May 27, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852


Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) submits these comments in response to the Federal Register notice entitled “Draft Guidance for Industry on Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Pathway”¹ (the draft guidance) issued by the U.S. Food and Drug Administration (FDA).

PhRMA is a voluntary, nonprofit association that represents the country’s leading innovative biopharmaceutical research and biotechnology companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Since 2000, PhRMA member companies have invested approximately $550 billion in the search for new treatments and cures, including an estimated $51.1 billion in 2013 alone.

I. GENERAL COMMENTS

The Food and Drug Administration Safety and Innovation Act (FDASIA) enhanced the authority of FDA “to consider appropriate scientific data, methods, and tools, and to expedite development and access to novel treatments for patients with a broad range of serious or life-threatening diseases or conditions.”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” including a modernization and expansion of FDA’s existing Accelerated Approval pathway.³

PhRMA has long supported FDA’s appropriate use of innovative approaches and regulatory flexibility to establish the safety and efficacy of new medicines to address unmet medical needs. It is particularly

³ Id. at Sec. 901(a)(1)(C). For example, the law provided for more expansive use of non-surrogate clinical endpoints as the basis for granting Accelerated Approval. Specifically, the new language expressly authorized FDA to grant Accelerated Approval based on the use of clinical endpoints that can be measured earlier in the development process than irreversible morbidity or mortality, and that are reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. See FDCA Sec. 506(c)(1)(A) as amended by FDASIA.
important that the FDA drug review process be grounded in a careful evaluation and balance of benefits and risks made in the broader context of disease rarity and severity, the availability or lack of alternative treatments, patient perspectives, and the body of available scientific evidence, and that labeling adequately presents relevant information about benefit-risk balance.

PhRMA appreciates that this draft guidance seeks to improve communication of information through labeling, including information regarding known and potential benefits and risks, and shares the FDA’s goal of ensuring that information on the use of drug and biological products (drugs) approved under the Accelerated Approval regulatory pathway is consistently presented in the appropriate sections within prescription labeling so that the information is clear and accessible to health care providers. PhRMA believes that labeling for all drugs, not just those approved under the Accelerated Approval pathway, should adequately describe approved indication(s), anticipated clinical benefit(s), and evidence that the Agency considered to approve the drug as safe and effective for its intended use(s). While there are additional labeling requirements for drugs approved under the Accelerated Approval pathway,4 PhRMA agrees with FDA that labeling for these drugs “is fundamentally the same as for drugs approved under the traditional pathway.”5

To assist FDA with its efforts, PhRMA submits the following comments on the Agency’s approach toward the development of the “Indication and Usage” statement in the prescribing information for drugs approved under the Accelerated Approval pathway.

1. **FDA should preserve the primary purpose of prescription labeling as well as preserve the intent of Accelerated Approval to expedite patient access to treatments for serious conditions**

PhRMA believes that the draft guidance’s proposal of limitations and caveats in the “Indications and Usage” statement could be misinterpreted to mean that products approved under the Accelerated Approval pathway have not met the statutory requirements of safety and efficacy required of all FDA-approved drugs. The result could be health care provider and public confusion, which could undermine the intent of the Accelerated Approval pathway and recent Congressional efforts to encourage its broader use. It is important that communication about residual uncertainty does not misleadingly imply that safety and efficacy standards have not been met. Therefore, for the reasons explained below and as specified in the Addendum, PhRMA recommends that FDA remove from the Indications and Usage section reference to “Continued Approval” and “Accelerated Approval.”

a. **Preserve the primary purpose of prescription labeling**

Past FDA statements support PhRMA’s position. FDA has previously stated that the purpose of the Accelerated Approval pathway is “to make drugs that provide meaningful improvement over existing therapies for serious illnesses widely available (through marketing) at the earliest time consistent with the law.”6 FDA also explained that drugs approved under the Accelerated Approval process “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.”7 FDA further clarified that Accelerated Approval is not “inconsistent with section 505(d) of the [FDCA],” as it reflects FDA’s “assessment about whether different types of

