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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-N-0500: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products; 78 Fed. Reg. 67985 (Nov. 13, 2013)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments to the Food and Drug Administration (FDA) on its proposal to amend the agency's Changes Being Effected (CBE) and related labeling regulations.[1] PhRMA is a voluntary, nonprofit association of the country's leading pharmaceutical research and biotechnology companies, which are dedicated to inventing medicines that allow patients to live longer, healthier, and more productive lives. In 2012 alone, PhRMA members invested approximately $50 billion in discovering and developing new medicines, representing the vast majority of private investment in new biopharmaceutical products in the United States.

Executive Summary

PhRMA supports the goal and several aspects of FDA's proposed rule: to enhance patient safety by ensuring uniform pharmacovigilance and approved labeling for both innovator and generic medicines. Especially when important new safety information arises in an environment in which there is more than one manufacturer distributing a drug (*i.e.,* a multisource environment), PhRMA believes that uniform pharmacovigilance and labeling requirements among application holders will help ensure that FDA and the public are made aware of such information as expeditiously as possible – regardless of whether the safety event at issue is related to the innovator or the generic medicine. Issues and questions can arise throughout a product's life cycle, including after generic medicines enter the market.[2] Making

[1] 78 Fed. Reg. 67,985 (Nov. 13, 2013).

[2] *See id.* at 67,988 ("[T]he median time from initial approval of the drug product to the time of making the safety-related labeling change was 11 years, which confirms that data supporting labeling changes may become available after approval of generic versions of the drug product."); *see also* H. Grabowski, et al., "Recent Trends in Brand-

generic manufacturers equal partners in pharmacovigilance is important, because once a generic version of a drug enters the market it rapidly takes up the vast majority of market share.[3] Ensuring robust pharmacovigilance by abbreviated new drug application (ANDA) holders will therefore be expected to reduce the chance that late-emerging safety signals might be missed or their identification delayed. Thus, in the interest of public health, all manufacturers should be actively involved in pharmacovigilance and in proposing labeling updates.

PhRMA supports a uniform approach to both innovator and generic manufacturers' important pharmacovigilance responsibilities – and supports the concept of parity in FDA's proposed rule. But PhRMA is concerned that allowing multiple versions of safety warnings and contraindications for the same products on the market could result in unnecessary confusion for healthcare professionals and patients. Therefore, PhRMA believes that the optimal public health solution for patients and prescribers would be for FDA to require the Agency's expeditious prior-approval of all safety-related labeling changes, regardless of whether the changes are submitted by the new drug application (NDA) holder or an ANDA holder. Under the FDA's current proposal, in the multisource environment, it would be possible for multiple generic manufacturers and the innovator to detect different safety signals and subsequently to propose different, and even conflicting, labeling changes. By requiring the agency's prior approval for all safety-related labeling changes in the multisource environment, FDA can serve a pivotal role in ensuring that safety information is provided in a consistent manner based on the safety reporting of all NDA and ANDA holders.

Accordingly, PhRMA supports the following approach for finalizing the rule:

- FDA should promptly finalize regulations that will ensure a uniform, patient-centric approach to pharmacovigilance and safety labeling obligations for both innovative and generic medicines.

- To avoid confusion over drug safety information among patients and healthcare professionals, FDA should continue its commitment to "sameness" in labeling and pre-approve all safety labeling changes for multisource medicines.

We explain below our reasons for supporting this approach, referred to as a symmetrical prior-approval supplement obligation, for the multisource environment.

Name and Generic Drug Competition," *Journal of Medical Economics*, December 10, 2013, http://www.ncbi.nlm.nih.gov/pubmed/24320785 (on average, new brand medicines faced generic competition at 12.6 years after brand launch).

[3] *See* 78 Fed. Reg. at 67,988. ("Among drugs for which a generic version is available, approximately 94 percent are dispensed as generic.");H. Grabowski et al., "Recent Trends in Brand-Name and Generic Drug Competition"(for brand medicines facing generic entry in 2011-2012, generics captured an average of 84% of the market within a year of entry, compared to just 56% in 1999-2000).

