Biotechnology Industry Organization

August 17, 2015

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

Re: Docket No. FDA–2015-D-1580: Patient Preference Information—Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and *De Novo* Requests, and Inclusion in Device Labeling; Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders; Availability

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance for Industry, FDA Staff and Other Stakeholders entitled "Patient Preference Information – Submission, Review in PMAs, HDE Applications, and *De Novo* Requests, and Inclusion in Device Labeling."

BIO is the world's largest trade association representing 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.

BIO welcomes this guidance and applauds the Center for Devices and Radiological Health (CDRH) for a thoughtful and well-written Draft Guidance. BIO strongly agrees that "...patients can and should bring their own experiences to bear in helping the Agency evaluate the benefit-risk profile of certain devices." Patient preferences provide invaluable input into clinical development programs that can improve both the efficiency and effectiveness of clinical research, as well as address the issues that are most important to patients.

BIO also acknowledges CDRH's efforts to provide transparency regarding how patient preference information will be incorporated into regulatory decision-making, particularly regarding benefit-risk assessments. We fully support continued efforts by the Agency to provide stakeholders with additional clarity in this important and evolving area of regulatory science.

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A. *Advancing the Science of Patient Preference Assessment*

As the science of collecting patient preference information evolves and matures, it is essential for FDA and stakeholders to work together to drive the process forward: from an ad hoc and anecdote-driven approach to a robust, systematic, and data-driven process that occurs throughout the drug development and review lifecycle. To incorporate the patient perspective more effectively throughout medical product development, it is crucial that FDA and industry evaluate and utilize appropriate scientifically robust methodologies for assessing patient views and perspectives and leverage FDA's structured benefit/risk framework throughout a therapy's lifecycle. This guidance makes significant contributions to the field by providing clear recommendations as to how this patient preference information can be collected and incorporated into regulatory decision-making.

B. *Applicability of Patient Assessment Methodologies to Drugs and Biologics*

The Draft Guidance states that "Because the mechanism of action for devices is often well-characterized and fairly localized, patient preference information may be more practical to obtain for devices than for pharmaceutical or biologic treatments, where more systemic effects occur and off-target adverse effects may not always be comprehensively anticipated." We respectfully disagree with this statement. While we acknowledge that at times it may be more practical or feasible to incorporate patient preferences into the design of a medical device over drugs and biologics (due to biological and scientific constraints), the framework developed by the Medical Device Innovation Consortium (MDIC) and CDRH and implemented in this Draft Guidance has considerable applicability to drug and biologic development.[1] The integration of patient preference information in the review of drugs and biologics is an area of urgent need for regulatory guidance.

The study methodologies proposed in the guidance, such as stated-preference (SP) and revealed preference (RP) methods apply equally to understanding of patients' views of unmet medical need, perceived benefit, and risk tolerance. Regardless of whether systemic effects and off-target adverse events occur more often in drug and biologic treatments than in devices, the value and need for assessing patient preference information is just as important for drug and biologics as it is with medical devices.[2] In fact, there are numerous examples in the scientific literature of how these survey methods can be utilized to assess patients' views on drugs and biologics.[3]

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[1] MDIC's report "A Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technology" supports BIO's viewpoint, stating that "Given MDIC's focus on regulatory science related to medical devices, this Framework Report has focused on how patient preference information might be used in the regulation of medical devices. Yet such preference information may be valuable in the regulation of pharmaceuticals and biologics as well (p. 85)." The report also touts the approach to developing patient preference information on Duchene's Muscular Dystrophy taken by the Parent Project Muscular Dystrophy as a good example of how this kind of information can be used to inform regulatory decision-making.

[2] The study methodologies proposed in the MDIC report provide the basis for the methodology recommendations in the draft guidance and "should be of value interested in collecting patient preferences regarding the use of pharmaceuticals and biologics (p. 85)."

[3] In Section IV "Recommended Qualities of Patient Preference Studies," the Agency references literature related to quantifying and collecting patient preference information that supports the use of this information in drug and

We encourage CDRH to work with their colleagues in the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) to share its considerable experience working with public-private partnerships (PPPs) and developing comprehensive patient preference guidelines. We further request that CDRH provide CDER and CBER with information on the available, scientifically-robust tools and methodologies to collect patient preference information for use in regulatory decision-making.

C. Combination Products

As the state of biomedical science evolves, we are witnessing a growing convergence between biotherapeutics and medical devices, including novel delivery systems, diagnostics, and combination products. In line with the comments above, we also recommend that the guidance include considerations on how CDRH will work with CDER and/or CBER on incorporating patient preference information into discussions regarding the development and review of drug/biologic-device combination products and companion diagnostics. Specifically, we are concerned that there is a lack of coordination with CDER and CBER on potential common tools and/or methodologies that could be used for the evaluation of drug/biologic-device combination products and companion diagnostics.

D. Leveraging Private-Public Partnerships

BIO also commends CDRH on its use of PPPs, in particular MDIC, which have been instrumental in providing a forum for stakeholders to interact and develop a patient preference-focused benefit-risk framework. A key element to the MDIC's success is CDRH's direct involvement in the partnership's leadership and technical working groups. Thus, BIO believes that PPPs will be most effective in driving consensus among the Agency, industry, and patient groups regarding consensus-building on the tools, methods, and approaches to promote the use of patient preference information to improve the efficiency of drug development and regulatory review of medical products.