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4 21 C.F.R. § 201.57(c)(2)(i)(B).
7 Id. (emphasis added).
data show that the same statutory standard has been met.”\(^8\) It was clearly the intent of FDA that Accelerated Approval not be regarded as a “conditional” approval; in the preamble to the Accelerated Approval Final Rule, FDA stated in response to a comment that had suggested use of the term “conditional approval” that “[t]he agency believes that what the procedures are called is much less important than what the procedures are. The shorthand term selected by the agency reflects the intent of the rule . . . The essence of the proposal is thus acceleration, not the imposition of conditions.”\(^9\) And most recently, FDA Commissioner Dr. Margaret Hamburg has stated with regards to the Accelerated Approval pathway that “[n]o matter what the approval pathway is, we consistently have the same statutory standards of ensuring safety and efficacy before a product is marketable in the U.S.” and that “[i]ncreased flexibility does not mean we’re abandoning standards or quality.”\(^10\)

PhRMA also believes that the proposal to add a new “continued approval” element to the “Indication and Usage” section is inconsistent with FDA’s general approach to crafting physician labeling and the primary purpose of that labeling. FDA acknowledges that “regulatory postmarketing study requirements typically are not included in labeling.”\(^11\) The approval of all drugs is subject to the requirement that the applicant comply with many postmarketing requirements, yet none appear in labeling. The primary intent of labeling is not to educate the prescriber on the regulatory process, but to provide “adequate directions for use”\(^12\) via “a summary of the essential scientific information needed for the safe and effective use of the drug.”\(^13\) A description of the evidence that the Agency considered to approve the drug as safe and effective for its intended use is already included elsewhere within the labeling.

The FDA’s proposal to add a new “continued approval” element is also inconsistent with prior FDA goals of keeping the “Indications and Usage” section of labeling “focused” and “succinct.” This was explicitly stated by FDA when the Physician Labeling Rule (PLR) was proposed in 2000:

“[p]roposed § 201.57(c)(2)(iv)(A) would modify current § 201.57(c)(3) to specify that if evidence is available to support the safety and effectiveness of the drug or biologic only in selected subgroups of the larger population with the disease or condition, or if evidence to support the indication is based on surrogate endpoints, the limitations in the usefulness of the drug (or, in the case of surrogate endpoints, the limitations of the supporting efficacy data) must be described succinctly. Reference should be made to the “Clinical Studies” section (proposed § 201.57(c)(15)) for a detailed discussion of the specific methodology and clinical data relevant to the limitation. The agency anticipates that this change would facilitate a more focused “Indications and Usage” section for the practitioner seeking basic information. For those practitioners seeking more detailed information, the reference to the “Clinical Studies” section should be sufficient to signal that additional information is available.”\(^14\)

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\(^8\) See Id. at 58944 (emphasis added).
\(^9\) See Id. at 58943.
\(^10\) See Virgil Dickson, “FDA commissioner defends fast-track approval programs,” Modern Healthcare, April 23, 2014 (quoting Dr. Margaret Hamburg at the 2014 annual conference of the Food and Drug Law Institute).
\(^12\) See The Federal Food, Drug, and Cosmetic Act (FDCA) at Sec. 502(f).
\(^13\) 21 C.F.R. § 201.56(a)(1); See also “Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels; Proposed Rule,” 65 Fed. Reg. 81082, 81082 and 81083 (December 22, 2000); “Labeling and Prescription Drug Advertising; Content and Format for Human Prescription Drugs; Final Rule,” 44 Fed. Reg. 37434 at 37435 (June 26, 1979).
Similarly, in the preamble to the PLR Final Rule, in response to a comment that requested that the “Indications and Usage” section specify the type of clinical trial that has been conducted to support each indication (e.g., placebo controlled, active-controlled), FDA stated that:

“[t]he agency believes that the “Clinical Studies” section is the appropriate section of labeling to discuss the details (e.g., trial design, outcome) of clinical trials, not the “Indications and Usage” section. The agency has concluded that greater clarity about the scope of the information to be included in the “Indications and Usage” section is warranted and has revised proposed § 201.57(c)(2) accordingly. This revision is consistent with having, as stated in the preamble to the proposed rule, a more focused “Indications and Usage” section (65 FR 81082 at 81091).”15

