GUIDANCE DOCUMENT

REVISING ANDA LABELING FOLLOWING REVISION OF THE RLD LABELING

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Guidance for Industry

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

January 2024
Generic Drugs

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Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
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Contains Nonbinding Recommendations

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

This guidance represents 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 office 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 This guidance finalizes the draft guidance for industry of the same title issued on January 27, 2022.[5] The final guidance provides clear expectations for when updates to labeling are required, the process for updating labeling, and the types of submissions for labeling updates.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

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[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)).

[5] 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#guidancesearch.

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)[6] for a drug product that is a duplicate[7] 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.[8]

A generic drug is generally required to have the same labeling as the RLD, except for changes required because of differences approved under a suitability petition[9] or because the generic drug and the RLD are "produced or distributed by different manufacturers."[10] 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."[11] FDA will refuse to approve an ANDA if information submitted in the ANDA is insufficient to show that the labeling proposed for the generic drug is the same as the labeling approved for the RLD, except for changes required because of differences approved in a suitability petition; or because the proposed generic drug and the RLD are produced or distributed by different manufacturers; or because aspects of the RLD's labeling are protected by patent or exclusivity, and such differences do not render the proposed drug product less safe or effective than the RLD for all remaining, nonprotected conditions of use.[12]

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

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

[7] 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 e.g., 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 products are typically referred to as "generic drugs."

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

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

[10] See section 505(j)(2)(A)(v) and (j)(4)(G) of the FD&C Act and 21 CFR § 314.94(a)(8)(iv) and § 314.127(a)(7).

[11] See § 314.94(a)(8)(iv).

[12] § 314.127(a)(7).

update its labeling.[13] A drug is misbranded if its labeling is false or misleading or does not provide adequate directions for use and adequate warnings.[14]

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.[15] 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 RLD. 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.[16] FDA recommends that ANDA holders and 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).[17] It is the ANDA holder or applicant's

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

[14] 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)).

[15] 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 2022, Rev. 2).

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

[17] See e.g., footnotes 9 and 15. There may be circumstances in which an ANDA holder updates its labeling, even though there has not been an update to the labeling for the corresponding RLD. For example, an ANDA holder 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). Another example is that if an ANDA applicant makes certain other changes to its product that are permissible, such as changes to a container closure system, then it can update the product labeling accordingly. For more information, please see the FDA guidance for industry *ANDA Submissions – Prior Approval Supplements Under GDUFA* (October 2022, Rev. 2) and the 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. 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 of the RLD 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 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 the draft guidance for industry guidance and applicants should refer to section 503D of the FD&C Act or the draft guidance for industry *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn*, as appropriate.

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/.

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,[18] labeling changes for an ANDA must be submitted in electronic format through the Electronic Submissions Gateway[19] 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).[20] Note that certain types of submissions (e.g., for

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

[19] 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.

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

certain positron emission tomography drugs) may be exempted from the Electronic Common Technical Document (eCTD) requirements.[21]

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.[22]

Such submissions should include:

- Form FDA 356h[23]
- Cover letter[24]
- Patent and exclusivity statement in cover letter and/or eCTD submission, as needed
- 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.[25] In certain limited circumstances, an applicant may submit revised labeling corresponding to an RLD labeling update after approval of the ANDA.[26]

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

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[21] 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).

[22] See the current version of the Comprehensive Table of Contents Headings and Hierarchy in "eCTD Submission Standards" at https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd.

[23] Available on FDA's Forms website at: https://www.fda.gov/about-fda/reports-manuals-forms/forms

[24] See FDA's guidance for industry *Cover Letter Attachments for Controlled Correspondence and ANDA Submissions* (June 2023).

[25] 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).

[26] See section 505(j)(10) of the FD&C Act and MAPP 5230.3, Rev. 1, *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.

recommendations in the FDA guidance for industry *ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018).

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 generally must submit labeling updates to their ANDAs to conform to RLD labeling updates,[27] using the appropriate reporting category as outlined in section 314.70.[28] 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 2022, Rev. 2).

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.

[27] As noted above in section II, certain differences in labeling may be permissible.

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