E. Practitioner Preference Information for Medical Devices

BIO notes that while the Draft Guidance applies to patients, many medical devices are actually utilized by healthcare practitioners. The Guidance reflects practitioner preference input in only three places. BIO recommends that the Agency clarifies how the Draft Guidance applies to user preferences and how this data would be included for review. For example, the surgeon replacing the knee may have different inputs from the patient receiving the knee.

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biologic development, including footnote 19 (Johnson et al. (2013)) and footnote 20 (Mussen et al. (2009)). Furthermore, many of the method-specific references in both the Draft Guidance and the MDIC report reference papers and methods that have been applied to drugs/biologics.

F. Conclusion

BIO appreciates this opportunity to comment on the "Patient Preference Information – Submission, Review in PMAs, HDE Applications, and De Novo Requests, and Inclusion in Device Labeling" Draft Guidance. Specific, detailed comments are included in the following chart. We look forward to continued dialogue with the Agency as it continues to develop guidance on the matter, and 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

cc: Robert M. Califf, MD, Deputy Commissioner for Medical Products and Tobacco
Janet Woodcock, MD, Director, Center for Drug Evaluation and Research
Karen Midthun, MD, Director, Center for Biologics Evaluation and Research

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 40-48	It is unclear if FDA intends to add further requirements to the design of medical devices, or is clarifying the applicability to patient preference studies.	BIO suggests FDA address whether the objectives of this guidance are to clarify how Design Control requirements (21 CFR 820.30) apply to Patient Preference studies, or if this guidance is in addition to Design Control requirements.
II. OVERVIEW AND SCOPE		
Lines 106-109	There is little documentation on the CDRH site about how to contact the Agency to discuss preference studies. There are also currently very few FDA staff who are ready to have a technical discussion on preference studies. Sponsors will also be reticent to meet with CDRH on this novel topic is there is a sense that such meetings can slow the development timeline.	BIO suggests that the guidance should outline the mechanism by which sponsors or other stakeholders can discuss preference studies with the FDA, especially for non-sponsor stakeholders who may not know about pre-submission meeting processes.
III. BACKGROUND		
Lines 193-195	"If FDA determines the device would expose patients to an unreasonable or significant risk of illness or injury, or the benefits do not outweigh the risks for some definable target population, FDA would not approve such a device." This sentence gives two reasons not to approve a device even if there is a subgroup for which benefits exceed risk. (1) The device would expose patients to an unreasonable or significant risk of illness or injury	BIO believes the points made in these lines are extremely important and warrant extensive explanation and examples. The two reasons for not approving a device are very distinct; BIO recommends that these two reasons for not approving a device are distinct, and should be described in detail in separate paragraphs/sections. One point in particular to address is that the second reason provided (that benefits do not outweigh the risks for some definable population) can be interpreted as contradicting the idea of approving preference-based subgroups—a major theme in the draft guidance overall.

SECTION	ISSUE	PROPOSED CHANGE
	and (2) the benefits do not outweigh the risks for some definable target population. The first reason needs much more detail. For example, if the unreasonable or significant risk occurs only in the subgroup whose preference indicate they regard benefits as exceeding risk, are the risk no longer unreasonable? Is the concern that the unreasonable risks can occur in all patients, including those whose preferences are such that benefits do not exceed risks? How does this differ from most cases, where by definition, patients whose preferences are such that benefits do not exceed risks would consider the risks unreasonable or significant? The first reason seems extremely important, but it is not clear what exactly is meant or how it is operationalized. The second reason may contradict the prior sentences and can be read to contradict one of the main points of the draft guidance. If there is a group of patients for which benefits exceed risks by virtue of preferences, then there almost always will be a different group of patients for which benefits do not exceed risks by virtue of preferences. As written, no B>R subgroup would get approved because of the existence of a B<R subgroup elsewhere in the population. While it is possible in theory for B~=R for most patients and a subgroup have B>R, this is not the type of result seen in preference studies.	
Lines 219-221	"However, revealed-preference methods often cannot be applied because a device profile of interest may not	BIO suggests that the guidance include other key reasons that revealed preference methods have limited utility.

SECTION	ISSUE	PROPOSED CHANGE
	yet be available for patients to choose when a device is under regulatory review." There are many other important reasons that revealed preference methods are problematic. These include limited access to treatments, bias due to limited information on the alternatives available or misinformation on those alternatives, bias due to insurance plans limiting or redirecting choices, and the impact of cost of choice.	
Lines 345-347	We agree that patient preference information is helpful in informing the selection of a patient reported outcome (PRO) that a sponsor may wish to incorporate into their development program. However, in the instance that a suitable PRO does not exist, we note that device development timelines do not typically permit the use of recently obtained patient preference information to develop a new PRO.	BIO recommends that the draft guidance note that the development of a new PRO based on recently obtained patient preference information may not be practical. The Guidance could also suggest that preference studies also have a role in designing the scoring algorithms for PRO instruments, as has been described in several recent articles. Finally, BIO recommends providing information from organizations such as PatientsLikeMe and other online communities that can offer unfiltered information on patient perspectives.
IV. RECOMMENDED QUALITIES OF PATIENT PREFERENCE STUDIES		
Line 382	"a) Representatives of the Sample and Generalizability of Results" Traditionally, preference surveys have been done with patient panels. However, there are concerns to considered when using panels for regulatory purposes: (1) ability to always achieve or assess alignment between panel and clinical trial populations (for example, when the trial population must meet a complex biomarker criterion); (2) panel diagnoses are	BIO suggests including a section on considerations for the source of the sample.

