Revising ANDA Labeling Following Revision of the RLD Labeling

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Jonathan Hughes, 301-796-9291.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2022
Generics

Revision 1

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Revising ANDA Labeling Following Revision of the RLD Labeling Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants and holders of an abbreviated new drug application (ANDA) in updating their labeling following revisions to the approved labeling[2] of a reference listed drug (RLD).[3] [4] This guidance provides recommendations on identifying RLD labeling updates and submitting ANDA amendments or supplements to update generic drug labeling. This guidance revises the guidance for industry *Revising ANDA Labeling Following Revision of the RLD Labeling* (April 2000). After it has been finalized, this guidance will replace the April 2000 guidance. Significant changes from the 2000 version include updates to outdated details about how to obtain information on changes to RLD labeling and how to submit revised ANDA labeling to FDA.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] In this guidance, we use the terms "approved labeling" or "labeling" to refer to labeling approved in New Drug Applications (NDAs) and ANDAs. This term includes, but is not limited to: Prescribing Information (PI), FDA-approved patient labeling (Medication Guides, Instructions for Use, and Patient Information (also called Patient Package Inserts)), and carton and container labeling.

[3] This guidance encompasses approved labeling for prescription and certain over-the-counter (OTC) drugs. For more information and resources on prescription drug labeling, please visit https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources. For OTC products, please refer to the FDA guidance for industry *Labeling OTC Human Drug Products Updating Labeling in RLDs and ANDAs* (October 2002).

[4] An *RLD* "is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (21 CFR 314.3(b)).

specific regulatory or statutory requirements are cited. The use of the word should in FDA guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

An ANDA is an application submitted and approved under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[5] for a drug product that is a duplicate[6] of a previously approved drug product. An ANDA relies on FDA's finding that the previously approved drug product—i.e., the RLD—is safe and effective. An ANDA generally must contain information to show that the proposed generic product: (1) is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences); and (2) is bioequivalent to the RLD.[7]

A generic drug is required to have the same labeling as the RLD, except for changes required because of differences approved under a suitability petition[8] or because the generic drug and the RLD are "produced or distributed by different manufacturers."[9] FDA regulations provide examples of permissible differences in labeling that may result when a proposed generic drug and the RLD are "produced or distributed by different manufacturers," including the omission of an indication or other aspect of labeling protected by patent or exclusivity and "labeling revisions made to comply with current FDA labeling guidelines or other guidance."[10]

As a general matter, all holders of marketing applications for drug products (both new drug applications (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.[11] A drug is misbranded if its labeling is false or misleading or does not provide adequate directions for use and adequate warnings.[12]

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[5] See 21 U.S.C. 355(j)).

[6] The term *duplicate* generally refers to a "drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug." See 54 FR 28872 at 28877 (July 10, 1989). However, the term *duplicate*, as used in this context, does not mean identical in all aspects to the listed drug. These prodcuts are typically referred to as "generic drugs."

[7] Section e.g., 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; see also e.g., § 314.94(a) (21 CFR 314.94(a)) and § 314.127(a) (21 CFR 314.127(a)).

[8] See section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93.

[9] See section 505(j)(2)(A)(v) and (j)(4)(G) of the FD&C Act and § 314.94(a)(8)(iv) and § 314.127(a)(7).

[10] See § 314.94(a)(8)(iv).

[11] See, e.g., 21 CFR 201.56(a)(2).

[12] See sections 301(a) and (b) and 502(a), (f), and (j) of the FD&C Act (21 U.S.C. 331(a) and (b) and 352(a), (f), and (j)).

Approved RLD labeling is revised by its application holder for a variety of reasons and is accomplished through the submission of information to the application under the appropriate reporting category.[13] An ANDA holder is expected to update its labeling after FDA has approved relevant changes to the labeling for the corresponding RLD. Prompt revision, submission to the Agency, and implementation of revised ANDA labeling are important to ensure that the generic drug continues to be as safe and effective as the corresponding RLDs. FDA may withdraw approval of an ANDA if the Agency finds that the labeling for the drug product that is the subject of the ANDA is no longer consistent with that for the RLD.[14] For ANDA applicants, FDA recommends that applicants submit revised ANDA labeling at the earliest time possible because the labeling of a generic drug generally must be the same as that of the RLD (with certain permissible differences).[15] It is the ANDA applicant's responsibility to monitor for RLD labeling changes and to submit revised ANDA labeling to FDA in a timely fashion.

III. HOW TO OBTAIN INFORMATION ON CHANGES TO RLD LABELING

ANDA applicants and holders should routinely monitor Drugs@FDA for recently approved RLD labeling updates and make any necessary revisions to their labeling. The web page for Drugs@FDA is https://www.accessdata.fda.gov/scripts/cder/daf/.

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[13] See 21 CFR 314.70 and 21 CFR 314.71; additional recommendations are contained in FDA guidances for industry *Changes to an Approved NDA or ANDA* (April 2004, Rev. 1) and *ANDA Submissions – Prior Approval Supplements Under GDUFA* (October 2017, Rev. 1).

[14] See section 505(e) of the FD&C Act and 21 CFR 314.150(b)(10).

[15] See e.g., footnotes 8 and 14. There may be circumstances in which an ANDA applicant updates its labeling, even though there has not been an update to the labeling for the corresponding RLD. For example, an ANDA applicant for a product that omits an indication included in the NDA RLD labeling because of patent or exclusivity protection updates the product labeling to include that indication upon expiration of the patent or exclusivity. See section 505(j)(2)(A)(v) of the FD&C Act and § 314.94(a)(8)(iv). If an ANDA applicant makes certain changes to its product, it updates the product labeling accordingly (e.g., changes to a container closure system). For more information, please see the FDA guidance for industry *ANDA Submissions – Prior Approval Supplements Under GDUFA* (October 2017, Rev. 1) and draft guidance for industry *Postapproval Changes to Drug Substances* (September 2018). When final, this guidance will represent the FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents).

