Biotechnology Industry Organization

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

Docket No. FDA–2014–D–0250: Draft Guidance for Industry on Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the *Draft Guidance for Industry on Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway.*

BIO represents more than 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.

BIO appreciates FDA's efforts to further clarify labeling practices for products approved under the Accelerated Approval pathway. BIO strongly supported provisions under the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) that encouraged FDA to "implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate." (§901)

To that end, we believe that it is appropriate for the Agency to assist review divisions in embracing the use of Accelerated Approval more expansively, and foster more consistent approaches to how these products will be labeled across different indications. If the Agency has greater certainty that the product label is appropriately communicating the full context of anticipated benefits, potential risks, and residual scientific uncertainty to healthcare professionals, then medical reviewers should have greater confidence in granting Accelerated Approvals on a more routine basis for serious and life-threatening indications across a variety of serious conditions. However, that goal must also be carefully balanced against potential unintended consequences that may hinder the utilization of important new medicines to treat serious diseases and address key public health priorities.

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I. Public Understanding of Meaning of "Accelerated Approval"

In the past, labels for products approved under Accelerated Approval have been substantially similar to products approved under traditional approval. This general parity in labeling is appropriate as Accelerated Approval products meet the same standard for safety and efficacy as products approved under traditional pathways.[1] In both cases, FDA has determined that the product meets the "Substantial Evidence" standard established by the Federal Food, Drug, and Cosmetics Act. While an Accelerated Approval may be on the basis of a surrogate or intermediate clinical endpoint that is reasonably likely to predict clinical benefit, it is no less of a "full" approval than any other product approved under FDA's rigorous standards.

However, there is a lack of public understanding of the regulatory distinctions among FDA's expedited programs for serious diseases, including Accelerated Approval, Fast-Track, Priority Review, and Breakthrough Therapy Designation. This can contribute to a misperception that these designations and approval pathways lead to approval based upon a lesser standard than products approved under traditional approval.

The Draft Guidance (lines 96-103) includes a description for inclusion in the product label of the *regulatory process* used by the Agency to approve the drug, which seems secondary and nonessential information to the prescriber for the purpose of deciding whether or not to prescribe the drug (e.g., "…*approved under accelerated approval based on…*").

BIO suggests removing any reference in the Indications and Usage (I&U) section to the regulatory mechanism by which the drug is approved, particularly in the Highlights. The I&U section should only contain information that is presented in a succinct, factual, and meaningful manner to the prescriber identifying 1) the approved indication based on data/substantial evidence criteria supporting it, and 2) a comprehensive account of limitations of use information and what confirmatory studies are planned/ongoing that further support the data/substantial evidence currently available that serves as the basis of the existing approval.

We recommend that information pertaining to "accelerated approval" be located in the Clinical Studies section of the label. This allows for a more succinct I&U section that describes approved indication/limitation of use information and gives a simple cross reference to the Clinical Studies section. In general, BIO suggests that any description of the limitations of usefulness and clinical benefit uncertainty associated with a product approved under Accelerated Approval should be placed in the Clinical Studies Section, rather than the I&U Section, and that any such information focus on describing the clinical data available rather than describing the regulatory process.

II. Adequate Balance between Benefits, Risks and Scientific Uncertainty

BIO also believes that it is important to place equal emphasis on the product's benefits and risks in the context of the body of available scientific information. However, the guidance tends to emphasize the uncertainty regarding the ultimate clinical benefit over

[1] 21 USC §355(d).

the FDA acceptance that the surrogate or clinical endpoint *is reasonably likely to predict the clinical benefit*. This imbalance can lead health care providers to shift away from using a product that would otherwise benefit patients suffering from serious conditions.

In particular, the Draft Guidance (Lines 68-72) recommends emphasizing the limitations/uncertainties about the drug's benefit, which is not the only intent of the I&U section. We recognize that inclusion of information pertaining to limitations of use is informative and necessary for prescribers. However, providing this type of information as recommended by this guidance creates an imbalance in how the benefit vs. risk/uncertainty is presented in this section. This could potentially confuse prescribers and result in a greater harm to public health by undermining prescriber and public confidence in the drug, especially in an unmet medical need situation.