Part I of our comments provides background on the important role of FDA-approved labeling in the regulatory regime governing approval of new medicines. Part II explains why a uniform approach to drug safety labeling – especially in a multisource environment – would enhance patient safety. In Part III, we explain why a prior-approval-supplement obligation is ultimately ideal for public health for safety labeling changes in the multisource environment. But if FDA is not willing to prevent differences in the safety labeling for an innovator drug and its generic equivalent(s) then, in the alternative, PhRMA supports finalizing the proposed rule with certain technical changes, as described in Part IV, to enhance patient health and safety.

I. Background

FDA's comprehensive national regulatory regime governing the approval of new medicines revolves around the FDA-approved labeling, often referred to as the prescribing information or PI. To approve a new medicine, FDA must conclude that the NDA demonstrates that the drug is safe and effective when used under the conditions described "in the proposed labeling."[4] Once approved, a medicine's FDA-approved labeling represents the official FDA-approved description of the product. The approved labeling therefore has, as FDA has stated, enormous "scientific, medical, legal, and administrative importance."[5] FDA has long considered such labeling to be the "centerpiece of risk management for prescription drugs."[6] As FDA has stated, this labeling "reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively."[7]

The understanding of a medicine's risk-benefit profile does not end with the product's approval. Rather, such understanding "necessarily evolves over the drug's life cycle."[8] Emerging information affecting a medicine's clinical profile must be incorporated into the product's labeling when there is adequate scientific substantiation to support a labeling change.

To ensure the integrity of the post-approval labeling process, namely that changes are adequately supported and made only when warranted, FDA generally requires that a sponsor submit a supplemental new drug application (sNDA) for a proposed labeling change and obtain prior approval from FDA of the sNDA before implementing a labeling change.[9] As

[4] 21 U.S.C. § 355 (d).

[5] 40 Fed. Reg. 15,392, 15,393 (Apr. 7, 1975).

[6] 71 Fed. Reg. 3,922, 3,934 (Jan. 24, 2006) (finalizing the Physician Labeling Rule (PLR)).

[7] *Id.*

[8] IOM Committee on the Assessment of the U.S. Drug Safety System, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* at S-2 (Sept. 22, 2006).

[9] *See, e.g.*, 21 C.F.R. § 314.70(b).

FDA stated six years ago, "[a]llowing sponsors to unilaterally amend the labeling for approved products without limitation—even if done to add new warnings—would undermine the FDA approval process required by Congress . . . . [and] disrupt FDA's careful balancing of how the risks and benefits of the product should be communicated."[10]

Desiring to serve the public health through expeditious dissemination of newly acquired safety-related information through labeling in certain circumstances, FDA created the CBE process in 1965 when communication between the agency and manufacturers, and between manufacturers and health care professionals, was slower and more cumbersome.[11] The CBE process was initiated as, and remains, a policy of enforcement discretion regarding "certain labeling changes that should be placed into effect 'at the earliest possible time'" based on newly acquired information.[12] CBE changes are a narrow exception to the general rule that labeling changes require FDA approval before implementation.

Although the CBE process allows sponsors to implement changes before FDA approval, FDA views a CBE supplement "as a mechanism primarily designed to provide information to FDA so that the agency can decide when safety information should be included in the labeling for a product."[13] And, according to FDA, "the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act."[14] In practice, even where the narrow CBE procedure applies, NDA and BLA holders often consult with FDA to seek the agency's agreement to significant labeling changes before using the CBE process. As the FDA has stated, such informal consultation with the agency allows sponsors "to avoid implementing labeling changes with which the agency ultimately might disagree (and that therefore might subject the manufacturer to enforcement action)."[15]

II. PhRMA Supports FDA's Goal of Enhancing Patient Safety By Creating Uniform Drug Safety Responsibilities for Innovator and Generic Manufacturers in a Multisource Environment

