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"Examining Concerns Regarding FDA's Proposed Changes to Generic Drug Labeling"

Statement of

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INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss FDA's proposed labeling rule which, if finalized, would speed the dissemination of new safety information about generic drugs to health professionals and patients by allowing generic drug makers to use the same process as brand drug manufacturers to update safety information in the drug product labeling. I should emphasize at the outset that this is a proposed rule and that FDA received comments on the proposal until March 13 of this year. We will consider those comments carefully, and the final rule may differ in some respects from the proposal to reflect public comments. While I am free to discuss the specifics of the proposal, I am not at liberty to discuss what we may or may not do when we issue a final rule.

FDA-approved generic drugs are copies of brand drugs and are the same as those brand-name drugs in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Generic drug manufacturing and packaging sites must pass the same quality standards as those of brand-name drugs. Generic drug manufacturers have the same requirements as brand drug manufacturers to develop written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences to FDA. More than 80 percent of all prescription drugs dispensed in the United States are for generic drug products.

Purpose of the Proposed Regulatory Action

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 301 et seq.) and the Public Health Service Act (the PHS Act) (42 U.S.C. 201 et seq.) provide FDA with authority over the labeling for drugs and biological products and authorize the Agency to enact regulations to facilitate FDA's review and approval of applications regarding the labeling for those products. As you know, on November 13, 2013, FDA issued a proposed rule to 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 information in advance of FDA's review of the change through a "changes being effected" (CBE-0) supplement.[1] The proposed rule would create parity among application holders, with respect to these safety-related labeling changes, by permitting generic drug application holders (abbreviated new drug

application (ANDA) holders) to distribute revised generic drug labeling that describes newly acquired safety-related information and, thus, may differ in certain respects, on a temporary basis, from the corresponding brand drug (the reference listed drug (RLD)) labeling at the time that the generic drug application holder submits a CBE-0 supplement to FDA. The proposed rule recognizes the obligation of all drug application holders to monitor safety information about the drugs they market and ensure that product labeling is accurate and up to date, and proposes a pathway to ensure that all drug application holders can fulfill that obligation and communicate important new safety information to prescribers and consumers. As noted, FDA sought comments from the public on the proposed rule, and the comment period closed on March 13, 2014.

Summary of the Major Provisions of the Proposed Regulatory Action

The proposed rule would enable generic drug application holders to update product labeling promptly to reflect certain types of newly acquired information related to drug safety, irrespective of whether the revised labeling differs from that of the corresponding brand drug. A generic drug application 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 application holder ("new drug application (NDA)" holder) for the corresponding brand drug at the same time that the supplement to the generic drug application is submitted to FDA, unless approval of the brand drug application has been withdrawn. This proposal would ensure that the brand drug application holder for the corresponding brand drug is promptly advised of the newly acquired information that was considered to warrant the labeling change proposed for the drug in the CBE-0 supplement.

If approval of the application for the corresponding brand drug has been withdrawn (for reasons other than safety or effectiveness), FDA's evaluation of the labeling change proposed by the generic drug application holder would consider any submissions related to the proposed labeling change from any other application holder, for drug products containing the same active ingredient. The proposed rule would create that pathway for the generic drug application holder to help ensure that safety information reaches prescribers and consumers in a timely way.

When safety-related labeling updates are implemented through the CBE-0 supplement process, there may be temporary differences in drug labeling. This currently occurs when branded drug application holders update their product labelings through the CBE-0 process, and the generic drug application holders must wait until FDA approves the change to the brand drug labeling to update generic drug labeling. Under the proposed rule, generic drug application holders would have the same ability as brand drug application holders to update product labelings with newly acquired safety-related information and FDA would reach a decision regarding the approvability of the labeling proposed by the generic and brand drug application holders regarding the safety issue at the same time.

In the current marketplace, in which approximately 80 percent of drugs dispensed are generic, and brand drug manufacturers may discontinue marketing after generic drug entry, FDA believes it is time to provide generic drug application holders with the means to update product labeling to reflect data obtained through post-marketing surveillance, even though this will result in temporary labeling differences among products. This proposed rule reflects the Agency's judgment that concerns related to temporary differences in labeling between generic drugs and their corresponding brand drugs are outweighed by the benefit to the public health, which would result from all application holders having the ability to independently update drug product labeling to reflect newly acquired information regarding important drug safety issues through CBE-0 labeling supplements.

To enhance transparency and 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 a dedicated Web page (or, alternatively, to modify an existing FDA Web page) on which FDA would promptly post information regarding the labeling changes proposed in a CBE-0 supplement.

