
Guidance for Industry

Labeling OTC Human Drug Products

Updating Labeling in RLDs and ANDAs

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

**October 2002
OTC**

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Labeling OTC Human Drug Products Updating Labeling in RLDs and ANDAs

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to assist manufacturers, packers, and distributors of over-the-counter (OTC) drug products marketed under abbreviated new drug applications (ANDAs) and the manufacturers of corresponding reference listed drugs (RLDs) implement the Agency's regulation on standardized content and format requirements for the labeling of OTC drug products. The guidance contains recommendations on how RLD and ANDA holders can update their labeling in a timely manner consistent with the regulation on OTC drug product labeling (21 CFR 201.66).

II. BACKGROUND

In the *Federal Register* of March 17, 1999 (64 FR 13254), the Food and Drug Administration (FDA) published a final regulation establishing standardized content and format requirements for the labeling of OTC drug products (Drug Facts Rule), codified at 21 CFR 201.66. Standardized labeling for OTC drug products is intended to make it easier for consumers to read and understand OTC drug product labeling and use such products safely and effectively.

The Drug Facts Rule covers all OTC drug and drug-cosmetic products, whether marketed under a new drug marketing application (NDA), abbreviated new drug application (ANDA), or OTC drug monograph (or product not yet the subject of a final OTC drug monograph). The implementation

¹ This guidance has been prepared by the Division of Over-the-Counter (OTC) Drug Products and the Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

dates are the same for products that were legally marketed under an NDA or ANDA before the date of the final regulation.

Sections 201.66(c)(1) through (c)(9) of the Drug Facts Rule provide the content requirements for labeling information, including information about active ingredients, their purpose, use, warnings, directions, other information, and inactive ingredients.

After publication of the Drug Facts Rule, the Agency was asked whether manufacturers of products marketed under ANDAs could use the new labeling content and format requirements *before* the RLD holders had revised their labeling, or whether ANDA holders were required to wait for their respective RLD holders to revise their labeling before submitting new ANDA labeling to make it the same as that of the RLD. These questions were raised because, under section 505(j)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)(2)), a drug product marketed under an ANDA must bear the "same labeling" as that approved for the RLD. The concern was that many generic manufacturers would not be able to comply with the compliance date for the Drug Facts Rule if they had to wait to copy the labeling updates of the RLDs.

To help clarify the Agency's expectations under the Drug Facts Rule, the Agency made available on February 22, 2001, a draft guidance for industry on Labeling OTC Human Drug Products Updating Labeling in ANDAs.

This is a final version of that guidance. It is intended to help RLDs and ANDAs meet the new OTC drug products labeling format requirement in light of the "same labeling" requirement set forth in section 505(j)(2) of the Act.

III. THE DRAFT GUIDANCE

In the February 22, 2001, draft guidance, the Agency suggested that manufacturers of generic OTC drug products (i.e., products marketed under ANDAs) could implement the new labeling format for their products *before* the RLD holders had submitted their labeling revisions to FDA. In support of this suggestion, the Agency noted that the same labeling requirement in section 505(j)(2) of the Act does not require ANDA labeling to be *identical* to that of the RLD. Among permissible differences, FDA regulations at 21 CFR 314.94(a)(8)(iv) allow an ANDA holder to include labeling that is different from that of the RLD where the ANDA labeling revisions are made to comply with current FDA guidelines or other guidance. The Agency reasoned in the draft guidance that the changes made to ANDA labeling to accommodate the Drug Facts panel would be changes made in response to the requirements of such a regulation — the Drug Facts Rule (21 CFR 201.66).

The draft guidance also reasoned that the majority of the format changes required by the Drug Facts Rule could be submitted to the Agency in an annual report to an application under 21 CFR 314.70(d)(3)² and would not necessitate the submission of a labeling supplement for preapproval.