SECTION	ISSUE	PROPOSED CHANGE
	typically self-reported; (3) there is potential bias due to self-selection for membership in panel; (4) there is potential bias due to having an internet-based sample, though this is lessening with time; (5) recall bias if the subjects are using personal experience with an illness for their responses to the survey; and (6) limited understanding of the alignment of panel samples between different countries. An alternative is embedding preference studies within clinical trial; however, there are also concerns with this choice such as: (1) clinical trial inclusion/exclusion criteria often result in a more rigidly defined population than that which will use the treatment post-approval; (2) patients that choose to enroll in a trial may have biases that are reflected in their preferences; and (3) an important harm may not be recognized until after the trial, therefore the preference may be missing an important attribute.	
Line 397	"b) Capturing Heterogeneity of Patients' Preferences" What constitutes a sufficient "sample size" is a challenging question. In many preference studies, the sample sizes may be in the range of several hundreds. As the draft guidance document pointed out, the sample needs to be representative and capture inter-subject variability. Since patient preference studies often lack a priori hypothesis testing, adequacy of sample size is often judged in an ad-hoc fashion, which is not really helpful from the perspective of scientific design and providing robust evidence.	Acknowledging that this guidance may evolve over time as our understanding increases, BIO believes that it would be helpful if FDA provide additional guidance about what scale of sample size may be considered adequate or reasonable.

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V. ADDITIONAL CONSIDERATIONS		
B. CONDITIONS OF APPROVAL		
Lines 577-583, 707-712	The draft guidance suggests that approval may be limited to the highest responders even in situations where the benefit-risk balance is possible for the entire study population. Additionally, patient subset analysis is typically pre-specified in order to support labeling for a medical product.	BIO suggests that FDA clarify what is meant by "smaller than expected improvement in the study population" as this does not necessary indicate that the benefit-risk balance is not positive for the study population. Following this comment, it may be appropriate to include the comment regarding post-hoc analysis for those instances where the benefit-risk balance is not positive for the entire study population. BIO also asks the Agency to clarify whether it is suggesting that a subset of patients may support approval based on post-hoc analysis.
Lines 590-592	"The Agency encourages sponsors and other stakeholders to have early interactions with the relevant review division if considering collecting patient preference information for regulatory purposes." There is little documentation on the CDRH site about how to contact the agency to discuss preference studies. There are also currently very few FDA staff who are ready to have a technical discussion on preference studies. As a result, sponsors may be reticent to meet with CDRH on this novel topic if there is a sense that such meetings can slow the development timeline. Given the novelty of the topic and CDRH's desire to encourage discussions with sponsors on preference studies, CDRH may wish to develop, modify or repurpose a mechanism for sponsor-CDRH	BIO recommends that the guidance should outline the mechanisms by which sponsors or other stakeholders can discuss preference studies with the FDA, especially for non-sponsor stakeholders who may not know about pre-submission meeting processes. Additionally, the guidance should also note if there are other/unique communication mechanisms to have these discussions

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	discussions specifically for preference studies, at least for the next few years.	
VII. COMMUNICATING PATIENT PREFERENCE INFORMATION IN DEVICE LABELING		
A. GENERAL LABELING RECOMMENDATIONS		
Lines 638-640	Additional communication to providers or patients creates an extra burden on the sponsors that may not be a necessary action to ensure adequate understanding of the data. The product labeling should clearly convey the most important information related to the study and use of the device.	BIO suggests that the Agency clarify whether it intends to require additional communication of the patient preference information included in labeling.
VIII. HYPOTHETICAL EXAMPLES		
Line 702	"A. Probable benefit outweighs probable risk for a subset of patients" This example is not particularly illustrative of patient preference, insofar as there is only one device described and typical practice of identifying appropriate indications would likely preclude the need for patient preference studies. If it is shown to work best in patients with the highest pain and functional limitations, then this should be reflected in the indications.	BIO suggests that FDA consider an example where a new device presents greater medical benefit at an increased risk to the patient, rather than a legally marketed predicate.
Lines 784	"E. Pediatric HDE and Patient/Patient Preferences" Pediatric HDE and Patient/Parent Preferences may be a departure from the title and scope of the guidance, since in this example, the term "patient preference" applies to people other than the patient. In this example, it is the caregiver and the physician making the decision to perform the pediatric implant procedure and not the patient.	BIO recommends that patient preference (or the attitude towards acceptability of risk) in the context of this guidance be define.