PhRMA supports FDA's goal of creating a system where all manufacturers in the multisource environment are equally engaged in pharmacovigilance activities and have symmetrical responsibilities with respect to safety-related labeling changes. As discussed herein, PhRMA believes that the agency ultimately should do so through a prior-approval regime for all safety-related labeling changes in a multisource environment. Nevertheless, FDA's proposed rule includes important features that PhRMA believes will further this goal and improve patient safety. In particular, PhRMA and its member companies agree with the agency

[10] *See* 73 Fed. Reg. 2,848, 2,849 (Jan. 16, 2008).

[11] *See* 78 Fed. Reg. at 67,987 (referencing 30 Fed. Reg. 993 (Jan. 30, 1965)).

[12] *Id.* (quoting 30 Fed. Reg. 993 (Jan. 30, 1965)).

[13] 73 Fed. Reg. at 2,849.

[14] 71 Fed. Reg. at 3,934.

[15] *Id.*

that "ensur[ing] that generic drug companies actively participate with FDA in ensuring the timeliness, accuracy, and completeness of drug safety labeling" will enhance patient safety.[16] Given that 80 percent of all drugs dispensed are generic drugs and, "[a]mong drugs for which a generic version is available, approximately 94 percent are dispensed as a generic," generic manufacturers must be engaged in meaningful pharmacovigilance to help detect important new information that may be relevant to the safe and effective use of all versions of a product.[17] PhRMA appreciates that FDA's proposed rule will require generic manufacturers to participate in the important process of ensuring that new safety information is put squarely before FDA for timely consideration, thereby enhancing FDA's knowledge about a product. This will result in more thorough, authoritative safety information for prescribers and their patients.

In addition, if the CBE mechanism is retained for safety labeling changes in the multisource environment, PhRMA supports FDA's proposal to require generic manufacturers to submit conforming safety-related labeling changes via a CBE supplement within thirty days of FDA's posting on its website the approval of the change to the labeling of a reference listed drug (RLD).[18] This approach supports uniformity in drug labeling and the goal of ensuring timely communication of important health information to the public. If manufacturers have the ability to disseminate updated labeling prior to FDA review, it follows that manufacturers should update that information as soon as possible after FDA has provided its feedback. Currently, FDA advises ANDA holders to revise product labeling "at the very earliest time possible" after a change is made to the RLD's labeling.[19] This has led to lag time (in some instances years) between the update of the RLD's labeling to reflect newly acquired safety information, on the one hand, and conforming changes to generic drug labeling, on the other hand.[20] The approach FDA has outlined in the proposed rule would be expected to reduce this lag time significantly and help prevent prescriber and patient confusion that would result from labeling differences among AB-rated products.

PhRMA further supports FDA's proposal to require that a manufacturer cease distribution of a medicine accompanied by labeling revised in a CBE supplement (and revert back to the previous labeling) where the CBE supplement fails to meet the CBE criteria – changes to reflect "newly acquired information" or "to add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling…."[21] As discussed above, CBE changes are the narrow

[16] 78 Fed. Reg. at 67,989.

[17] *Id.* at 67,988.

[18] *See* Proposed 21 C.F.R. § 314.70(c)(8)(iv), 78 Fed. Reg. at 67,993, 67,999.

[19] *See* Guidance for Industry: Revising ANDA Labeling Following Revision of the RLD Labeling, at 5 (May 2000).

[20] *See*, *e.g.*, Letter of Joseph P. Thomas to Leonard Green, Clerk, Sixth Circuit Court of Appeals at 1., *Smith v. Wyeth, Inc.*, No. 09-5460 (6th Cir. Mar. 17, 2011) (disclosing that by March 2011, PLIVA had not fully implemented a 2004 labeling change to the RLD labeling).