We suggest rewording these statements to present limitations of use and uncertainty in a more balanced way, so as not to take away focus from the "approved" benefits of the drug. As the I&U section is intended be concise and factual, BIO recommends that the label explicitly state in the Clinical Studies Section:

> *"X has met the substantial evidence standard for approval and FDA considers the surrogate [intermediate] clinical endpoints as reasonably likely to predict clinical benefit."*

III. "Continued Approval"

The Draft Guidance (lines 159-172) seems to imply that the Accelerated Approval is an incomplete approval, given the use of the language *"continued approval…may be contingent upon…",* whereas the drug has already met the substantial evidence standard. Including such language may raise uncertainty in the prescriber's mind about the drug product's benefits.

BIO strongly suggests revising this section to avoid use of "*continued approval*" language. Instead, this section should be worded so that prescribers will clearly understand that the product has met the substantial evidence threshold for approval, while also informing them that additional information/data will be obtained to further verify the drug's clinical benefits.

For example, a statement of the following type might be placed in the Clinical Studies section:

> *"The clinical benefit of this indication, currently approved based on <surrogate endpoint>, will be <confirmed/further supported> through post-market confirmatory evidence."*

IV. Insurance and Reimbursement Considerations

While FDA's approval is based upon an assessment of safety and efficacy, the broader policy considerations by FDA stakeholders must also take into account the pharmacoeconomic and other implications of the proposed labeling recommendations. Most insurers, including Medicare and Medicaid, will typically cover or provide physician

reimbursement for FDA approved therapies that are medically necessary. However, insurers will not always pay for therapies perceived as experimental or investigational. Patients already burdened by healthcare expenses due to an underlying, life-threatening disease or condition should have access to therapies that are safe, effective, and covered by insurance. Therefore, it is important that the FDA-approved label not send mixed messages to payers that a product approved under Accelerated Approval is anything less than a full approval that meets the same standard as other approvals, *i.e.*, FDA's substantial evidence standard. Any suggestion that a product is a "conditional approval" or has not fully demonstrated clinical benefit could result in non-coverage of the product by an insurer, which would undermine the intent of Accelerated Approval to improve patient access to treatments for serious and life-threatening conditions.

Conclusion:

BIO appreciates this opportunity to comment on the *Draft Guidance for Industry on Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway*. We believe the changes we have suggested for the label of a drug approved under Accelerated Approval are fully consistent with the Federal Food, Drug, and Cosmetic Act and implementing regulations, and, therefore, that a Sponsor could lawfully label such a product as suggested in our comments, notwithstanding the recommendations FDA provides in this guidance, if finalized. 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)

Biotechnology Industry Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 24-26	As written, the text describing the focus of the guidance is not specific to drugs granted Accelerated Approval. The text should be modified to make it clear that this applies to drugs approved via the Accelerated Approval process and not all drugs approved on the basis of a surrogate endpoint. For instance, diabetes drugs are approved based on a surrogate endpoint but are not approved via Accelerated Approval.	Suggest a rewrite of the sentence to include "Accelerated Approval" as follows: "…this guidance focuses on indications and usage statements for drugs granted [OR approved via] accelerated approval…"
II. BACKGROUND		
Lines 65-66	"*Special provisions exist for older drug labeling under § 201.56(e) and 21 CFR 201.80*." As stated in the introduction, this guidance is intended to help applicants develop an Indications and Usage section. This implies that the applicant will need to submit an efficacy supplement. If an older drug product, the drug labeling within the efficacy supplement will be required per 21 CFR 201.56(b) to be submitted in PLR format. Pointing the reader to the older	Suggest deleting sentence referencing the older labeling regulations. Suggest the Draft Guidance direct the applicant to update the labeling in Physician Labeling Rule (PLR) format per 21 CFR 201.56(b) & Feb 2013 PLR guidance. "~~Special provisions exist for older drug labeling under § 201.56(e) and 21 CFR 201.80.~~"