Another consequence of including Accelerated Approval information in the “Indications and Usage” section is that this information will also be inappropriately included in the “Highlights of Prescribing Information” section.16 According to FDA in the preamble to the PLR Final Rule, the Highlights section “summarizes the information…that is most important for prescribing the drug safely and effectively.”17 Describing the regulatory pathway, under which the product was approved, does not provide immediately useful prescribing information, such as the recommended dosage or a boxed warning that leads to prescribing the drug safely and effectively.18 If anything, its inclusion in the Highlights section will create the unbalanced perception that products approved under Accelerated Approval, by virtue of their approval pathway alone, are cause for concern, despite having met the full statutory standards of safety and efficacy.

b. Preserve the intent of enhancements to the Accelerated Approval pathway

Not only does the FDA’s draft guidance suggest changes that move labeling away from its primary purpose to provide prescribers with the vital information they need to prescribe drugs safely and effectively, it could undermine recent Congressional action designed to encourage use of the Accelerated Approval pathway while maintaining its approval standards. It is clear that Congress intended for its enhancements to the Accelerated Approval pathway in FDASIA to increase, and not limit, patient access to treatments for serious or life-threatening conditions.19 The “Sense of Congress” provision stated that FDA “should apply the accelerated approval and fast track provisions … to help expedite the development and availability to patients of treatments for serious or life-threatening diseases or conditions while maintaining safety and effectiveness standards for such treatments.”20 The “Construction” provision stated that the FDASIA amendments “are intended to encourage [FDA] to utilize innovative and flexible approaches to the assessment of products under accelerated approval” and confirmed that the substantial evidence standard applies to products approved under the Accelerated Approval process.21,22

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15 See “Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Final Rule,” 71 Fed. Reg. 3922 at 3944 (January 24, 2006).
16 See 21 C.F.R. § 201.56(d); see also “Draft Guidance for Industry on Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Pathway” at lines 105-107 (March 2014).
18 See Id.
19 See FDASIA at Sec. 901.
20 Id.
21 Id.
22 See also 158 Cong. Rec. S3564 (May 24, 2012), statement of Sen. Enzi, “To receive accelerated approval, the managers’ amendment requires that FDA determine that a surrogate or clinical endpoint is reasonably likely to be predictive of an effect on clinical benefit . . . as of the time of granting accelerated approval and the standards under section 505(c) of the FDCA or section 351(a) of the Public Health Service Act are met” (emphasis added).
Further demonstrating the purpose of enhancements to the Accelerated Approval pathway, FDA’s recent draft guidance on expedited programs for serious conditions recognizes that the FDASIA amendments “facilitate somewhat broader use of accelerated approval to expedite patient access to important treatments for serious conditions.” \(^23\) FDA explains that the new provisions “provide additional flexibility concerning the implications of available therapy on eligibility for accelerated approval,” “provide clarification” concerning the use of intermediate clinical endpoints as the basis for Accelerated Approval, and “make clear that FDA has the authority to consider pharmacologic or other evidence developed using biomarkers or other scientific methods or tools, in conjunction with other data, in determining whether an endpoint is reasonably likely to predict clinical benefit.” \(^24\)

Thus, as demonstrated by the statements above, the goal of broadening the use of the Accelerated Approval pathway is to expedite the marketing approval of products for serious illnesses or conditions that provide a meaningful advantage over available therapy to help more patients while still ensuring that the statutory approval standards have been met. PhRMA is concerned, however, that FDA’s proposed draft guidance could undermine this goal. Of particular importance, the draft guidance does not propose that the “Indications and Usage” statement disclose that these products have satisfied the substantial evidence standard or that the Agency deemed the clinical endpoints “reasonably likely” to predict the specific clinical benefit. Instead, FDA’s proposed “Indications and Usage” statement emphasizes the lack of an established clinical benefit and the fact that the product is subject to withdrawal if the confirmatory trials do not verify and describe the clinical benefit. Highlighting these limitations without providing the larger context leads to an unbalanced presentation of approval standards and supporting evidence. PhRMA is concerned that this approach could lead prescribers who are less familiar with, or not well-versed in, the Accelerated Approval pathway to conclude that a drug approved under the Accelerated Approval pathway has not met the substantial evidence standard and has not received full approval. This misunderstanding could lead physicians not to prescribe Accelerated Approval products or make the public unnecessarily skeptical of products approved under the Accelerated Approval pathway, which could deprive patients of access to new safe and effective drugs and, ultimately, harm public health. The unintended result would also be contrary to Congress’s intent in enacting FDASIA, i.e., to facilitate the Agency’s broader use of the Accelerated Approval pathway in order to expedite “access to novel treatments for patients with a broad range of serious or life-threatening diseases or conditions.” \(^25\)

