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September 9, 2016

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

COMMENT ON
UPDATING ANDA LABELING AFTER THE MARKETING APPLICATION FOR THE REFERENCE LIST DRUG HAS BEEN WITHDRAWN, DRAFT GUIDANCE FOR INDUSTRY
Docket No. FDA-2016-D-1673

Public Citizen's Health Research Group and Public Citizen, a consumer organization with members and supporters nationwide, submits these comments with regard to the draft guidance "Updating ANDA Labeling After The Marketing Application For The Reference Listed Drug Has Been Withdrawn," published in the Federal Register on July 11, 2016. Under the draft guidance, abbreviated new drug application (ANDA) holders for which the approval of the corresponding reference-listed drug (RLD) has been withdrawn for reasons other than safety or effectiveness may update labeling through one of two mechanisms: submission of a prior approval supplement (PAS), *see* 21 U.S.C. § 314.70(b); implementation of revisions in response to a request or instruction by the Food and Drug Administration (FDA). Guidance at 7.

As explained below, the draft guidance is a small step toward filling the safety gap that exists because generic drug manufacturers lack authority to initiate labeling changes based on new safety information. To more fully address the problem, we urge the FDA to move promptly to finalize the November 2013 proposed rule entitled "Supplemental Applications Proposing Labeling Changes For Approved Drugs And Biological Products," RIN 0910-AG94.

Discussion

The draft guidance addresses "changes necessary to ensure that labeling adequately describes information essential for safe and effective use; that labeling is accurate and meets current standards; and that labeling is not false or misleading" under section 502 of the Food, Drug, and Cosmetic Act. Guidance at 5. Importantly, the draft guidance confirms that all ANDA holders have an obligation to ensure that product labeling is accurate and neither false nor misleading. *Id*. at 2. The draft guidance also confirms that ANDA holders may use the PAS process to update labeling after the RLD has been withdrawn for reasons other than safety or effectiveness—a point to which we do not object. And of course, the point that ANDA holders should make prompt changes upon request by the FDA, Guidance at 7, should be uncontroversial. That said, neither the discussion in the draft guidance nor the pertinent

regulation provide a basis for limiting the guidance's scope to ANDA holders for which approval of the RLD has been withdrawn, as opposed to including all ANDA holders, or for allowing ANDA holders to use the PAS process to request permission for labeling changes but not to initiate the changes-being-effected (CBE-0) process, 21 U.S.C. § 314.70(c)(6).

First, with regard to the adequacy of labeling, neither the discussion in the draft guidance nor the relevant regulations support distinguishing between types of ANDA holders with respect to labeling updates. The draft guidance recognizes that

> *all* holders of marketing applications for drug products (*both* NDAs and ANDAs) have an ongoing obligation to ensure their product labeling is accurate, and not false or misleading. When new information becomes available that causes the labeling to become inaccurate, false or misleading, *the application holder* must take steps to update its labeling (see, e.g., 21 CFR 201.56(a)(2)). *Any* drug is misbranded if its labeling is false or misleading, or does not provide adequate directions for use and adequate warnings.

Guidance at 2 (emphasis added). These statements properly affirm obligations of all ANDA holders, as well as NDA holders. Likewise, the regulation setting forth the PAS process, 21 C.F.R. § 314.70(a)-(b), refers to "an approved application" and "the applicant"—words that cannot reasonably be read to apply to some ANDA holders but not to others. (The same is true for the CBE process, *see id*. at 314.70(c).)

Second, the draft guidance's recognition that ANDA holders have an "*ongoing obligation*" to ensure proper labeling and that "[w]hen new information becomes available that causes the labeling to become inaccurate, false or misleading, the application holder *must* take steps to update its labeling," Guidance at 2, strongly supports allowing ANDA holders to use not only the PAS process but also the CBE-0 process to make changes "to ensure their product labeling is accurate, and not false or misleading." *Id*. (emphasis added). We understand that the FDA chose not to address "independent" submission of CBE-0 supplements in this draft guidance. *Id*. at 7 n.11. Nonetheless, the quoted statements, as well as the language of regulations including 21 C.F.R. § 201.56(a)(2), demonstrate that ANDA holders, like NDA holders, must be permitted to revise labeling through independent submission of CBE-0 supplements.

Until 1985, the FDA generally required prior approval for labeling changes. *See* 47 Fed. Reg. 46622, 46634 (1982). The FDA revised this approach at the urging of the Pharmaceutical Manufacturers Association and Parke-Davis, who "petitioned FDA to expand the kinds of changes an applicant can make under an approved application and place in effect before receiving agency approval of the change." *Id*. at 46634-35. They argued that the pre-approval requirement was unnecessary, took FDA reviewers away from more important work, and caused costly delays. In response, the agency identified numerous types of changes that could be effected without prior approval, including "[c]hanges that add or strengthen a contraindication, warning, precaution, or statement about an adverse reaction, drug abuse, dependence, or overdosage, or any other instruction about dosage and administration that is intended to improve the safe use of the product." *Id*. at 46635. These changes, the FDA said, "would help concentrate the agency's limited resources more on applications for marketing, and would also permit pharmaceutical manufacturers to institute certain postmarketing changes sooner."

The concerns that motivated the FDA to adopt the CBE-0 option—the need to promptly inform physicians and patients, and the interest in efficiency and resource management—apply equally here. As was true then, the agency lacks the resources to be the primary instigator of post-approval labeling changes and cannot timely pre-approve every safety update to the labeling of every approved drug. And as was true then, safety information often comes to light or is clarified after initial approval. What is different now, though, is that generic drugs comprise such a large percentage of all prescriptions filled and such an overwhelming percentage of all prescriptions filled for off-patent products.

Therefore, to fulfill the goal of providing timely labeling updates to physicians and patients, the FDA should, at a minimum, permit ANDA holders for which approval of the RLD has been withdrawn for reasons other than safety and effectiveness to initiate labeling changes through the CBE-0 process, independent of any request from the FDA. To maximize the accuracy of labeling and compliance with 21 U.S.C. § 352(a) and 21 C.F.R. § 201.56(a)(2), all ANDA holders should be able independently to submit CBE-0 supplements.

As the Supreme Court has recognized, "[t]he FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." *Wyeth v. Levine*, 555 U.S. 555, 578-79 (2009) (footnote omitted). It has therefore been "a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times . . . [and] ensuring that its warnings remain adequate as long as the drug is on the market." *Id*. at 570-71. The current regulatory regime, in which the FDA has stated that ANDA holders may *not* revise labeling using the CBE-0 process, relieves a large category of manufacturers from this important responsibility, creating a serious safety gap that the agency has previously recognized and, nearly two years ago, proposed a solution for filling. Unfortunately, as the rule proposed in November 2013 sits in limbo, the draft guidance describes only a baby step in filling the safety gap.

VI. Conclusion

For the reasons stated above, we do not object to the draft guidance but urge the FDA to go further to address the concerns underlying it, in particular by finalizing the proposed rule, "Supplemental Applications Proposing Labeling Changes For Approved Drugs And Biological Products."

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