Guidance for Industry

Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications

DRAFT GUIDANCE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)
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Draft – Not for Implementation

GUIDANCE FOR INDUSTRY[1]

Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications

This draft guidance, when finalized, will represent the Food and Drug Administration's current thinking on this topic.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.

If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed changes.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

I. INTRODUCTION

This document is intended to provide guidance to applicants on referencing discontinued labeling for listed drugs in abbreviated new drug applications (ANDAs) submitted for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act). This issue is not addressed directly in the regulations governing the approvals of ANDAs at 21 CFR 314 subpart C. The Office of Generic Drugs (OGD) is proposing the most appropriate response to this regulatory question, and is making its current thinking on the matter available to the public through this guidance.

II. BACKGROUND

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman amendments) established the generic drug approval program used today to ensure that lower price generic drugs are made available to the public promptly upon the expiration of patent and exclusivity protections covering the innovator products. The generic drug approval process generally depends on the ANDA applicant establishing that the generic drug is the same as an approved innovator product (the listed drug) with respect to active ingredient, dosage form, strength, route of administration, conditions of use, and labeling.

[1] This draft guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER).

During the period when an innovator drug is being marketed, it may undergo a number of changes that are approved through new drug application (NDA) supplements. Such changes can include the addition of new indications, changes to the product formulation, and labeling changes. In the past, when ANDAs have been submitted, they have referenced only the innovator drug product labeling as it appears at the time of ANDA submission. However, recently a question has been raised as to whether, in certain circumstances, an ANDA can refer to discontinued labeling for the listed drug.

The issue of referencing discontinued labeling for the listed drug arises when the sponsor of the innovator drug product has obtained exclusivity or patent protection for a new aspect of product labeling and has removed the previous unprotected labeling for reasons other than safety or effectiveness. When the holder of the innovator drug obtains approval and market protection for a change to the drug and removes the corresponding unprotected information from the current labeling, there is no current complete labeling for the ANDA applicant to reference.[2] For example, the NDA holder may obtain approval and market protection for a new dosing regimen and remove the previous dosing regimen(s) from the labeling. In this situation, the ANDA applicant, which must include information regarding dosing regimen in its application, is blocked by the NDA holder's exclusivity from referencing the new dosing regimen contained in the innovator drug labeling, and all the previous dosing regimen information has been removed from the current labeling. This raises the question of whether applicants will be barred from obtaining approval for any ANDA for that innovator drug until the protection for the new dosing regimen expires, because relevant labeling is either protected or has been removed from the currently marketed product.[3]

In FDA's view, the appropriate approach to the situation depends on whether the previous labeling was withdrawn from the drug product for reasons of safety or effectiveness, and whether omission of the protected information will render the drug unsafe. This is the same approach taken by the Agency when an entire product, rather than just a portion of the labeling, is withdrawn from the market, and when a portion of the innovator labeling must be omitted from a generic drug label because of patent or exclusivity protection.

FDA’s proposed approach creates a process intended to assure that labeling removed from an innovator drug product for reasons of safety or effectiveness cannot be referenced in an ANDA. At the same time, this process will permit approval of ANDAs

[2] Contrast this with the situation in which an innovator has obtained approval for a new indication and patent or exclusivity protection that extends beyond the protection for other indications that remain on the labeling. The ANDA applicant may cite the innovator labeling that includes all of the approved indications, and only the protected indication will be omitted from the ANDA labeling when it is approved. *See Bristol-Myers Squibb v. Shalala*, 91 F.3d 1493 (D.C.Cir. 1996).

[3] In theory, the innovator could delay generic competition indefinitely by continuing to make minor — but protectable — changes to the drug, and removing unprotected labeling. If this approach were effective, the Agency also could expect to review many more labeling supplements, possibly for changes that, although sufficiently innovative to warrant patent or exclusivity protection, do not necessarily represent significant improvements in the currently marketed drug.

that reference labeling that, although removed from the currently marketed innovator product, nonetheless describes the safe and effective use of the drug. This approach will make safe and effective generic drug products available to the public as promptly as possible when relevant market protections have expired.

III. PROPOSED APPROACH

The Agency has determined that in certain circumstances an ANDA should be permitted to reference discontinued labeling for a listed drug. This generally should occur when:

1. The holder of the NDA for the innovator drug has obtained approval for a change in the drug labeling.

2. That change has received either a patent listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*) or market exclusivity under the Act.