[21] *See* Proposed 21 C.F.R. § 314.70(c)(8)(iii), 78 Fed. Reg. at 67,993, 67, 998-99; see also 21 C.F.R. § 314.70 (c)(6)(iii)(A).

exception to the general requirement of FDA approval before distribution of revised labeling. PhRMA supports FDA's goal of maintaining the boundaries of the CBE process by ensuring that only a narrow subset of labeling changes are implemented without the agency's prior approval.[22]

III. A Prior-Approval System for Safety-Related Labeling Changes in a Multisource Environment Is the Most Effective Means of Enhancing Patient Safety and the Public Health

To protect patients and help ensure that prescribers have authoritative, FDA-approved safety information available, FDA should maintain its central role in controlling the information disseminated through FDA-approved labeling. Accordingly, as described in Section II, PhRMA and its member companies support FDA's goal of enhancing public safety through the equalization of pharmacovigilance and labeling responsibilities among manufacturers. Rather than change course and decentralize the labeling of FDA-approved drugs in a multisource environment, however, PhRMA strongly believes that patient safety would be best served through implementation of a prior-approval system for all safety-related labeling changes made in a multisource environment.

Prior approval for safety-related labeling changes will serve the interest of patient safety better than the current system or the system contemplated under FDA's proposed rule, and will maintain FDA's important role in the labeling change process. Current FDA regulations establish that virtually all labeling changes require FDA assent, with "major changes" requiring FDA prior approval.[23] If FDA requires all manufacturers in a multisource environment to propose safety labeling changes, FDA's involvement in the labeling process will be even more critical than in the current regulatory scheme, as the agency can help ensure that labeling changes are made in a consistent and coherent manner and are not driven by potentially different sets of adverse event reports and diverse views of various manufacturers regarding the safety of a multisource medicine.

The approved labeling for a drug represents the official, FDA-sanctioned prescribing information for treatment, based on the high evidentiary standards of the Food, Drug, and Cosmetic Act (FDCA). Prior-approval for any safety-labeling change both reinforces FDA's primacy as the expert scientific authority in control of drug labeling and ensures that labeling changes carefully balance the need to provide scientifically valid and clinically meaningful information on the product's benefits and risks with the need to maintain consistency and avoid the inclusion of information that might be extraneous or distracting.

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[22] For practical reasons as well as to help preserve the agency's central role in the labeling change process, the rule should allow for a degree of flexibility and FDA discretion regarding the precise timing for such label reversions. This would be consistent with both the commentary accompanying the proposed regulation, *see* 78 Fed. Reg. 67,993, and the current CBE regulation, *see* 21 C.F.R. § 314.70(c)(7).

[23] *See* 21 C.F.R. § 314.70.

In a multisource environment, safety information is accumulated primarily through spontaneous adverse event reports, as opposed to clinical studies or other controlled post-marketing research. Because of the relative unreliability of such information compared to controlled sources, and its collection and reporting from disparate sources, the significance of such data typically requires extensive evaluation. Given FDA's unique ability to review safety information from all reporters and the agency's leading role in developing and implementing new active surveillance tools, FDA is well-equipped to oversee the analysis of aggregate data and advise on safety labeling changes before they are disseminated to the public. Prior-approval is also consistent with the current practice in the single-source environment: manufacturers often consult with FDA regarding any safety-labeling change in light of the agency's expertise in the field and its enforcement authority against misbranding. Therefore, PhRMA believes prior-approval is both practical and in the interest of patient safety.

Moreover, requiring FDA prior approval for all safety-related labeling changes in a multisource environment will help prevent potential confusion that might result from different versions of the same medicine having different labeling. Confusion regarding newly acquired safety information would be expected to have negative consequences for patient safety. For example, if the labeling of one version of a multisource product lacked new safety information that appeared in the labeling of another version of the multisource medicine, a physician could incorrectly assume that the omission was deliberate and that the medicine without the new safety information is safer. Requiring prior approval for all safety-related labeling changes would help prevent this scenario and other possible confusion by allowing FDA to approve common labeling that would apply to all approved versions of a product simultaneously.