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	labeling regulations is potentially confusing.	
III. ACCELERATED APPROVAL LABELING CONSIDERATIONS		
A. Indication Approved Under Accelerated Approval		
Line 96:	Only the first line of 96, "Drug X is indicated for {state indication}," is appropriate for inclusion under the I&U heading of the label Highlights section.	Highlights should be limited to the first sentence in Line 96: "*Drug X is indicated for {state indication}.*"
Lines 98-100:	Discussion of surrogate endpoint used should be included in the Clinical Trials section rather than the I&U section. Furthermore, there is too much focus on the risk of drug effectiveness not being established.	We suggest moving discussion of surrogate endpoint to Clinical Trials section. We also suggest the following at line 99: "Additional verification for this indication may be based on postmarket confirmatory evidence."
Lines 99-103	As currently written, the text seems to suggest (a) multiple, additional protocols are always required for a drug to convert from accelerated to full approval, and (b) these additional protocols would be independent from the first protocol that supported accelerated approval. The Agency has already advocated likely support for the situation when initial outcomes could be a basis for accelerated approval, and longer follow-up from the same single study (*e.g.*, providing overall survival (OS) follow-up) could support full approval.	The language should support opportunity for confirmatory data from (1) a single trial or (2) extended follow-up, expanded enrollment, or other options from the same trial that led to initial accelerated approval. As suggested in our general comments, we recommend the use of the term "postmarket confirmatory evidence." In addition, to support the option for a single confirmatory trial and to maintain consistency within the document, we suggest modifying "*confirmatory trials*" or "*confirmatory trial*" to "*confirmatory trial(s)*" and "*study*" or "*studies*" to "*study/studies*" throughout the text. Similarly, the terms "trial" or "trials" should be modified to "trial(s)" in other sections, (*e.g.,* in lines 79, 153, 167,

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	For example, line 102 uses "*(s)"* to describe possible singular "*clinical benefit(s).*" (Similarly, lines 163, 190, 192 all describe in singular "*the confirmatory study.*") Taken together, these seem to support the option for a single confirmatory trial. In contrast, line 103 and elsewhere describes plural "*confirmatory trials*."	172); and "in the postmarketing studies" in line 176 can be modified to simply "postmarketing."
1. Indications(s)		
2. Limitations of Usefulness and Clinical Benefit Uncertainty		
Lines 137-147	As discussed in our general comments, describing the regulatory process used to approve the drug in product labeling seems irrelevant for the prescriber. Rather, we recommend a focus on the substantial evidence (data) available upon which the drug approval is based.	We suggest removing the recommendation in this guidance to reference accelerated approval in the I&U section. Also suggest revision in lines 145-147 as follows: "This indication is approved ~~under accelerated approval~~ based on tumor response rate [see Clinical Studies (14.1)]. An improvement in survival or disease-related symptoms has not been established."
Lines 145-147:	The product approved under the Accelerated Approval pathway has satisfied the substantial evidence standard and FDA considered the surrogate or early clinical endpoint(s) as reasonably likely to predict the specific clinical benefit. We suggest rewording these statements to present limitations of use and uncertainty in a more balanced way so as not to take away focus from the "approved" benefits	Please include the following statement: "X has met the substantial evidence standard for approval and FDA considers the surrogate [intermediate] clinical endpoints as reasonably likely to predict clinical benefit." Another example of such a sentence is as follows: "An improvement in survival or disease-related symptoms has not been established, but tumor response rate is

