Marketing Status Notifications Under Section 506I of the Federal Food, Drug, and Cosmetic Act; Content and Format

Guidance for Industry

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

August 2020
Procedural

Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance is intended to assist holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) approved under section 505(c) and 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(c) and (j)), respectively, with submission of marketing status notifications required under section 506I of the FD&C Act (21 U.S.C. 356i). This guidance identifies the required content for these marketing status notifications and the format by which these notifications should be submitted to the Agency.

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.

II. BACKGROUND

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (Hatch-Waxman Amendments) specifically required FDA to publish and make publicly available, among other things, a list of drug products either approved under section 505(c) of the FD&C Act for safety and effectiveness or approved under section 505(j) of the FD&C Act.[2] FDA fulfills these requirements in its publication, *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book).[3]

[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] See section 505(j)(7)(A) of the FD&C Act.

[3] The Orange Book is available at https://www.accessdata.fda.gov/scripts/cder/ob/.

The Orange Book contains different drug product lists, including the "Prescription Drug Product List," the "Over-the-Counter (OTC) Drug Product List," and the "Discontinued Drug Product List."[4] The Prescription Drug Product and OTC Drug Product Lists are sometimes referred to as the *active* section of the Orange Book, and the Discontinued Drug Product List is sometimes referred to as the *discontinued* section of the Orange Book. The discontinued section of the Orange Book sets forth, among other items, drug products (1) that have been identified by the application holder as not being marketed or (2) whose marketing has been discontinued for reasons other than safety or effectiveness, as determined by FDA.[5] When FDA learns that any such drug product is not being marketed, FDA, based on its long-standing practice, moves that drug product from the active section of the Orange Book to the discontinued section of the Orange Book.[6]

FDA regulations require NDA and ANDA holders to notify the Agency of the marketing status of drug products approved under NDAs and ANDAs.[7] The FDA Reauthorization Act of 2017[8] (FDARA) added section 506I to the FD&C Act, which imposes additional marketing status reporting requirements as follows:

- ***Notification of withdrawal from sale*** — requires NDA and ANDA holders to provide a written notification to FDA 180 days prior to withdrawing an approved drug from sale.[9]

- ***Notification of drug not available for sale*** — requires NDA and ANDA holders to provide a written notification to FDA within 180 days of the date of approval of a drug if that drug will not be available for sale within 180 days of the date of approval.[10]

- ***One-time report on marketing status*** — required NDA and ANDA holders to provide a written notification to FDA within 180 days of enactment of FDARA[11] stating whether the NDA and ANDA holder's drug(s) in the active section of the Orange Book

[4] See the Orange Book Preface (39th ed., 2019) at vi.

[5] See id.

[6] See id. at xxiv.

[7] See, e.g., 21 CFR 314.81(b)(2)(ii)(*a*) and 314.81(b)(3)(iv).

[8] Public Law 115-52.

[9] Section 506I(a) of the FD&C Act. The statute further states that if a submission under section 506I(a) is not practicable 180 days before withdrawing the product from sale, that submission should be made "as soon as practicable but not later than the date of withdrawal" from sale. Generally, we anticipate that it would be practicable for an application holder to notify FDA immediately after it decides to withdraw the product from sale.

[10] Section 506I(b) of the FD&C Act.

[11] FDARA was enacted on August 18, 2017. This one-time report was due to FDA on Wednesday, February 14, 2018.

> were available for sale or if one or more of the NDA or ANDA holder's drugs in the active section had been withdrawn from sale or had never been available for sale.[12]

In considering whether a drug product has been withdrawn from sale, FDA notes that the Agency has previously indicated that withdrawal from sale is not limited to a permanent withdrawal of a product but can also include "any decision to discontinue marketing of [that] product."[13] In particular, FDA has described its policy on determining whether a product is considered to have been "withdrawn from sale" as follows:

> For purposes of section[] 505(j)(5) and 505(j)(6)(C) of the [FD&C Act], a drug shall be considered to have been 'withdrawn from sale' if the applicant has ceased its own distribution of the drug, whether or not it has ordered recall of previously distributed lots of the drug. A routine, temporary interruption in the supply of a drug product would not be considered a withdrawal from sale, however, unless triggered by safety or effectiveness concerns.[14]

This determination is aided by our review of available information indicating whether a drug product is unavailable, including annual reports. We also note that a drug is considered withdrawn from sale when the application holder ceases its own distribution, even if the application holder plans to eventually return to the market, so long as the application holder has not ceased distribution due to a routine, temporary interruption in supply. Likewise, FDA has considered a drug product to have been withdrawn from sale if the applicable NDA or ANDA holder has notified FDA that the drug product is not being marketed.[15]

Section 506I of the FD&C Act requires FDA to update the Orange Book "based on the information provided" by NDA and ANDA holders in these three marketing status notifications "by moving drugs that are not available for sale from the active section to the discontinued section of [the Orange Book], except that drugs [that are determined to] have been withdrawn from sale for reasons of safety or effectiveness shall be removed from [the Orange Book] in accordance with subsection 505(j)(7)(C)."[16] Also, section 506I of the FD&C Act authorizes FDA to move the NDA and/or ANDA holder's (or holders') drug products from the active section of the Orange Book to the discontinued section if an NDA or ANDA holder fails to submit any of these three marketing status notifications.[17] Application holders are notified electronically that a drug product will be moved to the discontinued section before the move is published in a monthly update.

