Biotechnology Innovation Organization

September 7, 2018

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

Re: Docket No. FDA-2018-D-1895: Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products —Content and Format

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the Draft Guidance titled Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products —Content and Format.

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BIO applauds FDA's issuance of the draft guidance to provide recommendations on the general principles to consider when drafting an indication and how to write, organize, and format the information in the Indications and Usage section of the labeling. In particular we commend the FDA for recognizing that an indication for a "broader population than the patient population studied in controlled trials may be appropriate after careful consideration of the generalizability of the evidence, consistencies in the disease process across different groups, and the drug's overall benefits and risks." This is especially important for therapeutic areas in which the patient population is small, the disease is heterogeneous with highly diverse clinical manifestations, and reliable and validated endpoints that span the spectrum of the disease may not be established. BIO also believes that the examples of Indications and Usage, and the Limitations of Use statements, provided in the guidance are generally reasonable and clear.

Identification of Outcomes, Endpoints, and Benefit(s) the Drug Conveys

BIO suggests this section could be strengthened by including language around surrogate endpoints used to support accelerated approvals. Specifically, as more innovative products get approved in new therapeutic areas based on novel surrogate endpoints, it would be beneficial to include information and a description to support how the surrogate endpoint "is reasonably likely to predict a clinical benefit." This will facilitate an appreciation of the effectiveness of such drug by those who are trying to interpret a label where approval was based on a novel surrogate endpoint for which they may have limited familiarity.

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200 P
202.488.6306 F
bio.org

Accelerated Approval

FDA should ensure that labeling preserves the intent of Accelerated Approval to hasten the availability of treatments for patients with serious or life-threatening diseases and limited or no treatment options.

BIO applauds the Agency's efforts to improve communication in labeling to empower health care providers with the information they need to best serve their patients.[1] BIO is concerned, however, with potential misinterpretation of the limiting statements for Accelerated Approval drugs as outlined in this section and as originally articulated in the 2014 draft guidance, entitled "Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway." It is critically important that health care providers, patients and payers do not misinterpret information that describes the nature of Accelerated Approval to mean that safety and efficacy standards have not been met.

Accelerated Approval is a valuable mechanism to address the challenges and limitations presented by small, difficult to study patient populations with high unmet need. It has been used extensively since its creation in 1992 in cancer and HIV, spurring tremendous advances in care from which patients today would not be benefiting had this pathway not been available. In 2012, Congress further encouraged FDA to apply this pathway beyond oncology and HIV to speed the availability of novel treatments for rare diseases through the Food and Drug Administration Safety and Innovation Act (FDASIA).[2] Specifically, FDASIA amended certain provisions of the Federal Food, Drug, and Cosmetic Act (FDCA) "to implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs"[3]

Congress and FDA have been very clear that drugs approved under accelerated approval meet the same, full statutory standards for safety and effectiveness as all other FDA approved drugs, including demonstrating substantial evidence of effectiveness. For over 25 years FDA has affirmed that there is a single approval standard and accelerated approval is full approval, not a partial, interim, or conditional approval. FDA explained that all drugs that receive Accelerated Approval "will have met the requisite standards for safety and effectiveness under [the FDCA] or [the PHS Act] and, thus, will have *full approval* for marketing."[4] Recent statements by FDA Commissioner Dr. Scott Gottlieb reinforce the reality that a "product that goes through FDA's accelerated approval process [meets] the gold standard for approval" and that such drugs "meet a high hurdle for access to the market."[5]

Furthermore, FDA has clarified that the primary purpose of labeling to provide prescribers with "adequate directions for use" via "a summary of the essential scientific information needed for the safe and effective use of the drug."[6] Health care providers may not understand the nuances of the regulatory approval process, and therefore could

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[1] 21 C.F.R. § 201.57
[2] Pub. L. No. 112-144, Sec. 901(a)(1)(E) (2012).
[3] *Id.* Sec. 901(a)(1)(C)
[4] *Id*. (emphasis added)
[5] Statement on October 17, 2017, FDA Commissioner Dr. Scott Gottlieb
[6] 21 C.F.R. § 201.56(a)(1)

misinterpret information about the limitations of Accelerated Approval drugs. To prevent such a misinterpretation, information about the risks inherent in the Accelerated Approval process should be balanced with context about the nature of the pathway that is well-documented in law and regulation.

For the above reasons, BIO encourages FDA to continue to explore ways to expedite access to safe, effective and innovative therapies for serious or life-threatening diseases or conditions, while ensuring prescribers are empowered with relevant information about risks and benefits through labeling.

BIO appreciates this opportunity to submit comments on the Draft Guidance titled Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products —Content and Format. We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
II. GENERAL PRICIPLES		
Updating the INDICATIONS AND USAGE Section		
Lines 199-206	The draft reads "The INDICATIONS AND USAGE section "must be updated when new information becomes available that causes the labeling to be inaccurate, false, or misleading" (§ 201.56(a)(2)). In addition, it is appropriate in certain circumstances for application holders to update this section to reflect current practices for writing indications for a particular group of drugs (for example, when more information becomes available about the drug, drug class, or specific disease or when the endpoints become better established). Application holders should review the INDICATIONS AND USAGE section regularly to ensure that it reflects current science and, to the extent possible, maintains consistency within a pharmacologic or therapeutic class."	Lines 199-200 accurately describe a Sponsors responsibility to update a label based on the false and misleading standard. However, BIO does not agree that all of the examples in lines 203-206 would constitute a Sponsors obligation based on the false and misleading standard. For example, BIO does not agree that a Sponsor's failure to update an indication statement to reflect class labeling would necessarily constitute a false and misleading violation. BIO recommends deleting lines 203-206 or limiting the content of that text to examples of scientific inaccuracy that causes labeling to be misleading pursuant to § 201.56.
III. CONTENT AND FORMAT OF THE INDICATIONS AND USAGE SECTION		
Limit of Use		
Lines 352-403	Inclusion of limitations of use (LOU) should be limited to circumstances where its inclusion is warranted.	In general, LOU should be placed judiciously to ensure appropriate use. FDA should consider language that clarifies LOU will be carefully considered as to not inadvertently or inappropriately restrict access and/or reimbursement. The FDA guidance examples should support the need to avoid redundancy in the label.
Lines 451-466	Situations in Which Limitations of Use Would Be Appropriate	FDA should consider rephrasing and providing clarification regarding the LOU example in this section to acknowledge LOU will be added to the drug's indication in situations where

SECTION	ISSUE	PROPOSED CHANGE
		the evidence demonstrates an absence of effect or an AE in a particular population, rather than an absence of evidence.
Other Considerations for Writing the INDICATIONS AND USAGE Section		
Lines 642-645	Attributes that distinguish how a product works or how it is used should be included in the indication statement instead of only allowing this type of labeling as part of the Highlights (assists in definition of the pharmacologic class). This is especially helpful when the pharmaceutical class has a large number of molecules and defining subsets within the pharmaceutical class based on how a drug is administered or related to the mechanism of action can provide more specific information regarding the population a product is intended for.	FDA should consider allowing attributes that distinguish how a product works or how it is used to be included in the indication statement instead of only allowing this type of labeling as part of the Highlights (assists in definition of the pharmacologic class).
Formatting the INDICATIONS AND USAGE Section		
Lines 649 -655	It is unclear what the circumstances under which bullets or subsections for multiple indications would be appropriate.	FDA should provide examples to clarify recommendations on this topic.