DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Re: Docket No. FDA-2011-P-0675

Dear Dr. Wolfe, Ms. Zieve, and Mr. Wolfman:

This responds to your citizen petition received on September 14, 2011 (Petition). Your Petition requests that the Food and Drug Administration (FDA or the Agency) amend its regulations at 21 CFR 314.70, through notice-and-comment rulemaking, to authorize the holder of an abbreviated new drug application (ANDA) to revise the product labeling for its generic drug in a manner that differs from the labeling for the corresponding reference listed drug (RLD) through submission of a *changes being effected* (CBE-0) supplement or a *prior approval* supplement (see Petition at 1 and 9). You also request that FDA amend 21 CFR 314.150(b)(10), which describes circumstances in which FDA may take steps to withdraw approval of an ANDA if the generic drug labeling is no longer consistent with the corresponding RLD labeling, to specify that this regulation does not apply to ANDA holders permitted to supplement labeling through CBE-0 or prior approval supplement procedures (Petition at 1-2). Finally, you request that FDA amend 21 CFR 201.57(c)(6)(i) to clarify that all ANDA holders are required to report safety concerns to FDA as soon as they become aware of a clinically significant hazard (see Petition at 2 and 9). With reference to the U.S. Supreme Court's decision in Pliva, Inc. v. Mensing, 131 S.Ct. 2567 (2011), you maintain that "drug safety is threatened when the regulatory and common-law incentives designed to motivate manufacturer diligence [with postapproval safety monitoring] weaken with shifting control of market share" from brand name to generic drug manufacturers (Petition at 7).

We have carefully reviewed your Petition and the comments on your Petition submitted to the public docket by Morton Grove Pharmaceuticals, Inc., on September 30, 2011; Pharmaceutical

Associates, Inc. (PAI), on October 14, 2011; Actavis, Inc. (Actavis),[1] on November 8, 2011; and the American Association for Justice (AAJ) on March 2, 2012.

On November 8, 2013, FDA issued a proposed rule that would amend its regulations to revise and clarify procedures for application holders to change the labeling of an approved drug or biological product to reflect certain types of newly acquired safety-related information in advance of FDA's review of the change (see "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products"; proposed rule, available at https://www.federalregister.gov/public-inspection and attached as Appendix A). To the extent that this proposed rule, if finalized, would address some (but not all) of your requested revisions to the regulations, your Petition is granted in part and denied in part. Because many of the issues raised by your Petition and the comments submitted to the Petition docket would be more appropriate to address in the context of the proposed rule, we encourage you and other interested parties to review the proposed rule and submit comments to the public docket established for this rulemaking (Docket No. FDA-2013-N-0500).

I. BACKGROUND

When new information becomes available that causes information in drug product labeling to be inaccurate, the application holder must take steps to change the content of its labeling, in accordance with 21 CFR 314.70 and 314.97. All holders of marketing applications for drug products have an ongoing obligation to ensure their labeling is accurate and up to date.

For most substantive changes to product labeling, an application holder is required to submit a prior approval supplement and receive FDA approval for the change (see § 314.70(b)). However, in the interest of public health, the regulations permit certain labeling changes based on newly acquired safety-related information about an approved drug to be implemented upon receipt by the Agency of a changes being effected supplement (see § 314.70(c)(6)(iii)).

Although FDA has expressed differing views on this issue over the years, FDA generally has advised that an ANDA holder may use the CBE-0 supplement process only to update its product labeling to conform with approved labeling for the RLD or to respond to FDA's specific request to submit a labeling change under this provision, and may not unilaterally change ANDA labeling in a manner that differs from the labeling of the RLD (see 21 CFR 314.150(b)(10); see also 57 FR 17950 at 17961, April 28, 1992, and "Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices"; proposed rule, 73 FR 2848 at 2849; footnote 1; January 16, 2008). Thus, under current regulations, if an ANDA holder believes that newly acquired safety-related information should be added to its product

[1] Actavis was the petitioner in the companion cases (Actavis Elizabeth, LLC v. Mensing and Actavis, Inc. v. Demahy) that were decided together with Pliva v. Mensing.

labeling, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic drug(s) and the *brand name* RLD should be revised (see 57 FR 17950 at 17961).