If approval of the RLD's application has been withdrawn for reasons other than safety or effectiveness, the labeling of a pending or marketed ANDA product may need to be updated. The *Consolidated Appropriations Act, 2021* (Pub. L. No. 116-133 (Dec. 2020)), contains provisions that added new section 503D to the FD&C Act (codified at 21 U.S.C. 353d). Section 503D provides a process to update labeling for certain generic drugs that reference an RLD where the approval has has been withdrawn for reasons other than safety or effectiveness. FDA also has draft guidance on this topic, but this draft guidance does not address the process for updating labeling under section 503D of the FD&C Act because it was issued prior to the enactment of Section 503D (see draft guidance for industry *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn* (July 2016)). When final, this guidance will represent the FDA's current thinking on this topic. Updating ANDA labeling when the NDA RLD has been withdrawn for reasons other than safety or effectiveness is outside the scope of this guidance and applicants should refer to section 503D of the FD&C Act or *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn*, as appropriate.

In addition, FDA maintains LISTSERVs that provide information about new approvals and announcements related to labeling updates. For email updates, subscribe to *CDER Drug Safety Labeling Changes* and *CDER New* at https://www.fda.gov/about-fda/contact-fda/get-email-updates.

All approved RLD labeling is available from FDA's Division of Freedom of Information. Applicants who wish to obtain labeling using this mechanism should send a written request via mail, fax, or the internet to:

Food and Drug Administration
Division of Freedom of Information
Office of the Executive Secretariat, OC
5630 Fishers Lane, Room 1035
Rockville, MD 20857

301-796-3900 (phone); 301-827-9267 (fax)
http://www.accessdata.fda.gov/scripts/foi/FOIRequest/index.cfm

IV. HOW TO SUBMIT REVISED LABELING

A. Process

Consistent with the statute,[16] labeling changes for an ANDA must be submitted in electronic format through the Electronic Submissions Gateway[17] as described in the FDA guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 2020, Rev. 7).[18] Note that certain types of submissions (e.g., for certain positron emission tomography drugs) may be exempted from the Electronic Common Technical Document (eCTD) requirements.[19]

ANDA applicants and holders should submit the respective labeling documents in the appropriate modules and sections according to the "Comprehensive Table of Contents Headings and Hierarchy" located at FDA's eCTD web page.[20]

[16] See 21 U.S.C. 379k-1.

[17] See the Electronic Submissions Gateway web page at https://www.fda.gov/industry/electronic-submissions-gateway for technical details related to submitting documents through FDA's Electronic Submissions Gateway.

[18] For more information, please visit www.fda.gov/eCTD.

[19] See page 6 of the FDA guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 2020, Rev. 7).

[20] See the Comprehensive Table of Contents Headings and Hierarchy, Version 3.7 (revised October 1, 2020), in "eCTD Submission Standards" at https://www.fda.gov/media/93301/download.

Such submissions should include:

- Form FDA 356h
- Cover letter
- Patent and exclusivity statement, as needed, in cover letter
- Revised labeling
- A side-by-side comparison of the proposed ANDA labeling with the approved labeling of the RLD with all differences annotated and explained, as described in § 314.94(a)(8)(iv)

B. Type of Submission

ANDA applicants and holders should note that, in general, the submission of an unsolicited labeling amendment during a review cycle may impact the goal date.[21] In certain limited circumstances, an applicant may submit revised labeling corresponding to an RLD labeling update after approval of the ANDA.[22]

1. Unapproved ANDAs

For unapproved ANDAs, applicants should submit labeling changes to conform to RLD labeling updates in an amendment, following the procedures outlined in 21 CFR 314.96 and recommendations in the FDA guidance for industry *ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA.*

2. Tentatively Approved ANDAs

Similarly, for tentatively approved ANDAs, an applicant should submit labeling changes to conform to RLD labeling updates in an amendment to the tentatively approved application. For recommendations on the timing and content of amendments to tentatively approved ANDAs to facilitate submission in a timely fashion and enable final approval on the earliest date on which the ANDA may lawfully be approved based on patent and/or exclusivity protections, refer to the FDA guidance for industry *ANDA Submissions – Amendments and Requests for Final Approval to Tentatively Approved ANDAs* (September 2020).

3. Approved ANDAs

For approved ANDAs, ANDA holders must submit labeling updates to their ANDAs to conform to RLD labeling updates (except for claims protected by patent and/or exclusivity) and use the

[21] For more information on the timing of amendments and goal dates, see the FDA guidance for industry *ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018).

[22] See section 505(j)(10) of the FD&C Act and MAPP 5230.3, *Generic Drug Labeling Revisions Covered Under Section 505(j)(10) of the Federal Food, Drug, and Cosmetic Act*, at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp.

appropriate reporting category as outlined in § 314.70.[23] Additional recommendations can be found in the FDA guidances for industry *Changes to an Approved NDA or ANDA* (April 2004, Rev. 1) and *ANDA Submissions – Prior Approval Supplements Under GDUFA* (October 2017, Rev. 1).

C. Other Considerations

ANDA applicants and holders should consider all aspects of labeling when submitting an update to ensure their submissions conform to the updates made to the labeling of the RLD. For instance, when updating labeling for a particular section (e.g., WARNINGS AND PRECAUTIONS), ANDA applicants and holders should consider whether conforming updates to other sections of the labeling (e.g., DOSAGE AND ADMINISTRATION) are necessary because of updates made to the labeling of the RLD.

[23] See 21 CFR 314.97 (referencing 314.70 and 314.71).