



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

[Docket No. FDA-2013-N-0500]

Withdrawal of Proposed Rule on Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; withdrawal.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is announcing the withdrawal of the proposed rule on “Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products” that published in the *Federal Register* of November 13, 2013. FDA is taking this action in light of concerns expressed by commenters and considerations regarding Agency resources. FDA is continuing to consider ways to improve the communication of important, newly acquired drug safety information to healthcare providers and the public and to facilitate efforts to keep drug product labeling up to date throughout the product lifecycle.

DATES: The proposed rule published November 13, 2013 (78 FR 67985), is withdrawn as of [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: For access to the docket, go to <https://www.regulations.gov> and insert the docket number found in brackets in the heading of this document into the “Search” box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Janice L. Weiner, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6270, Silver Spring, MD 20993-0002, 301-796-3601, janice.weiner@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and FDA regulations, the Agency makes decisions regarding the approval of marketing applications, including supplemental applications, based on a comprehensive analysis of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling (see 21 U.S.C. 355(c) and (d); 42 U.S.C. 262). All drugs have risks, and healthcare practitioners and patients must balance the risks and benefits of a drug when making decisions about medical therapy. As a drug is used more widely or under diverse conditions, new information regarding the risks and benefits of a drug may become available, and may include new risks or new information about known risks. Accordingly, all holders of new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs) 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), 314.98(a), and 600.80(b)). Application holders also must comply with applicable reporting and recordkeeping requirements, including submission of an annual report (which contains, among other things, 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 the 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 21 U.S.C. 355(k) and 21 CFR 314.81).

When new information becomes available that causes labeling to be inaccurate, false, or misleading, all drug and biological product application holders must take steps to change the content of their product labeling in accordance with §§ 314.70, 314.97, and 601.12 (21 CFR 314.70, 314.97, and 601.12) (see 21 CFR 201.56(a)(2); see also 21 U.S.C. 331(a) and (b) and 352(a), (f), and (j)). While all drug and biological product application holders have these obligations, under current regulations, the procedures available to ANDA holders to update the labeling of generic drugs differ in certain respects from the procedures available to NDA holders and BLA holders to update product labeling. In addition, there are limitations on the procedures available to NDA holders and BLA holders to make certain updates to the Highlights of Prescribing Information of drug and biological product labeling that are subject to the content and format labeling requirements described in §§ 201.56(d) and 201.57 (21 CFR 201.56(d) and 201.57) (commonly referred to as the “Physician Labeling Rule” (PLR) format).

In the *Federal Register* of November 13, 2013 (78 FR 67985), FDA proposed to amend its regulations to revise and clarify procedures for application holders of an approved drug or biological product to change the product labeling to reflect certain types of newly acquired safety-related information in advance of FDA’s review of the change by submitting a “changes being effected” (CBE-0) supplement to FDA. A CBE-0 supplement is an exception to the general requirement for FDA approval of a prior approval supplement containing revised product labeling before distribution. The proposed rule, if finalized, would have enabled ANDA holders for generic drugs to independently update and promptly distribute revised product labeling to reflect certain types of newly acquired safety-related information, even though the revised labeling may temporarily differ from that of the corresponding reference listed drug (RLD or brand drug) upon submission of a CBE-0 supplement to FDA. FDA’s proposed revisions to its

regulations to allow generic drug manufacturers to update product labeling through CBE-0 supplements in the same manner as brand drug manufacturers were intended to improve communication of important, newly acquired drug safety information to healthcare providers and the public. The proposed rule, if finalized, also would have removed the limitation on submission of CBE-0 supplements by any application holder for certain changes to the Highlights of Prescribing Information in PLR-format product labeling. For further information about these and other proposed regulatory changes described in the proposed rule, see 78 FR 67985.

FDA received numerous comments on the proposed rule from a diverse group of stakeholders. In view of requests to meet with FDA to present alternatives to the proposed regulatory changes described in the proposed rule and to promote transparency, FDA held a public meeting on March 27, 2015, at which any stakeholder had the opportunity to present or comment on the proposed rule or any alternative proposals intended to improve communication of important, newly acquired drug safety information to healthcare professionals and the public. In the February 18, 2015, document announcing the public meeting (80 FR 8577), FDA reopened the docket for the proposed rule until April 27, 2015, to receive submissions of additional written comments on the proposed rule as well as alternative proposals presented during the public meeting.

Several comments supported finalizing the rule as originally proposed. Other comments supported the goals of the proposed rule, but expressed concern that temporary labeling differences between generic drugs and the corresponding brand drug could complicate healthcare decision making. Comments in support of the proposed rule maintained that it would enhance drug safety by making healthcare practitioners and the public aware of new safety-related

information about a drug more quickly. Several comments also opined that tort liability for failure to adequately warn patients of a known hazard may be an incentive for drug manufacturers to ensure that their product labeling reflects the most current safety information.

Comments in opposition to the proposed rule raised policy, legal, and cost considerations. A number of comments asserted that generic drug application holders do not generally receive or possess all the data necessary to evaluate postmarket safety information and to support safety-related labeling changes. Comments expressed concern that additional or different warnings in generic drug labeling, even if temporary, may undermine confidence in generic drugs and their therapeutic equivalence to the brand drug. Comments throughout the healthcare delivery system also expressed concern about the confusion that might result if there were different versions of safety labeling for multiple generic versions of the same drug until FDA decided whether to approve the labeling changes proposed in the CBE-0 supplements. Several comments asserted that the proposed rule would impose significant burdens on the generic drug industry that would necessarily increase the cost of generic drugs or lead to market exit, which may increase the risk of drug shortages. However, most concerns regarding economic impact focused on the increased risk of tort litigation against generic drug manufacturers and others in the healthcare system.