The FDA Web page would provide information about pending CBE-0 supplements for safety-related labeling changes, including but not limited to: the active ingredient, the trade name (if any), the application holder, the date on which the supplement was submitted, a description of the proposed labeling change and source

of the information supporting the proposed labeling change (e.g., spontaneous adverse event reports, published literature, clinical trial, epidemiologic study), a link to the current labeling for the drug product containing the changes being effected, and the status of the pending CBE-0 supplement (e.g., whether FDA is reviewing the proposed labeling change, has taken an action on the CBE-0 supplement, or has determined that the supplement does not meet the criteria for a CBE-0 supplement). It is expected that a valid safety concern regarding a generic drug product also would generally warrant submission of a supplement for a change to the labeling by the application holder for the corresponding brand drug, as well as other generic drug application holders. The CBE-0 supplements would remain posted on FDA's Web page until FDA has completed its review and issued an action letter. If the CBE-0 supplement is approved, the final approved labeling will be made available on the proposed FDA Web page through a link to FDA's online labeling repository at <http://labels.fda.gov>¹. After an adequate time period to communicate FDA's decision regarding approval of the CBE-0 labeling supplements and to facilitate submission of conforming CBE-0 supplements by other application holders, as appropriate, the original entry on FDA's Web page would be archived. Approved labeling would continue to be available at <http://labels.fda.gov>².

A supplement to an approved generic drug application for a safety-related labeling change that is submitted in a prior approval supplement or in a CBE-0 supplement would be approved upon approval of the same labeling change for the corresponding brand drug. The proposed rule would establish a 30-day time frame in which all generic drug application holders would be required to submit a CBE-0 supplement with conforming labeling changes after FDA approval of a revision to the labeling for the corresponding brand drug. Currently, FDA advises generic drug application holders to revise product labeling to conform to the labeling of the corresponding brand drug "at the very earliest time possible."^[2] In light of the range of time frames in which ANDA holders currently submit such labeling supplements, we are proposing to revise these regulations to clarify FDA's expectations regarding the time frame for submission of conforming labeling changes.

The proposed rule also would amend the regulations to allow submission of a CBE-0 labeling supplement for certain changes to the "Highlights of Prescribing Information" for drug products, with labeling in the Physician Labeling Rule (PLR) format. This is intended to remove an unnecessary impediment to prompt communication of the most important safety-related labeling changes (e.g., boxed warnings and contraindications) for drug products with labeling in the PLR format.

Finally, FDA regulations provide that FDA may take steps to withdraw approval of a generic drug application if its labeling is no longer consistent with the labeling for the corresponding brand drug, subject to certain exceptions specified in the regulations. 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 corresponding brand drug due to safety-related labeling changes submitted by the generic drug application holder in a CBE-0 supplement.

Recent Court Decisions

In two recent cases, the United States Supreme Court considered the issue of whether Federal law preempts state law tort claims against pharmaceutical manufacturers for failing to provide adequate warnings in drug product labeling ("failure-to-warn claims") (see *Pliva, Inc. v. Mensing*, 131 S.Ct. 2567 (2011) and *Wyeth v. Levine*, 555 U.S. 555 (2009)). In *Pliva v. Mensing*, the Supreme Court held that the difference between brand and generic drug application holders' ability to independently change product labeling through CBE-0 supplements leads to different outcomes on whether Federal labeling requirements preempt state law failure-to-warn claims. In *Wyeth v. Levine*, the Supreme Court decided that Federal law does not preempt a state law failure-to-warn claim that a brand drug's labeling did not contain an adequate warning. The Supreme Court found that the drug manufacturer could have unilaterally added a stronger warning to product labeling under the CBE-0 regulation as applied to brand drug applications, and absent clear evidence that FDA would not have approved such a labeling change, it was not impossible for the manufacturer to comply with both Federal and state requirements. The Supreme Court reaffirmed that "through many amendments to the [FD&C Act] and to FDA regulations, it has remained a central premise of Federal drug regulation that the manufacturer bears responsibility for the content of its label at all times" (555 U.S. at 570-571).

Two years later, in *Pliva v. Mensing*, the Supreme Court decided that Federal law does preempt a state law failure-to-warn claim that a generic drug's labeling did not contain an adequate warning. The Supreme Court deferred to FDA's interpretation of its CBE-0 supplement and labeling regulations for generic drug applications 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 Professional" letters, which FDA "argues . . . qualify as 'labeling'" (131 S.Ct. at 2576). The Supreme 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 corresponding brand drug and satisfy its state law duty to provide adequate labeling (131 S.Ct. at 2578).