In Pliva v. Mensing, the U.S. Supreme Court held that the difference between the ability of new drug application (NDA) holders for *brand name* drugs and ANDA holders for generic drugs to independently change product labeling through a CBE-0 supplement leads to different outcomes on whether Federal labeling requirements preempt State law tort claims against pharmaceutical manufacturers for failing to provide adequate warnings in product labeling (*failure-to-warn claims*). The Court deferred to FDA's interpretation of its CBE-0 supplement and labeling regulations for ANDAs, and found that Federal law did not permit a generic drug manufacturer to use the CBE-0 supplement process to unilaterally strengthen warnings in its labeling or to issue additional warnings through *Dear Health Care Provider* letters, which FDA "argues ... qualify as 'labeling'" (131 S.Ct. at 2576). The Court found that, under the current regulatory scheme, it was impossible for a generic drug manufacturer to comply with its Federal law duty to have the same labeling as the RLD and satisfy its State law duty to provide adequate labeling (131 S.Ct. at 2578). As a result, the Court decided that Federal law preempts a State law failure-to-warn claim that a generic drug's labeling did not contain an adequate warning. The Court concluded by stating: "As always, Congress and the FDA retain the authority to change the law and regulations if they so desire" (131 S.Ct. at 2582).

II. DISCUSSION

The U.S. Supreme Court's decision in Pliva v. Mensing prompted FDA to evaluate its current regulations because this decision, as well as the recent decision in Mutual v. Bartlett,[2] may alter the incentives for generic drug manufacturers to comply with current statutory and regulatory requirements to conduct robust postmarketing surveillance, evaluation, and reporting, and to ensure that their product labeling is accurate and up to date.[3] In the current marketplace, in which approximately 80 percent of drugs dispensed are generic drugs[4] and, as we have learned, brand name drug manufacturers may discontinue marketing after generic

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[2] In Mutual v. Bartlett, 133 S. Ct. 2466 (2013), the U.S. Supreme Court decided that Federal law also preempts State law design-defect claims that turn on the adequacy of a generic drug's warnings.

[3] See, e.g., Wyeth v. Levine, 555 U.S. 555, 579 (2009) ("Failure-to-warn actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times. Thus, the FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation").

[4] See IMS Institute for Healthcare Informatics, "The Use of Medicines in the United States: Review of 2011," April 2012 (available at http://www.imshealth.com/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/IHII_Medicines_in_U.S_Report_2011.pdf).

drug entry, FDA believes it is time to provide ANDA holders with the means to independently update product labeling to reflect data obtained through postmarketing surveillance, even though this will result in temporary labeling differences among products. The proposed rule, if finalized, would allow generic drug manufacturers, like brand manufacturers, to independently update product labeling to reflect certain newly acquired safety information as part of the drug manufacturer's independent responsibility to ensure that its product labeling is accurate and up to date.

A. Overview of Selected Provisions of the Proposed Rule on CBE-0 Supplements

The proposed rule would create parity among application holders with respect to these safety-related labeling changes by permitting ANDA holders to distribute revised generic drug labeling that differs in certain respects, on a temporary basis, from the RLD labeling upon submission of a CBE-0 supplement. An ANDA holder would be required to send notice of the labeling change proposed in the CBE-0 supplement, including a copy of the information supporting the change, to the NDA holder for the RLD, unless approval of the NDA has been withdrawn. To make the safety-related changes to drug labeling described in a CBE-0 supplement readily available to prescribing health care providers and the public while FDA is reviewing the supplement, FDA proposes to establish an FDA Web page on which FDA would promptly post information regarding the labeling changes proposed in a CBE-0 supplement.