Requiring prior approval for safety-related labeling changes for a multisource medicine will also prevent unnecessary labeling changes that could lead to prescriber and patient confusion if FDA rejects a CBE-0 supplement. As FDA recognizes, "how to address a safety concern often [is] a matter of judgment, about which reasonable persons with relevant expertise may disagree, and this may be reflected in different approaches to proposed labeling changes based on newly acquired safety information."[24] Innovators and generic manufacturers might propose, in response to newly acquired safety information, different changes to their labeling. In contrast to this approach, requiring FDA's prior approval of such changes will ensure that innovators and generic manufacturers do not unilaterally implement labeling changes that might ultimately have to be reversed after FDA decides how the newly acquired safety information should appear across all labeling of a multisource product. Avoiding unnecessary and multiple labeling changes will help maintain the fundamental public health purpose of and public confidence in the FDA-approved labeling of medicines.

Finally, implementing a prior-approval regime for safety-related labeling changes will maintain prescriber and patient confidence in the therapeutic equivalence of generic and

[24] 78 Fed. Reg. at 67,991.

innovative products. Consistent labeling will, as FDA has stated, "assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart."[25]

IV. PhRMA's Recommended Technical Changes

If FDA decides to permit generic manufacturers to make safety-related changes using the CBE process, PhRMA makes the following technical suggestions on the proposed rule below, which we urge FDA to consider before finalizing its proposal.

1. Changes to the Highlights of Prescribing Information

FDA proposes to revise its regulations to permit CBE supplements for changes to the Highlights of Prescribing Information (Highlights) of drug labeling. PhRMA believes that continuing to require FDA approval of Highlights changes is important for maintaining clear prescriber understanding of the most important risks and benefits of new medicines and for patient safety.

The Highlights of Prescribing Information is, as FDA states, a "concise extract of the most important information" required in drug labeling, including "the most important information regarding drug-related risks."[26] Under current FDA regulations, most changes to the Highlights section of drug labeling are considered "major changes" and therefore require FDA approval before implementation.[27] FDA requires prior approval of changes to the Highlights section because of "the difficulty involved in summarizing the complex information presented in the full prescribing information."[28] As recently as 2008, FDA affirmed that where changes to the contraindications, warnings and precautions, and adverse reactions sections of drug labeling require corresponding changes to the Highlights section, the changes to the Highlights section must be approved by FDA in a prior approval supplement.[29]

PhRMA believes that continuing to require FDA approval of changes to the Highlights section is important for helping to ensure patient safety. The Highlights section is

[25] 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992).

[26] 65 Fed. Reg. 81,082, 81,087, 81,088 (Dec. 22, 2000) (proposing the PLR Rule).

[27] *See* 21 C.F.R. § 314.70(b)(2)(v)(C). Certain minor changes to the Highlights section may be adopted without prior agency approval. *See id.*

[28] 78 Fed. Reg. at 67,993.

[29] *See* 73 Fed. Reg. at 2,850 n.4 ("Because all contraindications must be described in Highlights . . . and because Highlights cannot be amended by a CBE supplement . . . adding or substantively amending a contraindication requires a prior approval supplement, unless FDA requests that the change be made" in a CBE supplement and approves a waiver request for such change.).

intended to "draw attention to those sections of the labeling that are most important."[30] Confirming that FDA agrees with and approves how Highlights information is presented is therefore of utmost importance to patient safety. FDA's initial judgment to require prior approval of Highlights was correct and underscores the need for FDA to pre-approve all safety labeling changes. Safety changes described in other sections of the label are more than likely to be summarized in the Highlights. PhRMA understands that FDA has typically waived this requirement for CBE-0 supplements. However, as previously noted, in practice, NDA holders often consult with FDA to seek the agency's agreement, particularly for changes in Highlights, before using the CBE process.