Accordingly, PhRMA recommends that FDA remove the proposed “continued approval” element of the “Indications and Usage” section from the final guidance. In particular, the sentence on Lines 99-103 which begins “Continued approval for this indication …” should be deleted (please refer to the Addendum for additional suggested line-by-line changes). PhRMA believes that the proposed “continued approval” statement is not essential scientific information that a practitioner needs for the safe and effective use of the drug. If FDA does not agree with PhRMA’s recommendation to remove the “continued approval” element, then PhRMA suggests that this information be placed in the “Clinical Studies” section of the labeling. In this case, PhRMA recommends that FDA consider using the following example statement to replace language in lines 99-103 and 166-172: “Confirmatory study(ies) are planned or ongoing.”

Similarly, PhRMA recommends that information in Lines 98-99 (i.e., “An improvement in {identify the specific clinical benefit that remains to be established} has not been established.”) be more appropriately included in the “Clinical Studies” section, not in the “Indications and Usage” section.

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\(^24\) Id.

\(^25\) See FDASIA at Sec. 901.
In addition, PhRMA recommends that FDA remove the reference to Accelerated Approval in the “Indications and Usage” statement in lines 96-97 and 145. PhRMA believes that referencing Accelerated Approval in the “Indications and Usage” statement is not warranted. However, if FDA believes the reference to Accelerated Approval is necessary in Full Prescribing Information, then PhRMA proposes that the “Indications and Usage” statement disclose that the product approved under the Accelerated Approval pathway has satisfied the substantial evidence standard or that FDA considered the surrogate or early clinical endpoint(s) as reasonably likely to predict the specific clinical benefit. An example of such a statement is as follows: “An improvement in survival or disease-related symptoms has not been established, but [insert specific surrogate endpoint] is predicted to lead to improvement in [insert expected clinical benefit].”

2. FDA should continue to explore ways to enhance its use of existing regulatory flexibility to expedite patient access to treatments for serious conditions and to ensure relevant information about both benefits and risks is accurately communicated in labeling

As stated above, PhRMA is concerned that emphasizing the limitations of usefulness in the “Indications and Usage” statement, as well as highlighting the fact that the product is subject to withdrawal if the confirmatory study(ies) do not verify and describe the clinical benefit, without providing the larger context, would lead to an unbalanced presentation of approval standards and supporting evidence for the Accelerated Approval pathway. PhRMA believes that regulatory flexibility is crucial for both sponsors and FDA to ensure timely patient access to new medicines while preserving FDA’s high safety and efficacy standards. FDASIA provides that Accelerated Approval may be subject to one or both of the following requirements:

“(A) That the sponsor conduct appropriate post-approval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit.”

“(B) That the sponsor submit copies of all promotional materials related to the product during the preapproval review period and, following approval and for such period thereafter as the Secretary determines to be appropriate, at least 30 days prior to dissemination of the materials.”

Regarding the statutory limitations of Accelerated Approval stated above, PhRMA recommends that FDA exerts the “one or both” flexibility afforded from FDASIA. For example, with rare diseases, disease subsets, and gene therapy products, patient populations are inherently limited. Rather than requiring results from additional separate study(ies) “where there is uncertainty as to the relationship of the surrogate endpoint to the clinical benefit, or of the observed clinical endpoint to ultimate outcome,” we suggest the possibility that more flexibility be afforded in some justifiable cases, such as using long-term safety follow-up from a study that supported Accelerated Approval to verify and describe the results of surrogate markers or clinical endpoints. Consistent with the above comments, this information can be reflected in the “Clinical Studies” section of labeling.