II. Withdrawal of the Proposed Rule

Having reviewed the comments on the proposed rule and further considered the proposal, FDA is withdrawing the proposed rule on “Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products” published in the *Federal Register* of November 13, 2013. The concerns raised in the comments reflect significant competing interests, and FDA acknowledges that the proposed rule, if finalized, would present significant potential downsides. In light of those potential downsides, the Agency does not believe that

finalizing the proposed rule would be an appropriate use of Agency resources. Rather, the Agency believes that such resources would be better used on other efforts to improve the communication of important, newly acquired drug safety information to healthcare professionals and the public, as discussed in greater detail below.

The withdrawal of this proposed rule does not alter the ongoing obligation under FDA's current regulations for all holders of marketing applications for drug and biological products--including ANDA holders--to ensure their product labeling is accurate, and not false or misleading, and to take steps to update their product labeling when new information becomes available that causes the labeling to become inaccurate, false, or misleading (see § 201.56(a)(2); see also 21 U.S.C. 331(a) and (b) and 352(a), (f), and (j)). This obligation serves an important public health function because new information regarding the risks and benefits of a drug may become available over time from various sources, including from postmarketing adverse drug experience reports and published literature, and updates to product labeling may be necessary.

In addition to the ongoing obligation described above, ANDA holders must generally maintain the same labeling as the RLD throughout the lifecycle of the generic drug product. ANDA holders can, however, propose certain updates to product labeling by submitting a prior approval supplement that contains adequate supporting information for the proposed change. FDA will determine whether the proposed labeling change is appropriate, and whether the labeling for the RLD and corresponding generic drug(s) should be revised. If the approval of the NDA for the RLD has been withdrawn at the NDA holder's request because the RLD is no longer being marketed and certain other conditions are satisfied (see 21 CFR 314.150(c)), the NDA holder can no longer update labeling for the withdrawn RLD, but ANDA holders can still propose labeling updates through the submission of a prior approval supplement. In such cases,

if FDA determines that the proposed labeling change is appropriate and approves the supplement, the Agency may request that other ANDA holders and any ANDA applicants relying on the same withdrawn RLD make the same updates (see FDA draft guidance for industry “Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn,” 81 FR 44883, July 11, 2016) (Draft Guidance on Updating ANDA Labeling) (Ref. 1).

As noted, the proposed rule would have removed the current prohibition against the submission of CBE-0 supplements by NDA and BLA holders to change information in the Highlights of Prescribing Information portion of drug labeling. If an NDA holder or a BLA holder seeks to submit a CBE-0 supplement to change information in the Highlights of Prescribing Information to reflect newly acquired information for any of the reasons described in § 314.70(c)(6)(iii) or § 601.12(f)(2), as applicable, the NDA holder or BLA holder can normally obtain permission to do so under the current regulation by contacting FDA. In response to an applicant’s inquiry about submission of a CBE-0 supplement for a change that would affect the Highlights of drug labeling, FDA typically waives the limitation on submission of a CBE-0 supplement under 21 CFR 314.90 or specifically requests that the applicant proceed with a CBE-0 supplement under § 314.70(c)(6)(iii)(E) or § 601.12(f)(2)(i)(E).

FDA is continuing to consider ways to improve the communication of important, newly acquired drug safety information to healthcare professionals and the public, and to facilitate efforts to keep drug product labeling up to date throughout the product lifecycle. Although the proposed rule focused on labeling updates to reflect newly acquired information related to drug safety, we recognize that there are general challenges for keeping generic drug labeling up to date when the RLD labeling is no longer being updated, including when FDA has withdrawn

approval of the NDA for reasons other than safety or effectiveness. The Agency is actively evaluating ways to facilitate the updating of generic drug labeling to help ensure that drug labeling reflects the most current information. For example, FDA's fiscal year (FY) 2019 Budget Request includes an investment to support efforts to update generic drug labeling, with an initial focus on oncology products, as part of the Agency's efforts to ensure that patients and their providers have access to up-to-date information to inform clinical decisions (Ref. 2). These efforts to ensure that more generic drugs have up-to-date product labeling reflecting the latest treatment information can also encourage wider adoption of generic drugs, broadening access to lower-cost alternatives to brand drugs for the American people.

The withdrawal of this proposed rule does not preclude the Agency from reinstating rulemaking concerning the issues addressed in the proposal. Should we decide to undertake such rulemaking in the future, we will re-propose the action and provide new opportunities for comment. Furthermore, this proposed rule is only intended to address the withdrawal of the proposed rule on "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products" published in the *Federal Register* of November 13, 2013, and not any other pending proposals that the Agency has issued or is considering, including the Draft Guidance on Updating ANDA Labeling (Ref. 1) or the Agency's efforts to update the labeling of certain oncology drug products under FDA's FY2019 Budget Request (Ref. 2). If you need additional information about the subject matter of the withdrawn proposed rule, you may review the Agency's website (<https://www.fda.gov>) for any current information on the matter.

III. References

The following references are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m.,

Monday through Friday; they are also available electronically at <https://www.regulations.gov>.

FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. FDA, draft guidance for industry, “Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn,” July 2016 (available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm510240.pdf>).

2. U.S. Department of Health and Human Services, Food and Drug Administration, “Fiscal Year 2019 Justification of Estimates for Appropriations Committees” (available at <https://www.fda.gov/downloads/aboutfda/reportsmanualstudies/reports/budgetreports/ucm603315.pdf>).

Dated: December 10, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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