3. The NDA sponsor has removed or revised the labeling describing the corresponding unprotected aspects of the drug.

4. The change to the drug product is not one for which a suitability petition may be filed (21 CFR 314.93).

5. The sponsor wishing to reference the discontinued labeling has submitted a petition requesting that the Agency determine whether the previous labeling was withdrawn for reasons of safety or effectiveness, or the Agency has undertaken its own inquiry regarding the withdrawal of the previous labeling.

6. The Agency has determined that the previous innovator labeling was not withdrawn for reasons of safety or effectiveness.

7. The Agency has determined that omission of the protected information will not render the drug product less safe or effective than the currently marketed innovator product.

IV. SUBMISSION OF ANDAS

A. Statutory Requirements

The generic drug approval process is based on the ANDA applicant establishing that its product is the same as a drug previously approved by FDA. Among other things, an ANDA must provide information to show that the conditions of use, route of administration, dosage form, and strength of the proposed product have been previously approved for a listed drug (section 505(j)(2)(A) of the Act). If an ANDA applicant wants approval of a change to the route of administration, dosage form, strength, or the substitution of an active ingredient in a combination drug product, it can obtain approval

for this change through a suitability petition (section 505(j)(2)(C)). The ANDA also must include information to show that the labeling for the proposed drug is the same as the labeling approved for the listed drug, except for differences approved through a petition, or because the proposed drug and listed drug are produced by different manufacturers (section 505(j)(2)(A)(v)).

A listed drug is a drug included on a list published by FDA of drugs approved for safety and effectiveness under section 505(c) (section 505(j)(7)) of the Act. This list is published in the *Orange Book*. A drug whose approval was withdrawn or suspended under section 505(e) for reasons of safety or effectiveness, or that has been withdrawn from sale for reasons of safety or effectiveness, cannot serve as a listed drug for approval and is removed from the *Orange Book* (section 505(j)(4)(I) and (j)(7)(C)).

B. Regulatory Requirements

Identification of a listed drug is a crucial component of the ANDA approval process. An ANDA must refer to a listed drug (21 CFR 314.94(a)(3)). The characteristics and labeling of the listed drug generally will be duplicated in the characteristics and labeling of the product proposed in the ANDA (21 CFR 314.94(a)(3)-(9)). A drug approved in an ANDA must be the same as the listed drug in terms of active ingredient(s), dosage form, strength, route of administration, and conditions of use, except for conditions of use for which approval cannot be granted because of exclusivity or an existing patent (21 CFR 314.92(a)(1)). Certain differences will be permitted for products for which a suitability petition has been approved, or because the drug proposed in the ANDA and the listed drug are produced or distributed by different manufacturers. These differences can include omission of an indication or other aspect of labeling that is protected by patent or exclusivity (21 CFR 314.94(a)(8)(iv)). Aspects of a listed drug's labeling that are protected by patent or exclusivity may be omitted from the labeling proposed in an ANDA if the resulting differences in the labeling do not render the proposed drug product less safe or effective for all the remaining, unprotected conditions of use (21 CFR 314.127(a)(7)).

An ANDA may refer to a listed drug that is an approved product currently being marketed, or that is an approved product which has been withdrawn from the market by the sponsor.[4] If an ANDA applicant references a listed drug that the sponsor has ceased to market, the FDA must determine whether the drug was removed from the market for reasons of safety or effectiveness before the ANDA can be approved (21 CFR 314.161). If the Agency has not made such a determination on its own initiative, the ANDA relying

[4] FDA regulations define *listed drug* at 21 CFR 314.3(b) as "a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of [the Orange Book], or any current supplement thereto." Note: section 505(j)(5) of the Act has been renumbered as 505(j)(6).

on the discontinued drug must be accompanied by a petition requesting FDA to determine whether the drug was withdrawn from the market for reasons of safety or effectiveness (21 CFR 314.122).

C. Past Practice

In the past, when an applicant submitted an ANDA, the only labeling available for the listed drug has been labeling on the currently marketed form of the listed drug. The regulations require an ANDA to include a copy of the "currently approved labeling for the listed drug" (21 CFR 314.94(a)(8)). If the generic product will have labeling that is different from that of the listed drug, the ANDA applicant should state the reason for such differences and explain why such differences are permitted. As described above, certain differences from the innovator labeling are permitted.