² Changes to labeling that go beyond the interchangeable terms allowed in Agency regulations (i.e., in 21 CFR 330.1(i) or (j)) should be submitted to the Agency in a supplement for preapproval. Questions about the need to submit a labeling supplement for

In support of this suggestion, the draft guidance noted that the preamble to the Drug Facts Rule (64 FR 13254 at 13272) states that the adoption of the new labeling format for most OTC drug products marketed under an NDA or ANDA *would be considered an editorial or minor change*.

In addition, to help facilitate the relabeling process, the Agency drafted 10 updated labeling examples and posted them on the Internet for review.

IV. GENERAL POLICY

The Agency is exercising its enforcement discretion by providing manufacturers of generic OTC drug products two options for revising the labeling of their products to meet the new labeling requirements under 21 CFR 201.66. First, manufacturers may revise their product labeling at this time in accord with the Agency's product-specific labeling examples included with this guidance. Manufacturers may continue to use such labeling until the Agency approves revised labeling for the corresponding RLD that meets the requirements under § 201.66 and posts a copy of that approved labeling on the Internet. At that time, the ANDA holder should further revise its labeling using the Agency's May 2000 Guidance for Industry entitled "Revising ANDA Labeling Following Revision of the RLD Labeling." Second, manufacturers need not revise their product labeling at this time, but can wait until the Agency approves revised labeling for the RLD that meets the requirements under § 201.66 and posts a copy of that approved labeling on the Internet. At that time, the ANDA holder should revise its labeling using the May 2000 Guidance for Industry identified above. The Agency's exercise of this enforcement discretion commenced on May 16, 2002 (see 65 FR 38191 and 67 FR 16306) and continues for each specific ANDA product until the Agency approves revised labeling for the corresponding RLD.

The Agency believes its exercise of enforcement discretion will help ensure that both OTC RLD holders and OTC ANDA holders update their product labeling in a way that is consistent with the precise format and content requirements under 21 CFR 201.66 and the "same labeling" requirements under section 505(j)(2) of the Act. The Agency's exercise of enforcement discretion is prompted by the proximity of the Drug Facts Rule compliance date and the desire to relieve ANDA holders from the potential burden of having to relabel their products multiple times to comply with requirements of 21 CFR 201.66, 21 CFR 314.94(a), and 21 USC 505(j)(2).

A. Implementation

As part of this guidance, the Agency is making available and posting on the Internet 14 product-specific labeling examples, which apply to about 60 percent of all ANDA OTC drug products (see section V). The Agency also intends to prepare additional labeling examples for other OTC drugs marketed under ANDAs and add them to this guidance and post them on the Internet.

As part of the exercise of its enforcement discretion, the Agency is allowing any manufacturer of a generic OTC drug product (i.e., a product marketed under an ANDA) to implement the new Drug

preapproval should be directed to the appropriate Agency division. See also CDER's guidance *Changes to an Approved NDA or ANDA* (November 1999).

Facts labeling format for its product *before* FDA posts approved labeling for its applicable RLD so long as the generic's labeling update complies with 21 CFR 201.66. The Agency recommends that ANDA holders use the Agency's labeling examples when revising their labeling before updated RLD labeling has been approved. ANDA holders that follow the Agency's labeling examples will be considered in compliance. During the period of enforcement discretion, the Agency will not initiate an enforcement action based upon 21 CFR 201.66 or 314.94(a)(8)(iv) against any OTC ANDA drug product that complies with 21 CFR 201.66, regardless of the status of the RLD's labeling or the "same labeling" requirements in 21 CFR 314.94 and 21 USC 355(j)(2).

However, once FDA posts the approved RLD labeling updates on the Internet, ANDA holders should update their product labeling, if necessary, to be the same as their corresponding RLDs. In May 2000, the Agency issued a Guidance for Industry entitled *Revising ANDA Labeling Following Revision of the RLD Labeling*. That guidance explains that the sponsor of an ANDA is responsible for ensuring that the labeling contained in its application is the same as the currently approved labeling of the RLD. Because the labeling of a generic drug product must be the same as its innovator (other than those differences described in 21 CFR 314.94(a)(8)(iv)), the guidance states that the revision should be made at the very earliest time possible. If an ANDA holder foresees potential delay in the revision of its generic drug labeling, that sponsor should contact the Office of Generic Drugs.

