Annual Reportable Labeling Changes for NDAs and ANDAs for Nonprescription Drug Products

Guidance for Industry

DRAFT GUIDANCE

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

March 2024
Labeling

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

The purpose of this guidance is to provide recommendations to applicants of approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for nonprescription drug products on documenting minor labeling changes in the next annual report in accordance with 21 CFR §§ 314.70(d) and 314.97. This guidance also provides examples of such minor labeling changes.

This guidance does not address labeling changes for prescription drug products. This guidance also does not address major and moderate labeling changes to approved NDAs and ANDAs for nonprescription drug products under §§ 314.70(b)-(c) and 314.97.[2] Nor does this guidance address chemistry, manufacturing, and controls (CMC) postapproval manufacturing changes.

For additional information on making and reporting changes to an approved NDA or ANDA and for distributing a drug product made with such changes, refer to §§ 314.70, 314.71, and 314.97. In addition, an applicant should consider relevant CDER guidance documents for recommendations on reporting categories and information that should be submitted to support a change to an approved NDA or ANDA, including the guidances for industry *Changes to an Approved NDA or ANDA*, *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports* (March 2014), and *ANDA Submissions – Prior Approval Supplements Under GDUFA* (October 2022).

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

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

[2] See the guidance for industry *Changes to an Approved NDA or ANDA* (April 2004). 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.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Certain nonprescription drug products that are new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) are subject to approval on the basis of an NDA or ANDA submitted under sections 505(b) or 505(j) of the FD&C Act, respectively. A "nonprescription drug" is a drug that is not subject to the requirements of section 503(b)(1) of the FD&C Act.[3]

FDA evaluates whether the data and information submitted as part of an NDA or ANDA for a nonprescription drug product demonstrate that the drug product is safe and effective for nonprescription use under the conditions prescribed, recommended, or suggested in its proposed labeling.[4] A nonprescription drug must be labeled with adequate directions for use.[5] Adequate directions for use are the directions under which the consumer (layman) can use the drug safely and for the purposes for which it is intended.[6] Therefore, labeling for a nonprescription drug product[7] enables consumers to appropriately self-select and use the nonprescription drug product safely and effectively without the supervision of a health care practitioner.

In order for FDA to approve an application for a nonprescription drug, particular studies may be required to demonstrate that the drug product can be used safely and effectively in the nonprescription setting. This may include consumer studies to demonstrate that the drug product is safe and effective for use without the supervision of a health care practitioner (i.e., nonprescription setting), including label comprehension studies,[8] self-selection studies,[9] and actual use studies.[10]

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[3] Section 503(b)(1) refers, in relevant part, to a human drug that "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug."

[4] See sections 505(d) and 503(b)(1) of the FD&C Act (21 U.S.C. 355(d) and 353(b)(1)).

[5] See section 502(f)(1) of the FD&C Act.

[6] See 21 CFR 201.5.

[7] A nonprescription drug product is subject to applicable labeling requirements of the FD&C Act and FDA regulations (e.g., 21 CFR part 201).

[8] Label comprehension studies assess consumer understanding of major communication elements on the labeling. See the guidance for industry *Label Comprehension Studies for Nonprescription Drug Products* (August 2010).

[9] Self-selection studies test whether consumers can apply information in the drug product's labeling to their personal medical situations and make correct decisions to use or not use the drug product. See the guidance for industry *Self-Selection Studies for Nonprescription Drug Products* (April 2013).

[10] Actual use studies provide information on how consumers will use the drug product once purchased.

After FDA approves an NDA or ANDA, an applicant may make, or in certain cases propose to FDA, changes to the approved application. Section 506A of the FD&C Act and FDA regulations under 21 CFR §§ 314.70, 314.71, and 314.97 establish certain requirements for making and reporting to FDA changes to an approved NDA or ANDA, including an NDA or ANDA for a nonprescription drug product. The regulations address changes that must be approved by FDA before distribution of a drug product made with such changes, as well as changes for which FDA approval is not required before distribution and changes that must be submitted in annual reports. Changes to an approved NDA or ANDA, including labeling changes, are categorized into one of three reporting categories: major, moderate, or minor.[11]

Minor changes include certain changes that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.[12] Minor changes to an approved NDA or ANDA may be implemented immediately by the applicant without the applicant submitting a supplement to FDA.[13] The applicant must document minor changes, including minor labeling changes, in its next annual report in accordance with 21 CFR § 314.81(b)(2)[14] (i.e., the annual report covering the period when the change or changes occurred) submitted to FDA.[15] The annual report must include a summary of any changes in labeling, including minor changes, that have been made since the last report listed by date in the order in which they were implemented, or if no changes have been made, a statement of that fact.[16]