The question of whether an ANDA could refer to previously approved but subsequently altered labeling had not arisen previously. Therefore, until recently, the Agency had not had a reason to develop a policy on the appropriate response to this situation.[5] Now, with what could be a growing practice among innovator sponsors of substituting protected labeling for unprotected labeling, the Agency has determined that in certain situations, it may approve an ANDA for a drug product with labeling that was previously approved for the listed drug, but which the listed drug is no longer carrying.

V. REFERENCING DISCONTINUED LABELING FOR A LISTED DRUG IN AN ANDA

For an ANDA applicant to refer to discontinued labeling for a listed drug, the following conditions should exist.

A. Existence of Exclusivity or Patent Protection

An ANDA generally should refer to discontinued labeling for the listed drug only when, at the time the ANDA is submitted (or while it is pending), an essential part of the labeling for the currently marketed innovator drug is protected by exclusivity or a patent, and the corresponding unprotected labeling has been removed. This approach is based on the desire to minimize confusion in the marketplace arising from the availability of drugs that are the same in many respects, but have slightly different labeling.[6]

[5] In 1998, the Office of Generic Drugs provided an informal opinion to an innovator company that had removed unprotected dosing information from its label stating that the Agency would not approve an ANDA that does not contain the same dosing and administration information as the listed drug. That opinion, however, was given in a case in which the discontinued labeling information was determined by the Agency to have been removed from the innovator drug for reasons of safety or effectiveness. To address any concern that the approach described in this guidance can be considered a change from past interpretation, the guidance is being released in draft for public comment prior to implementation.

[6] There are already situations in which ANDAs will be approved for drug products that are

B. Identifying Appropriate Labeling

The ANDA applicant should identify the discontinued labeling for the listed drug to which it will refer. Generally, this will be the labeling as approved in the innovator application just prior to the addition of the protected part labeling and deletion of the unprotected part of labeling.

C. Submission of Petition Requesting Determination of Reasons for Change to Labeling

Once the ANDA applicant has identified the discontinued labeling for the listed drug to which it will refer, the applicant should submit a petition as described in 21 CFR 314.122, seeking a determination by FDA that the discontinued labeling was not withdrawn from the listed drug for reasons of safety or effectiveness. An ANDA for the drug may be submitted at the same time the petition is submitted, but the ANDA will not be approved until the Agency has determined that the discontinued labeling for the listed drug was not withdrawn for reasons of safety or effectiveness. FDA also may, on its own initiative, begin the process of determining whether labeling was discontinued for reasons of safety or effectiveness.

D. FDA Determination on Safety and Effectiveness

The Agency will determine whether the labeling was discontinued for reasons of safety or effectiveness. If the labeling was discontinued for reasons of safety or effectiveness, it cannot be referred to by the ANDA applicant. Such a determination will be based on the same factors and information FDA considers when determining whether a product withdrawn entirely from the market was withdrawn for reasons of safety or effectiveness (see 54 FR 28872, 28907-08; July 10, 1989). In addition, the Agency will determine whether omission of protected information from the labeling would render the proposed drug product less safe or effective for all the remaining, unprotected conditions of use.[7] The Agency will publish its determination in the *Federal Register,* as described in 21 CR 314.161.

E. Therapeutic Equivalence Ratings

Whether a drug approved in an ANDA that refers to discontinued labeling for the listed drug will be rated therapeutically equivalent to the currently marketed innovator product will depend upon the differences in the labeling.

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different from the marketed innovator drug. For example, an ANDA may be approved for fewer than all of the indications approved for the innovator drug. There can also be differences in labeling related to excipients, handling and administration of the drug related to excipient differences, and differences arising from revisions in labeling guidelines (21 CFR 314.94(a)(8)(iv)).

[7] New labeling will not be protected by exclusivity if it describes new risks or warnings (54 FR 28872, 28899, July 10, 1989; 59 FR 50338, 50356-57, October 3, 1994).

F. Expiration of Exclusivity or Patent Protection

Once the exclusivity or patent protecting the current innovator labeling has expired, the ANDA applicant whose product references the discontinued labeling should file a supplement to its ANDA to make the labeling conform to the labeling of the marketed innovator product.