The May 2000 guidance further explains that prompt revision, submission to the Agency, and implementation of revised labeling are important to ensure the continued safe and effective use of generic drug products. The Agency believes that the Drug Facts labeling for all OTC drug products (especially those of the same type) should be as uniform and consistent as possible. Such uniformity ensures compliance with 21 CFR 314.94(a) and serves an important public health goal behind the Drug Facts Rule — reducing consumer confusion.

RLD holders that follow any of the Agency's product-specific labeling examples or otherwise comply with 21 CFR 201.66 need not file a preapproval supplement for their labeling revision and may submit the changes in their annual report in accord with 21 CFR 314.70(d). Similarly, ANDA products that follow the FDA's product-specific labeling examples or otherwise comply with 21 CFR 201.66 need not file a preapproval supplement for their labeling revision and may submit the changes in their annual report in accord with 21 CFR 314.97 and 314.70(d). This is also true for any updates that ANDA holders make to their OTC drug labeling to comply with 21 USC 355(j)(2), 21 CFR 314.94, 314.97 and/or 201.66 after the Agency posts the approved RLD labeling on the Internet.

The Agency has developed its labeling examples to assist both RLD and ANDA holders to update their labeling in an uniform manner and at a reduced cost. However, RLD and ANDA holders are not legally required to use the Agency's labeling examples. RLD holders may adopt an alternative approach so long as it complies with 21 CFR 201.66. Because ANDA holders eventually need to have the same labeling as the RLD, the Agency has decided to exercise its enforcement discretion with regard to OTC ANDA labeling. Manufacturers and repackers of OTC ANDA drug products who do not wish to update their labeling to meet section 201.66 before the expiration of the period of enforcement discretion are not required to do so.

The Drug Facts Rule requires all RLDs and ANDAs approved before May 16, 1999, to comply with the new labeling by May 16, 2002. The Drug Facts Rule also requires RLDs and ANDAs approved after May 16, 1999, to comply immediately upon approval of the application. Although the Agency has not enforced this requirement for ANDAs to date, it expects any OTC RLDs approved after May 16, 1999, to comply with the new Drug Facts labeling format by May 16, 2002, unless the manufacturer obtains or has obtained a deferral of this date.

As noted above, the Agency is granting a grace period for all currently marketed OTC ANDA products to relieve them of the potential burden of having to update their labeling more than once to comply with format changes made by their RLDs. This exercise of enforcement discretion is also being extended to any ANDA approved on or after May 16, 2002 until the RLD labeling for that product in the new Drug Facts format has been approved by FDA. These ANDA products will be allowed to use the existing RLD labeling or the Agency's recommended labeling examples for the product. Once the RLD labeling is approved in the Drug Facts format, the holders of these ANDA products should update their labeling, just like the ANDAs approved before May 16, 2002, so that all comparable ANDA products meet the requirements of 21 CFR 201.66, 21 CFR 314.94, and 21 USC 505(j)(2) at approximately the same time.

B. Preapproval Supplements

Manufacturers of OTC RLD drug products who believe they need to or wish to submit a preapproval supplement should submit that supplement as soon as possible if they have not already done so. Manufacturers of OTC ANDA drug products may also submit a preapproval supplement at their discretion. The Agency will review these supplements as expeditiously as possible and may develop additional labeling examples that all manufacturers of similar products can use. Any additional labeling examples that the Agency develops will be made available on the Internet as part of this guidance (see section V).

C. Deferral Requests

ANDA holders who do not believe they can comply by the end of the grace period should submit a deferral request in accordance with 201.66(e) and state why the request meets one or more of the criteria in that section and the amount of additional time that may be needed. The Agency is not providing an across-the-board extension of time for ANDA holders to update their labeling beyond the exercise of enforcement discretion mentioned throughout this guidance.

