and studies of patient preferences and perspectives across a broad constituency of patients may provide the most representative feedback of patients' views, there continues to be a role for greater input by patient special government employees. For example, patient SGEs play a unique role in reviewing confidential information related to an ongoing development program or pending application, or to take on specific assignments or "homework" to help support the review from a patient perspective.

BIO would welcome more elaborative discussion in the FDA's guidance document regarding how to balance the roles of preference views from a broader patient population and patient SGEs in the regulatory decision making that ensures consistency and transparency from a process perspective.

We suggest that the PPP could work with industry and patient advocacy groups to develop a draft guidance for FDA consideration on best practices for the identification, selection, and use of patients to serve as special government employees to consult with the Agency during product development, FDA review, and once products are on the market. We are encouraged by FDA's willingness to leverage the experience of patient advocacy groups and that in time, more patient SGEs will have the qualifications to participate in technical product discussions. Best practices should include training for

SGEs that would establish guidelines for when a patient SGE should refrain from participating in discussions outside of their expertise.

Patient SGEs may also contribute to FDA's direct engagement with patient groups. For example, patient SGEs might help identify patients that are able to provide input representative of the breadth of the patient population throughout the regulatory process. This could help both FDA reviewers and industry understand the needs and concerns of patients living with diseases targeted for medical product development. FDA's Professional Affairs and Stakeholder Engagement staff[vi] should be involved to provide patient SGEs with training in FDA requirements and good regulatory review procedures, and the identification and dissemination of best practices by patient SGEs about how to effectively contribute to the regulatory review process.

Given that many of the best experts in a particular disease may have affiliations with industry, the requirement that patient representatives have no industry connections or financial partnerships should be revisited. This approach excludes those patients typically most informed about their disease, the drug/device development process, and the efforts of patient advocacy groups. Sophisticated patient advocacy organizations have established governance processes and outreach structures which help to ensure that their patient representative is speaking credibly on behalf of their own patient constituency, rather than a single unaffiliated patient chosen by chance. We suggest a "transparency" or "sunshine" approach similar to that used for publications in peer-reviewed journals and participation on an FDA Advisory Committee be applied to patient SGEs. Authors and participants may have industry ties but must be explicit about them and recuse themselves when appropriate.

Additionally, the FDA system for identifying, confirming, and screening patient SGEs should be revamped to ensure the increasing requests for their participation can be fulfilled in a timeframe consistent with the review performance goals under PDUFA V. A process to facilitate timely input is important in general, but particularly important for diseases where there is limited disease-specific experience within the Agency. The process should enable reviewers to either get input prior to Type A, B, or C meeting, or to have an SGE present at the meetings in compliance with the current PDUFA meeting timelines. BIO recommends the following:

- Automating the process for requesting, identifying, and, when necessary, renewing patient SGEs or screening for specific conflicts in particular for INDs for unmet medical needs. Automating the process may alleviate the current time constraint challenges;

- Obtaining timely patient feedback is critical to ensure the feedback can be shared with the sponsor and incorporated into the development program. Include a specific section on patient feedback/input in the FDA minutes of meetings discussing treatment for unmet medical needs;

- Develop a communication framework to ensure the Office of Health and Constituent Affairs has adequate time to identify appropriate SGEs (*i.e.*, patients or caregivers that have experience with the disease that is the topic of the meeting);

- Clarify the conflict-of-interest policy rules for patient representatives, in particular the inclusion and exclusion criteria regarding participation in clinical trials, leadership role within advocacy organizations, relationships with industry, and the SGE's public policy position;

- Leverage industry's knowledge of patient recruitment by requesting SGE nominations from the general public, including industry; and

- Identify the requirements to qualify as an essential patient and clarify what types of information are necessary for patient representatives to obtain a conflict waiver related to particular matters. Patient perspectives are valuable for the development of all drugs, but are most valuable for poorly understood rare diseases. For many rare diseases, the patient populations are very limited and frequently all patients/potential SGEs with very rare diseases may be leaders of a patient organization. Consequently, many patients and caregivers have conflicts due to their role on patient advocacy organizations or as advisors to industry on development programs. Identification of the requirements to qualify as an essential patient may increase the success of granting essential patients conflict waivers.

VIII. Protection of Confidential Commercial Information

It is important that engagement between patient groups, industry, and FDA be conducted in such a manner that does not undermine a firm's competitive standing in the marketplace and appropriately protects confidential commercial information (CCI) and trade secrets. This could be achieved through the use of non-disclosure agreements and/or a prospective agreement of which non-competitive topics would be covered in the discussion.

IX. Conclusion

BIO appreciates this opportunity to comment on FDA activities for patient participation in medical product discussions. By incorporating patient input at each stage of the process in a transparent and structured manner, we can help to align drug development and FDA review toward the medical outcomes of greatest interest to patients and their caregivers that we all serve. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

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

REFERENCES:

[i] FDA website: Public Workshop - The Patient Preference Initiative: Incorporating Patient Preference Information into the Medical Device Regulatory Processes, September 18-19, 2013 http://www.fda.gov/medicaldevices/newsevents/workshopsconferences/ucm361864.htm

[ii] Medical Device Innovation Consortium website: http://mdic.org/

[iii] FasterCures website: http://www.fastercures.org/r-and-d-policy/benefit-risk-assessment/

[iv] Medical Device Innovation Consortium, *Patient Centered Benefit-Risk Assessments (PCBR)*, http://mdic.org/projects/pcbr/

[v] National Health Council, Statement for the Record, 21st Century Cures Initiative Hearing, July 11, 2014, www.nationalhealthcouncil.org/NHC_Files/Pdf_Files/NHC-21stCenturyCuresInitiative-Patient_Engagement.pdf

[vi] Professional Affairs and Stakeholder Engagement website: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm385522.htm