3. FDA should not implement this guidance until it becomes final

PhRMA recommends that FDA consider all stakeholder comments and publish final guidance prior to implementing any of the proposed changes in this draft guidance. As FDA has stated, in reference to its own Good Guidance Practices, “Industry, consumers and other stakeholders play a significant role in the agency’s guidance development processes…[d]raft proposals can help the agency better understand

26 FDCA Sections 506(c)(2)(A) and (B) as amended by FDASIA Sec. 901.
27 See “Draft Guidance for Industry on Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Pathway” at lines 57-59 (March 2014); see also 21 C.F.R. § 314.510 and § 601.41.
stakeholder positions.”

FDA’s implementation of the draft guidance would appear to be in contravention of FDA’s own Good Guidance Practice regulations that provide, generally, that FDA “solicits public input on a Level 1 guidance prior to implementation, and in preparing the final guidance, the Agency reviews and considers the comments that it has received.”

PhRMA is concerned that there could be negative public health consequences to implementing the draft guidance as currently written and believes that FDA should wait to implement this guidance after its finalization. Additionally, to mitigate the burden of any necessary labeling changes, such final guidance should only be applied prospectively.

4. FDA should integrate its efforts to communicate uncertainty in labeling with the Agency’s PDUFA V benefit-risk initiatives

PhRMA believes that efforts to improve effective communication of benefit-risk information, including any uncertainties, in labeling are important for all drugs, not just those approved under the Accelerated Approval pathway. However, we believe that the recommendations in the draft guidance have limited, or potentially negative, impact on such efforts. As stated above, until shown otherwise, a product approved under the Accelerated Approval pathway is, like all other FDA-approved drugs, considered to be safe and effective for its intended use, with its benefits outweighing its risks. PhRMA suggests that FDA integrate its efforts regarding communicating benefit, risk, and any uncertainty for the Accelerated Approval pathway with the Agency’s PDUFA V benefit-risk initiatives. For example, FDA could continue discussion of these issues as part of the Agency’s public workshops on benefit-risk considerations. Of note, FDA’s workshop to gather stakeholder input on how to communicate information on benefit, risk and uncertainty just occurred on May 12, 2014, and PhRMA believes that the recommendations in this draft guidance preempt a proper consideration of the input provided on the importance of and potential methods for communicating information about benefit-risk balance and uncertainty therein.

PhRMA strongly supports the Agency in its efforts to implement a structured approach to benefit-risk assessment. PhRMA also shares FDA’s belief that the value of a structured approach is to improve and facilitate communication between stakeholders, including patients, consumers, healthcare professionals and sponsors, regarding the benefits and risks of existing and new medicines. Another benefit of a structured approach is to promote consistency in the assessment of what information and data are relevant and most impactful in consideration of benefit-risk balance. Although FDA’s regulatory decisions are informed by an extensive body of evidence on the safety and efficacy of a proposed product, the Agency expressly identified sources of uncertainty that they frequently encounter, and are required to evaluate, during the regulatory review process, including “absence of information, conflicting findings, marginal results.”

FDA also identified the following two specific areas of uncertainty that the Agency would like to explore and better understand: “the uncertainty in how well the benefit-risk assessment based on pre-market clinical trial data translates to the post-market setting” and uncertainty about “a new finding that

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32 Id.
becomes available in the post-market setting where the basis for the finding comes from sources of varying levels of rigor. PhRMA agrees with FDA that the identified focus areas warrant further study and discussion with stakeholders, and believes that it would be beneficial to use the PDUFA V benefit-risk public workshops to explore potential ways of dealing with uncertainty in benefit-risk assessment. As stated above, PhRMA believes that labeling for all drugs, not just those approved under the Accelerated Approval pathway, should adequately present relevant benefit-risk information and recommends that FDA develop approaches to more effectively communicate uncertainty in the assessment of benefits and risks.

II. SPECIFIC COMMENTS

In addition to the general comments above, PhRMA would like to recommend specific line-by-line comments as outlined in the Addendum below. PhRMA hopes that FDA finds these comments useful as the Agency develops recommendations on information to be included in the “Indications and Usage” section of labeling for drugs approved under the Accelerated Approval pathway.