If FDA finalizes its proposal to permit generic manufacturers to submit CBE labeling changes, FDA approval of the Highlights section will become even more important. This is so because differences between innovator and generic product labeling will inevitably exist as a result of generic manufacturers unilaterally changing their labeling via CBE supplements. Ensuring that the summary presented in the Highlights section is uniform across all versions of a multisource medicine is critical to prescriber and patient understanding of a product. PhRMA therefore urges FDA to reconsider its proposal to allow CBE supplements for changes made to the Highlights section.

2. Changes to Medication Guides

Similarly, PhRMA believes that continuing to require FDA approval of changes to Medication Guides is important for patient safety. FDA's proposed rule does not specifically address how it intends to handle proposed changes to patient Medication Guides. Under existing regulations, changes to Medication Guides – like changes to the Highlights section – require prior approval. Medication guides are patient information documents for drugs that pose serious public health concerns,[31] and they contain safety information and must be consistent with the labeling for doctors.[32] Accordingly, for reasons similar to those expressed in relation to the Highlights section, PhRMA urges FDA to prohibit CBE supplements for changes to Medication Guides.

3. Public Posting of Proposed CBE Changes

FDA proposes the public posting of *pending* CBE changes on the theory that this will assist in informing treatment decisions and in protecting patient safety. PhRMA believes, however, that public posting is likely to lead to prescriber and patient confusion, which would not benefit, and could potentially harm, public health.

[30] 65 Fed. Reg. at 81,087.

[31] 21 C.F.R. § 208.1(a).

[32] 21 C.F.R. § 208.20(a)(2).

FDA proposes to include on its website a page in which the agency will "promptly post information regarding the labeling changes proposed in a CBE-0 supplement while FDA is reviewing the supplement."[33] FDA intends this webpage to "enhance transparency and facilitate access by health care providers and the public to labeling containing newly acquired information about important drug safety issues so that such information may be used to inform treatment decisions."[34] The website will include, among other things, a description of the proposed change, a link to the current labeling for the medicine containing the proposed changes, the source of information for the proposed changes, and the status of the pending CBE supplement.[35]

PhRMA's primary concern with this proposal is that prescribers and patients might not understand that although a particular change is posted on the FDA website, the agency and application holders may not have determined the scientific validity of – and FDA has not approved – the proposed change. Over time, this, in turn, could undermine their confidence in and reliance on the FDA-approved labeling as the authoritative statement about a prescription medicine. PhRMA is also concerned about prescriber and patient confusion stemming from varying and potentially conflicting proposed changes to the same multisource medicine being posted publicly before FDA has vetted the proposed changes. In its preamble, FDA notes that "a valid safety concern regarding a generic drug product . . . would generally warrant submission of a supplement for a change to the labeling by the NDA holder for the RLD, as well as other ANDA holders."[36] This comment in the preamble might encourage various manufacturers of a multisource medicine to submit CBE supplements for the same (or similar) safety issue. But as FDA has also recognized, "how to address a safety concern often [is] a matter of judgment."[37] There is therefore a high probability that the proposed changes submitted by different manufacturers will vary. Yet, FDA is proposing to post these differing changes on its website, without explanation from, or review by, the agency of how these differences affect (or do not affect) the risk-benefit profile of the multisource medicine. PhRMA is concerned that posting different proposed changes to the labeling for the same multisource medicine will confuse physicians and patients and impair their treatment decisions unnecessarily.

PhRMA supports a robust conversation among affected application holders and the agency regarding proposed safety-related labeling changes. But until agreement with the agency is reached on the precise wording of any changes necessary for all package inserts of a multisource medicine, we believe it would be inappropriate for FDA to disseminate unapproved

[33] *See* Proposed 21 C.F.R. § 314.70(c)(8); 78 Fed. Reg. at 67,989, 67,998.

[34] 78 Fed. Reg. at 67,990.

[35] *See id*. at 67,989.

[36] *Id.*

[37] *Id*. at 67,991.