The Agency does not see the need to implement a Special Supplement - Changes Being Effected for the labeling revisions required by § 201.66. However, manufacturers may submit such a supplement if they wish to do so. This guidance describes when a manufacturer may submit the labeling changes in an annual report in accord with 21 CFR 314.97 and 314.70(d)(3) (see section VI). If a manufacturer finds the need for an expedited review of labeling that requires FDA approval of a supplement, it can request an expedited review under 21 CFR 314.70(b).

V. FDA RECOMMENDED LABELING EXAMPLES FOR SOME PRODUCTS

The Agency stated in its Drug Facts Rule that it expects 522 submissions (350 to NDAs and 172 to ANDAs) for labeling changes under 21 CFR 201.66(c) and (d). Submissions to NDAs will vary as many different products are marketed under NDAs. However, submissions to ANDAs will be concentrated in the following products:

- ibuprofen tablets
- acetaminophen suppositories
- cimetidine tablets
- loperamide tablets and oral solution
- miconazole vaginal cream and suppositories
- minoxidil topical solution [2 %]
- naproxen sodium tablets

Thirty-five submissions are expected on ibuprofen, and more than five submissions are expected for each of the other drug products listed above. Together, these drugs constitute about 50 percent of all OTC drug product ANDAs.

To facilitate the implementation of the new Drug Facts section of the labeling for these pre-approved products, the Agency has developed labeling examples for RLD and ANDA manufacturers to follow for each of the products listed above. The labeling examples show each specific product's labeling in the new format. Since publication of the draft guidance, the Agency has also prepared four additional labeling examples for the following products:

- minoxidil topical solution [5 %]
- clemastine fumarate tablets
- doxylamine succinate tablets
- pseudoephedrine hydrochloride extended release tablets

The Agency considered previously approved RLD labeling in developing these examples, which the Agency considers as meeting the requirements of 21 CFR 201.66 and 314.70. Thus, manufacturers of RLDs who use these labeling examples do not need Agency preapproval. Similarly, as part of its exercise of enforcement discretion, the Agency will not initiate an enforcement action based upon 21 CFR 201.66 or 314.94(a)(8)(iv) against any OTC ANDA product that uses one of these labeling examples at any time between the date on which this guidance is published and the date on which the grace period expires, regardless of the status of the labeling for its corresponding RLD. As noted above, however, the ANDA's labeling may need to be updated at the end of the grace period to mirror the precise approved labeling updates made by its RLD.

The Agency's labeling examples can be found on the Internet with this guidance.³ The Agency may develop additional labeling examples for other ANDA OTC drug products, and they also will be

³ This and other Agency guidances are available on the Internet at <http://www.fda.cder/guidance/index.htm>. The product-specific labeling examples and the approved RLD updates also are (and will be) available at www.fda.gov/cder/otc/.

made available for review at the same locations. Any person with any comment regarding any of the examples developed in the future may submit such comment to the public docket for this guidance.

When using the labeling examples, it should be noted that interchangeable terms can be used in certain places (see 21 CFR 330.1(i) and (j)). For example, although the Agency uses the word *doctor* in its labeling examples, the term *physician* can also be used where appropriate.

VI. SUBMISSION OF NEW LABELING IN AN ANNUAL REPORT

Manufacturers of OTC RLDs can submit their Drug Facts labeling changes in their annual reports according to 21 CFR 314.70(d)(3) and need not submit a supplemental application to the Agency for preapproval under several different circumstances:

- If they follow the Agency's labeling examples to make their changes
- If they do not follow the Agency's labeling examples, but change their labeling in accordance with 21 CFR 201.66 and 330.1(i) or (j)
- Where the Agency has not provided any labeling examples, if they change their labeling in accordance with 21 CFR 201.66 and 330.1(i) or (j)

Manufacturers of OTC ANDA drug products may also submit such changes in their annual reports according to 21 CFR 314.97 and 314.70(d)(3) and need not submit a supplemental application for preapproval.

Manufacturers should submit preapproval supplements to their NDA or ANDA, as appropriate, if they make changes to the content of the labeling or wording changes that go beyond those provided for in 21 CFR 314.70, 314.97, 314.94, or 330.1(i) or (j).