III. CONCLUSION

In summary, PhRMA shares the FDA’s goal of ensuring that information on the use of drugs and biological products approved under the Accelerated Approval regulatory pathway is consistently presented in the appropriate sections within prescription labeling so that the information is clear and accessible to health care providers. PhRMA believes that the draft guidance could be misinterpreted to mean that products approved under the Accelerated Approval pathway have not met the statutory requirements of safety and efficacy required of all FDA-approved drugs. The result could be health care provider and public confusion, which could undermine the intent of the Accelerated Approval pathway and recent Congressional efforts to encourage its broader use. PhRMA urges FDA to preserve the intent of Accelerated Approval to expedite patient access to treatments for serious conditions, and to preserve the primary purpose of prescription labeling as a mechanism to provide information to health care providers so they may prescribe medicines safely and effectively.

PhRMA appreciates the opportunity to submit these comments and hopes the Agency will find them helpful in the development of the final guidance document. PhRMA trusts that FDA will continue to seek stakeholder input as it continues to implement the FDASIA provisions related to the Accelerated Approval pathway and other expedited programs for serious conditions, and is firmly committed to working with the Agency to continue to provide hope and relief to patients with serious or life-threatening diseases and conditions.

Respectfully submitted,

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33 Id at 9-10.
### ADDENDUM

PhRMA would like to recommend specific line-by-line comments and changes as outlined below:

| Lines 20-37 | While this draft guidance, when finalized, will represent FDA’s current thinking (see Lines 8-9), PhRMA believes it is not appropriate to implement provisions in this draft guidance prior to considering stakeholders’ feedback and finalization of the guidance. PhRMA recommends that FDA clarify that the guidance will apply prospectively after guidance finalization. |
| Lines 24-26 | PhRMA recommends that FDA clarify that the guidance applies to drugs approved under the Accelerated Approval pathway only, 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.) PhRMA suggests that FDA revise the text as follows:  

> “More specifically, this guidance focuses on indications and usage statements for drugs approved via accelerated approval on the basis of a surrogate endpoint or an effect on a clinical endpoint other than survival or irreversible morbidity.” (addition underlined). |
| Lines 89, 96-99, and 137-147 | PhRMA believes that referencing Accelerated Approval in the “Indication and Usage” statement is not warranted and recommends that FDA delete “under accelerated approval” in lines 96-97 and 145.  

If FDA believes the reference to Accelerated Approval is necessary in Full Prescribing Information, then PhRMA proposes that the “Indications and Usage” statement disclose that the product approved under the Accelerated Approval pathway has satisfied the substantial evidence standard or that FDA considered the surrogate or early clinical endpoint(s) as reasonably likely to predict the specific clinical benefit. An example of such a statement is as follows: “An improvement in survival or disease-related symptoms has not been established, but [insert specific surrogate endpoint] is predicted to lead to improvement in [insert expected clinical benefit].”  

Further, PhRMA recommends that information in Lines 98-99 (i.e., “An improvement in {identify the specific clinical benefit that remains to be established} has not been established.”) is more appropriately included in the “Clinical Studies” section, not in the “Indications and Usage” section. |
| Lines 91, 99-103, and 149-172, 180 | PhRMA recommends that FDA delete the “continued approval” language.  

If FDA does not agree with PhRMA’s recommendation to remove the “continued approval” element, then PhRMA suggests that this information be placed in the “Clinical Studies” section of the labeling, not in the “Indications and Usage” section. In this case, PhRMA recommends that FDA change “trials” to “study(ies)” in Lines 166-172 to more accurately reflect potential types of supporting evidence. An example of such a statement is as follows: “Confirmatory study(ies) are planned or ongoing.” |
| Lines 130-133 | PhRMA recommends that FDA clarify that, per 21 C.F.R. § 314.510, verification of the specific clinical benefit is only required “where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.” |
| Lines 209-215 | PhRMA suggests that, similar to other sections in the draft guidance, it would be helpful for FDA to include an example of the required statement concerning the withdrawn indication. |
| Line 228 | The “Warnings and Precautions” section of the labeling 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 the providers of the change in labeling and related safety concerns. PhRMA recommends adding the following sentence at the end of the guidance: |
|     | “The change to the prescribing information, describing the risk or hazard, may also be accompanied by a Dear Health Care Provider Letter explaining that the drug is no longer approved for the withdrawn indication.” |
| Page 2, footnote 6 | PhRMA also suggests that FDA consider adding a reference in this guidance to the FDA guidance on DHCP letters to accompany the suggested edit above.34 |