A safety-related labeling change that is submitted by an ANDA holder in a CBE-0 supplement would be approved upon approval of the same labeling change for the RLD (unless approval of the NDA for the RLD has been withdrawn), so that the approved labeling for the generic drug continues to be the same as the approved labeling for its RLD. The proposed rule would establish a 30-day time frame in which all ANDA holders would be required to submit a CBE-0 supplement with conforming labeling changes after FDA approval of a revision to the RLD labeling.

As previously noted, FDA regulations provide that FDA may take steps to withdraw approval of an ANDA if the generic drug labeling is no longer consistent with the labeling for the RLD, subject to certain exceptions specified in the regulations (see § 314.150(b)(10)). The proposed rule would amend the regulations to add a new exception for generic drug labeling that is temporarily inconsistent with the labeling for the RLD due to safety-related labeling changes submitted by the ANDA holder in a CBE-0 supplement.

For additional information regarding the proposed rule, please refer to Appendix A. FDA's notice of proposed rulemaking provides instructions for the public to submit comments on the proposed rule. FDA will review the comments submitted to the public docket established for the proposed rule before taking further action.

B. All Application Holders Are Required to Report Safety Concerns to FDA As Soon As They Become Aware of a Clinically Significant Hazard

The proposed rule does not specifically address your request that FDA amend its regulations to clarify that all ANDA holders are required to report safety concerns to FDA as soon as they become aware of a clinically significant hazard (see Petition at 2 and 9). FDA denies this request because the current regulations at 21 CFR 314.80, 314.81, and 201.57(c)(6) clearly apply to ANDA holders (see 21 CFR 314.98).[5]

As a drug is used more widely or under diverse conditions, new information regarding the risks and benefits of a drug may become available. Accordingly, all application holders are required to develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA (see 21 CFR 314.80(b) and 314.98(a)). All application holders must promptly review all adverse drug experience information that they obtain or otherwise receive from any source, foreign or domestic, and comply with applicable reporting and recordkeeping requirements (see §§ 314.80(b) and 314.98(a)). Application holders also must comply with requirements for other postmarketing reports under 21 CFR 314.81 and section 505(k) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). These requirements include submission of an annual report (including a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product, and a description of actions the applicant has taken or intends to take as a result of this new information) and, if appropriate, proposed revisions to product labeling (see § 314.81; see also 57 FR 17950 at 17965 (describing requirement for "ANDA applicants to submit a periodic report of adverse drug experiences even if the ANDA applicant has not received any adverse drug experience reports *or initiated any labeling changes*") (emphasis added)).

All holders of marketing applications for drugs have an ongoing obligation to ensure their labeling is accurate and up to date. A drug is misbranded in violation of the FD&C Act when its labeling is false or misleading, or does not provide adequate directions for use and adequate warnings (see 21 U.S.C. 331(a) and (b) and 352(a), (f), and (j)).

The proposed rule, if finalized, would allow ANDA holders to comply with the requirement to update labeling promptly to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug, as well as other risk

[5] See, e.g., PAI Comment at 4, note 1, citing Petition at 9 (explaining that "[t]here is no need, as Public Citizen requests, to 'clarify the view. . . . that all ANDA holders have a duty to report safety concerns to the FDA.' ... The regulations are already clear on this point"); see also AAJ Comment at 3 (maintaining that "both the [RLD] holder, generally referred to as the brand manufacturer, and generic drug manufacturers are subject to the requirement that their approved 'labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved'").

information required by the regulations (see 21 CFR 201.57(c) and 201.100(d)(3)), without FDA's special permission and assistance. In the meantime, ANDA holders who believe that drug product labeling needs to be updated to reflect newly acquired safety-related information should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic drug(s) and the RLD should be revised.

III. CONCLUSION

For the reasons discussed above, your Petition is granted in part and denied in part. We look forward to your comments on the proposed rule, and thank you for your interest in this matter.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research