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	of the drug. As the I&U section is intended be concise and factual, BIO recommends that the label explicitly state in the Clinical Studies Section the "approved" benefits of the drug.	predicted to lead to improvement in xx."
Lines 145-147	This guidance provides opportunity to expand the examples given under the section "Limitations of Usefulness and Clinical Benefit Uncertainty". As now written, lines 145-147 shows a single, simplistic example that does not evoke much consideration/innovation about how product labeling can be a useful mechanism to accelerate access to new medicines, but within a defined subgroup or with some degree of acceptable uncertainty.	The following is a suggestion for another example that could be added after the one on lines 145-147: "XXX is a kinase inhibitor approved based on progression free survival [see Clinical Studies (14.1)] observed in a study of largely symptomatic patients with progressive, locally advanced or metastatic YYY cancer. Use of XXX in patients with indolent or asymptomatic or slowly progressing disease should be carefully considered because of treatment related risks of XXX."
3. Continued Approval		
Lines 151-172	As discussed in our general comments, this section seems to imply that the Accelerated Approval is an incomplete approval, given the use of the language *"continued approval…may be contingent upon…"* whereas it has already met the substantial evidence standard to receive approval. Including such language may raise uncertainty in the prescriber's mind about the drug product's benefits. Since additional studies are required for Accelerated Approval, additional	BIO suggests revising this section to avoid use of "*continued approval*" language. This section of the indication language should be worded such that prescribers will clearly understand that the product has achieved a substantial evidence threshold for approval, while also informing them that additional information/data may be obtained to further justify the drug's clinical benefits. Example statements in the Clinical Studies section may more clearly represent the intended message to prescribers as follows: "The clinical benefit of this indication currently approved

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	information *will* be obtained; whether or not this information/data affects the Accelerated Approval is the *may*. Additionally, as noted in the comments for lines 99-100, there is too much focus on the risk of drug effectiveness not being established.	based on <surrogate endpoint> will be <confirmed/further supported> through post-market confirmatory evidence." Additionally, the header on line 149 should be amended to: "Post-Market Confirmatory Evidence" BIO suggests the following at Line 158: "…that ~~continued approval~~ additional verification based on confirmatory evidence for that indication…" We also suggest at Lines 166 and 171: **"**Additional verification based on confirmatory evidence for this indication…"
Lines 164-172	The two examples illustrated below seem quite definitive, potentially giving the impression that they are the only two possible scenarios: *"Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials."* *"Continued approval for this indication may be contingent upon demonstration of improvement in survival in confirmatory trials."*	It would be helpful to add a general statement such as: "Other wording is possible, depending on the particulars of the accelerated approval." BIO also suggests changing "trials" to "studies", as not all demonstrations of improvement would be via clinical trials (*e.g.*, epidemiological, pathophysiological, therapeutic, and pharmacologic evidence could be used).
B. When Clinical Benefit has been Verified		
C. Withdrawal of an Accelerated Approved Indication		

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1. Lack of Evidence Concerning the Withdrawn Indication		
Line 209 – 215:	If an Accelerated Approval indication is withdrawn the label should be revised to reflect such changes.	We recommend that the indication, dosage and administration, and clinical studies information should be removed from the respective sections. Finally, we recommend that this statement only remain in the label for 12 months as a Major Change. Further, explanation of when the labeling should revised to include a limitation of use concerning the withdrawn indication may be required. Examples of the wording (as provided in other sections of the guidance) would be helpful.
2. Safety Information Concerning the Withdrawn Indication		
Lines 226-228	The Draft Guidance states "*The description of the risk or hazard also should be accompanied by a statement that the drug is not approved for the withdrawn indication*." The Warnings and Precautions (W&P) section of the label may not be the only means of risk communication available for a drug Sponsor to utilize. For example, communication of this type of information may also be appropriate via dissemination of a Dear Health Care Provider (DHCP) letter notifying healthcare providers of the change in labeling and related safety concerns.	Recommend that the sentence be reworded as follows: "The change to the prescribing information, describing ~~description of~~ the risk or hazard, may also ~~should~~ be accompanied by a Dear Health Care Provider Letter explaining ~~statement~~ that the drug is no longer ~~not~~ approved for the withdrawn indication." Consideration should also be given to adding a reference in this guidance to the FDA guideline on DHCP letters.