– and potentially non-authoritative – PIs on the FDA website. We therefore urge the agency to reconsider its proposal to publicly post pending CBE changes.

If FDA decides to post pending CBE-0 changes on the agency's website, it should commit to doing so within a specific period of time (*e.g.*, 10-14 days after receipt of the proposed change) instead of the current proposal, which would require FDA to do so "promptly." Similarly, FDA should commit to removing information from the website within a specific period of time after it concludes that the information does not warrant a labeling change. Such features would enhance the timeliness of safety labeling information posted on FDA's web site.

Moreover, if FDA does decide to post pending CBE changes on its web site, FDA should make clear that application holders have the ability to communicate about the information contained in such labeling without fear that those views will be deemed to misbrand the medicines under the FDCA. In the context of a proposed public debate of the scientific validity a particular labeling change, all application holders should be able to discuss truthful and non-misleading safety information contained in their pending CBE as well as their positions on the rationale for the proposed safety-related changes.

4. Expectations of the NDA Sponsor Upon Receipt of ANDA-Holder's CBE

FDA is proposing to require that when a generic manufacturer submits a CBE supplement, the generic manufacturer will also notify the NDA holder of the proposed change and provide a copy of the information supporting the change. If FDA finalizes this proposal, PhRMA and its member companies believe that FDA must manage such a process in order to ensure timely, uniform, and data-driven changes to FDA-approved labeling, especially in a multisource environment. An ANDA holder's proposed labeling change, and the sharing of the CBE supplement with the NDA holder, should not constitute a de-facto regulatory request from FDA to the NDA holder.

Although NDA holders will maintain their existing obligations concerning pharmacovigilance and updates to labeling, FDA should clarify that it is not suggesting that the NDA holder will be in a position to, and will be expected to, confirm or refute each specific safety change being proposed by the ANDA holder outside of these existing obligations. NDA holders are already obligated under 21 C.F.R. § 314.80 to evaluate all available safety information from any source. Accordingly, upon receipt of an ANDA holder's proposed CBE labeling change, FDA should notify all relevant application holders that the agency is considering the changes, making further changes, or considering comments from another applicant. FDA should notify each application holder as soon as the agency's analysis is completed. FDA's initial notification to other application holders should also state that such companies should not implement a new or different CBE change regarding the safety signal at issue until FDA reviews the initial CBE request and confirms its appropriateness for all applications. Such minor FDA management of CBE processing would constitute a small

administrative burden, but it could prevent distinct cascading CBE labeling changes upon an initial labeling proposal that, in the end, FDA may reject.

5. Labeling Discussions for Safety-Related Labeling Changes for Innovator Drugs and their Generic Equivalents

FDA has not explained how the agency intends to conduct labeling discussions across manufacturers of innovator drugs and their generic equivalents when it has received multiple CBEs relating to the same safety issue for a multisource medicine. PhRMA believes that such labeling discussions in situations where multiple manufacturers submit proposed changes via a CBE for a similar warning for a particular product and the proposed changes are not identical (i.e., there are wording variations), could be time-consuming and complex. PhRMA therefore requests additional information about how the agency plans to conduct such labeling discussions, and more specifically, how FDA plans to resolve issues that will arise when different manufacturers have differing views on how a particular safety issue should be reflected in labeling.

In addition, when there are different proposed labeling changes to address the same safety issue for multiple products, FDA should have an obligation to act within a pre-specified and expeditious timeframe, particularly considering the potential for confusion by healthcare professionals and patients in the absence of FDA action. PhRMA suggests that a decision within 90 days is an appropriate timeframe for FDA consideration of such changes prompted by competing CBEs for a multisource medicine.