Determining the reporting category for a change to nonprescription drug labeling may present certain considerations that differ from changes to prescription drug labeling. Changes to the approved labeling for a nonprescription drug product may affect consumers' ability to appropriately self-select and use the nonprescription drug product safely and effectively without the supervision of a health care practitioner. Thus, changes to nonprescription labeling may not be considered minor even though similar changes may be considered minor when applied to the labeling of a prescription drug product. For example, certain changes in the layout of the package or container label for a prescription drug product that are consistent with FDA regulations (e.g., 21 CFR part 201), without a change in the content of the labeling, might not affect the safe and effective use of the prescription drug product, because it is used under the supervision of a healthcare practitioner. In contrast, changes in the layout of the package or container label and other changes to nonprescription drug labeling could affect consumers' ability to comprehend the nonprescription drug labeling and to appropriately self-select and use the nonprescription drug product such that the change would not be a minor change under 314.70(d).

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[11] See §§ 314.70 and 314.97. Also see the guidance for industry *Changes to an Approved NDA or ANDA*.

[12] See § 314.70(d).

[13] Ibid.

[14] Ibid.

[15] See §314.70(d); §314.81(b)(2). Additionally, a representative sample of, among other things, the package labels must be submitted in the annual report. § 314.81(b)(2)(iii)(*a*).

[16] See § 314.81(b)(2)(iii)(*c*).

FDA generally does not expect that editorial and similar minor labeling changes to nonprescription drug labeling would affect consumers' ability to appropriately self-select and use the nonprescription drug product without the supervision of a healthcare practitioner. Based on FDA's experience approving nonprescription drug labeling, FDA is providing examples of such editorial or similar minor labeling changes for nonprescription drug products that may be appropriate to include in an annual report.

III. RECOMMENDATIONS

A. Examples of Editorial or Similar Minor Labeling Changes

Certain changes that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product, including an editorial or similar minor change in labeling, must be documented by the applicant in the next annual report.[17] FDA considers the following to be examples of minor changes that would be appropriate for inclusion in the applicant's next annual report:

- Correcting misspellings, punctuation, or grammatical errors
- Revising a manufacturer's, packer's, or distributor's name consistent with the FDA-approved application
- Revising a manufacturer's, packer's, or distributor's contact information (e.g., phone number, address) or website address
- Adding or revising the manufacturing site information consistent with the FDA-approved application
- Adding, revising, or deleting a national drug code number to reflect the applicable drug listing information pursuant to 21 CFR 207
- Adding, revising, or deleting the universal product code (UPC) or UPC barcode
- Revising any of the following elements on an instant redeemable[18] or in-pack coupon: expiration date of coupon; information about the package size or sizes of the nonprescription drug product to which the coupon applies, provided that such package size or sizes are consistent with the nonprescription drug product's approved course of treatment count; fixed value discount (e.g., "$1 off"), offer restrictions (e.g., "void if copied, transferred, prohibited, taxed, or restricted"); information required for retailer processing (e.g., UPC or offer code, redemption mailing instructions); and any necessary legal copy (e.g., fraud and policy notice)

[17] See § 314.70(d)(2)(x); see also 21 CFR 314.81(b)(2.).

[18] For purposes of this guidance, an instant redeemable coupon is a coupon that is placed externally on the carton, usually on the principal display panel (PDP), for consumers to use at check-out.

- Introducing or adding a new instant redeemable or in-pack coupon (not including peel-off PDP coupons) that only includes the nonprescription drug product name, expiration date of coupon, package size of the nonprescription drug product to which the coupon applies, fixed value discount (e.g., $1 off), offer restrictions (e.g., "void if copied, transferred, prohibited, taxed, or restricted"), information required for retailer processing (e.g., UPC or offer code, redemption mailing instructions), and any necessary legal copy (e.g., fraud and policy notice); provided that (1) the coupon is for only the nonprescription drug product it accompanies (i.e., coupon is not for, or does not also address, a different product); (2) if affixed, the coupon does not obscure or change required elements of the labeling; (3) removal of the coupon by the consumer does not affect the readability of required elements of the labeling; and (4) the coupon is not redeemable for a net quantity of the nonprescription drug product that is inconsistent with the nonprescription drug product's approved course of treatment count

- Removing a time-limited *flag* (e.g., "new count size" or "new flavor") from a product's PDP[19]

- Relocating a logo (or graphic) that appears in the FDA-approved labeling provided that (1) the size of the logo (or graphic) remains the same or decreases; (2) the relocation does not decrease the font size of required elements of labeling; and (3) the relocation does not interfere with (i.e., compete with, interrupt, or distort) or decrease the prominence, readability, or legibility of the required elements of labeling[20]

- Adjusting the graphic design of the PDP in the FDA-approved labeling after removing a logo (or graphics) or a flag provided that the adjustment does not decrease the font size of required elements of labeling and does not decrease the prominence, readability, or legibility of the required elements of the PDP

- Modifying the orientation of the carton PDP (e.g., vertical to horizontal or vice versa) provided that (1) there are no changes to the carton or container dimensions; (2) there are no changes to the content of the labeling, other than certain minor (e.g., editorial) changes;[21] (3) there is no reduction in font size of the required elements of labeling; (4) the modification does not decrease the prominence, readability, or legibility of the required elements of the PDP; and (5) there are no changes that create insufficient space for the prominent placement of the required elements of labeling

[19] *Flag* is a term used to designate an attention-getting label signal that alerts consumers to read the label carefully because of significant new information. Such flags are generally removed 6 months after introduction into the marketplace.