As a result of the decisions in *Wyeth v. Levine* and *Pliva v. Mensing*, an individual can bring a product liability action for failure to warn against a branded drug application holder, but generally not a generic drug application holder, and thus, access to the courts is dependent on whether an individual is dispensed a brand-name or generic drug. The *Mensing* decision alters the incentives for generic drug manufacturers to comply with current requirements to conduct robust post-marketing surveillance, evaluation, and reporting, and to ensure that the labeling for their drugs is accurate and up to date.

We are proposing to change our regulations to expressly provide that generic drug application holders may distribute revised labeling that differs from the corresponding brand drug upon submission of a CBE-0 supplement to FDA. FDA's proposed revisions to its regulations would create parity between branded drug application holders and generic drug application holders with respect to submission of CBE-0 supplements for safety-related labeling changes based on newly acquired information. This proposal is also intended to ensure that generic drug companies actively participate with FDA in ensuring the timeliness, accuracy, and completeness of drug safety labeling in accordance with current regulatory requirements. If this proposed regulatory change is adopted, it may eliminate the preemption of certain failure-to-warn claims, with respect to generic drugs.

Legal Authority

The FD&C Act (21 U.S.C. 301 et seq.) and the PHS Act (42 U.S.C. 201 et seq.) provide FDA with authority over the labeling for drugs and biological products, and authorize the Agency to enact regulations to facilitate FDA's review and approval of applications regarding the labeling for those products. Section 502 of the FD&C Act (21 U.S.C. 352) provides that a drug or biological product will be considered misbranded if, among other things, the labeling for the product is false or misleading (21 U.S.C. 352(a); see also 42 U.S.C. 262(j)). Under section 502(f) of the FD&C Act, a product is misbranded unless its labeling bears adequate directions for use, including adequate warnings against, among other things, unsafe dosage, methods, duration of administration, or application. Moreover, under section 502(j) of the FD&C Act, a product is misbranded if it is dangerous to health when used in the manner prescribed, recommended, or suggested in its labeling.

In addition to the misbranding provisions, the premarket approval provisions of the FD&C Act authorize FDA to require that product labeling provide adequate information to permit safe and effective use of the product. Under section 505(c) of the FD&C Act (21 U.S.C. 355), FDA will approve an NDA only if the drug is shown to be both safe and effective for its intended use under the conditions set forth in the drug's labeling. Under section 505(j) of the FD&C Act, FDA will approve an ANDA only if the drug is, with limited exceptions, the same as a drug previously approved under section 505(c) of the FD&C Act, with respect to active ingredient(s), dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics, and is bioequivalent to the RLD.

Section 351 of the PHS Act (42 U.S.C. 262) provides additional legal authority for the Agency to regulate the labeling of biological products. Licenses for biological products are to be issued only upon a showing that the biological product is safe, pure, and potent (42 U.S.C. 262(a)). Section 351(b) of the PHS Act prohibits any person from falsely labeling any package or container of a biological product. FDA's regulations in 21 CFR part 201 apply to all prescription drug products, including biological products.

In addition, section 701(a) of the FD&C Act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act. FDA's regulations relating to CBE-0 supplements are supported by this provision. In 1965, FDA determined that, in the interest of drug safety, manufacturers should make certain safety-related changes to their product labeling at the earliest possible time.[3] Thus, for nearly 50 years, FDA, as the Agency entrusted with administration and enforcement of the FD&C Act and the protection and promotion of the public health, has required NDA holders, and subsequently biologics license application holders, to update drug product labeling with important, newly acquired safety information through submission of a CBE-0 supplement.

FDA's authority to extend the CBE-0 supplement process for safety-related labeling changes to generic drug application holders arises from the same authority under which our regulations relating to branded drug application holders and biologics license application holders were issued.

CONCLUSION

In conclusion, I want to emphasize that this proposed rule, if finalized, *is intended to improve the communication of important drug safety information about generic drugs to both prescribers and patients*. We look forward to reviewing comments to the proposed rule. As noted previously, the comment period closed on March 13, 2014. Because there is a pending rulemaking at FDA concerning these issues, I may have to limit my response to your questions. I will try to answer any questions you may have. Thank you.

[1] See "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," published in the Federal Register on November 13, 2013, and available online at <http://federalregister.gov/a/2013-26799>³.

[2] See guidance for industry on "Revising ANDA Labeling Following Revision of the RLD Labeling" (2000).

[3] See 30 FR 993, January 30, 1965.

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