PhRMA also requests that the agency clarify how it would protect an innovator's confidential commercial information, as the agency discusses a safety-related labeling change among multiple manufacturers. In many instances, the innovator will have access to relevant information in the original NDA that is considered confidential commercial information and must be protected by law.[38]

[38] *See e.g.*, *Citizens Comm'n on Human Rights v. FDA*, 92-CV-5313, 1993 WL 1610471, *7 (C.D. Cal. May 10, 1993) (holding that "an NDA by definition contains trade secret information because it contains significant information about how a pioneer drug product is formulated, chemically composed, manufactured, and quality controlled," and that "the withheld information from the NDA consists also of commercial information, obtained from a person, and considered privileged or confidential," which is exempt from disclosure under the Freedom of Information Act.) *aff'd in part, remanded in part sub nom. Citizens Comm'n on Human Rights v. FDA*, 45 F.3d 1325 (9th Cir. 1995); *Pub. Citizen Health Research Grp. v. FDA*, 539 F. Supp. 1320, 1327 (D.D.C. 1982) *aff'd in part, rev'd in part*, 704 F.2d 1280 (D.C. Cir. 1983) (noting that "because documentation of the health and safety experience of their products will be instrumental in gaining marketing approval for their products, it seems clear that the manufacturers of [the product at issue] have a commercial interest in the requested information," and that this information could be considered "confidential" within the meaning of Exemption 4).

6. Symmetry of Pharmacovigilance Requirements

PhRMA suggests that if FDA intends to make safety-labeling change requirements symmetrical for innovator and generic manufacturers, which necessarily anticipates more proactive pharmacovigilance on the part of generic manufacturers, it must also ensure that their pharmacovigilance obligations are symmetrical. Generic manufacturers will be better positioned to make informed decisions about potential safety-related labeling changes if they have the same robust pharmacovigilance duties as innovators.

Under current regulations, unlike innovators, generic manufacturers need not conduct literature reviews to help ensure complete safety reporting, nor are ANDA holders required to report adverse events arising from *any* jurisdiction in which a product is marketed.[39] In fact, 21 C.F.R. § 314.98 specifies that ANDA holders are required to comply with only the reporting and record keeping requirements of 21 C.F.R. § 314.80.

PhRMA believes that making clear that the pharmacovigilance responsibilities of generic manufacturers match those of innovators will improve patient safety. A drug's risks cannot be fully understood based on pre-approval testing alone. This is particularly true where a drug's risks are rare or have long latency periods. Thus, safety issues can arise even after generic market entry.[40] Ensuring that generic manufacturers operate and maintain effective pharmacovigilance systems will help guarantee that any postmarketing safety issues will be expeditiously captured and reported to FDA, regardless of whether they resulted from administration of an innovator or generic medicine.

PhRMA believes that increasing generic manufacturer pharmacovigilance activities will also assist FDA in making informed labeling decisions. Expanding generic manufacturer postmarketing surveillance will increase the amount of safety information available to FDA. This increased knowledge will allow FDA to make more informed labeling decisions as the agency's understanding about the risk-benefit profile of a drug evolves over time.

Conclusion

PhRMA appreciates FDA's attention to issues surrounding generic manufacturers' ability to revise their labeling to reflect newly acquired safety information. PhRMA believes that the best approach to safety-related labeling changes in a multisource environment is for FDA to provide prior approval of all such changes on for the RLD and all generic versions. If FDA nonetheless believes that permitting generic manufacturers to submit CBE supplements remains the best approach, then PhRMA urges FDA to make the technical

[39] *See* 21 C.F.R. § 314.80(b) (requiring only applicants with an approved application under 21 C.F.R. § 314.50 (the regulation governing NDAs) to conduct literature reviews and report adverse events from any jurisdiction).

[40] *See* 78 Fed. Reg. at 67,988 (recognizing that data supporting safety-related labeling changes may arise after generic approval).

changes identified in these comments to enhance patient safety, reduce confusion among prescribers and patients, and clarify the agency's expectations with regard to pharmacovigilance and safety labeling responsibilities. Regardless of which method FDA adopts, in order to enhance patient safety, PhRMA encourages FDA to act promptly to implement equal pharmacovigilance and safety reporting requirements for innovator and generic application holders.

Respectfully submitted,

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