[20] See the draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022). When final, this guidance will represent the FDA's current thinking on this topic. 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.

[21] See 21 CFR 314.70(d) and the examples in this guidance.

- Modifying color schemes on the container label and carton labeling, including minor color changes to the PDP, provided that the modification (1) does not decrease the prominence, readability, or legibility of the required elements of the labeling and (2) does not increase visibility of nonprescription drug product claims while minimizing other required elements of the labeling[22]

- Modifying color on the Drugs Fact Label (DFL) in a manner that is consistent with the requirements of applicable FDA regulations (e.g., 21 CFR 201.66(d)(3))

- Adding new package count, excluding multiunit packages, without a change to the drug product's approved container closure system and within its approved stability bracket[23] (i.e., no CMC supplement is required to be submitted for approval), provided that the new package count (1) does not involve a change to labeling content or formatting other than listed net quantity of contents, (2) does not exceed any maximum package count described in the approved application, and (3) is consistent with any approved course of treatment count

- Revising bonus or free dosage units on approved bonus flag and revision of the declaration of net quantity of contents reflecting total package count provided that the total package count (1) does not exceed any maximum package count described in the FDA-approved labeling, (2) is consistent with the nonprescription drug product's approved course of treatment count, and (3) if a particular package count size was specified in the approved application, does not differ from that package count size.

- Relocating a required tamper-evident statement from inside the DFL to outside the DFL or relocating a required tamper-evident statement approved outside the DFL to another location outside the DFL. The statement must remain prominently placed[24] on the nonprescription drug product package.[25]

- Modifying the orientation of the DFL on the carton (e.g., horizontal to vertical orientation of DFL on carton or vice versa or a change from one panel to multiple carton panels) provided that there are no changes, other than certain minor (e.g., editorial) changes,[26] (1) to the carton or container dimensions; (2) to the content in the DFL; (3) that create

[22] See the draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*.

[23] In the annual report cover letter, the applicant should reference the approval letter of the application or the CMC supplement number in which FDA approved the container closure system and stability bracket.

[24] FDA does not consider the bottom panel of the carton or container or the inside of the carton to be a prominent location.

[25] See 21 CFR § 211.132(c)(1)(ii).

[26] See 21 CFR 314.70(d) and the examples in this guidance.

insufficient space for the prominent placement of the required elements of labeling; and (4) to the order and flow of headings, subheadings, and information in the DFL

B. Additional Considerations for Minor Labeling Changes

Applicants should be aware of the following:

- Generally, changes to the content in the DFL of an approved nonprescription drug product are not considered minor changes and may not be documented in an annual report.[27] However, certain changes to the DFL may be considered minor, including changing color of DFL and moving the tamper-evident statement from the DFL to the outer carton (see section III.A. of this guidance for examples).

- In certain cases involving implementation of multiple minor changes, the totality of the minor changes could affect consumers' ability to understand the required labeling information and to appropriately self-select and use the nonprescription drug product.[28] In such cases, applicants should submit a supplement, rather than an annual report. Where appropriate, if an applicant includes multiple changes in its annual report, especially changes to the PDP that cause the outer packaging to look new or different, FDA may request that the applicant submit a supplemental NDA or ANDA.

- When FDA reviews submitted annual reportable changes, it is FDA's practice to acknowledge the changes at the time of submission of the annual report. Labeling changes submitted in annual reports are not FDA-approved and should not be considered or described as such. FDA would consider the annual reportable changes for approval in any subsequent supplemental NDA or ANDA that the applicant submits. [29] At times, multiple annual reportable changes, especially to the PDP where the outer packaging looks new or different, FDA will request a prior approval supplement be submitted to approve that particular label with multiple changes.

- FDA reviews previously submitted annual reports. Upon review of the annual report, FDA may determine that a labeling change was inappropriate for documentation in an annual report, notify the applicant of the correct supplement category, and request the submission of such supplement.[30]

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[27] See §§ 314.70 and 314.97. Also see the guidance for industry *Changes to an Approved NDA or ANDA*.

[28] See the guidance for industry *Changes to an Approved NDA or ANDA*.

[29] When submitting a labeling supplement, applicants must include a list of all changes contained in the supplement and should include any minor labeling changes that the applicant submitted, or is to submit, in the next annual report. See 21 CFR 314.70(a)(6).

[30] See the guidance for industry *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports*.