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[12] Section 506I(c) of the FD&C Act. As stated in note 11, the one-time update was due on February 14, 2018. Accordingly, this guidance removes the recommendations on submission of this update, which were included in the draft guidance of the same name. The Orange Book was updated, as appropriate, as the one-time updates were reviewed and processed.

[13] See "Abbreviated New Drug Application Regulations," final rule, 57 FR 17950 at 17956 (April 28, 1992).

[14] "Abbreviated New Drug Application Regulations," proposed rule, 54 FR 28872 at 28907 (July 10, 1989).

[15] Orange Book Preface (39th ed., 2019) at xxiv.

[16] Section 506I(e) of the FD&C Act.

[17] Section 506I(d) of the FD&C Act.

III. CONTENT AND FORMAT OF MARKETING STATUS NOTIFICATIONS

The subsequent subsections of this guidance provide information on submitting the marketing status notifications required under section 506I of the FD&C Act to FDA.[18] For each of these notifications, the notification may serve as its own cover letter (i.e., no separate cover letter is needed).

A. Notification of a Withdrawal From Sale

1. Content of the Notification of a Withdrawal From Sale

A notification of a withdrawal from sale must include:

1. The National Drug Code(s) (NDCs) under which the drug is listed (21 CFR part 207)
2. The established name of the drug
3. The proprietary name of the drug, if applicable
4. The NDA or ANDA number
5. The strength of the drug
6. The date on which the drug is expected to no longer be available for sale
7. The reason for the withdrawal[19]

An application holder that markets a drug product under multiple NDCs should only submit notification that the drug product is withdrawn from sale when the application holder has ceased marketing the product under all relevant NDCs. Notification should not be provided if some NDCs are being discontinued but additional NDCs will remain on the market for a particular strength. When notification is provided, the application holder should include a statement of all NDCs being discontinued in its notification to meet the first requirement outlined above. When an application holder is determining the date that a drug product is "expected to no longer be available for sale,"[20] note that FDA generally considers it reasonable for this to be the date on which the application holder will or did cease its own distribution of the drug product, because that is the date the application holder itself has stopped making the drug product available for sale. Applicants should provide an actual date to meet this requirement of the notification (#6). FDA also recommends that the notification include, if known, the last date of manufacturing of the drug product as well as the last date of distribution and lot expiration dates.

[18] Please note that changes to drug product listings that fall outside the scope of this guidance (e.g., a change in ownership or a name change) should be submitted via correspondence to the approved application.

[19] Section 506I(a) of the FD&C Act.

[20] Section 506I(a)(6) of the FD&C Act.

Similarly, an NDA holder that markets both a branded drug product and an authorized generic[21] for that drug product should only submit notification that the drug product is withdrawn from sale when both the branded drug product and the authorized generic will cease marketing.

2. Submission of the Notification of a Withdrawal From Sale

The applicant should submit a notification of a withdrawal from sale in a letter to the applicable NDA or ANDA file through the electronic submissions gateway.[22] The notification should prominently identify the submission as an "**ADMINISTRATIVE CHANGE / NOT AVAILABLE FOR SALE.**" A copy of this Notification of a Withdrawal from Sale submission should be submitted to CDERCollections@fda.hhs.gov for NDAs only. This letter does not replace an application holder's obligation to submit a separate written request under 21 CFR 314.150(c) if it is seeking a voluntary withdrawal of approval of an application or abbreviated application.

As noted above, the notification of a withdrawal from sale is required 180 days prior to withdrawing an approved drug from sale (or if 180 days is not practicable, as soon as practicable but not later than the date of withdrawal).[23] To help keep the Orange Book up to date, these notifications should not be made earlier than 180 days before withdrawing the product from sale.

B. Notification of a Drug Not Available for Sale

1. Content of the Notification of a Drug Not Available for Sale

A notification that a drug is not available for sale within 180 days of the date of approval of the drug must include:

1. The established name of the drug
2. The proprietary name of the drug, if applicable
3. The NDA or ANDA number
4. The strength of the drug
5. The date on which the drug will be available for sale, if known
6. The reason for not marketing the drug after approval[24]

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[21] An authorized generic "is a listed drug, as defined in [21 CFR 314.3(b)], that has been approved under section 505(c) of the [FD&C Act] and is marketed, sold, or distributed directly or indirectly to the retail class of trade with labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trademark that differs from that of the listed drug" (21 CFR 314.3(b)).

[22] The electronic submissions gateway is available at https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/. Questions related to electronic submissions should be emailed to the CDER Electronic Submission (ESUB) Team at esub@fda.hhs.gov.

[23] Section 506I(a) of the FD&C Act.

[24] Section 506I(b) of the FD&C Act.

When providing the reason for not marketing the drug after approval, FDA notes that the following examples have been provided as reasons: a lack of demand; a license agreement; an interruption in the supply of drug product components; or issues related to production for a commercial launch at day 180. These examples are not an exhaustive list. FDA also recommends that the notification include, if known, the anticipated start date of manufacturing of the drug product as well as the start date of distribution.

2. Submission of a Notification of a Drug Not Available for Sale

The applicant should submit a notification that a drug will not be available for sale in a letter to the applicable NDA or ANDA file through the electronic gateway. The notification should prominently identify the submission as an "**ADMINISTRATIVE CHANGE / NOT AVAILABLE FOR SALE.**"

We note that if an application holder intends to market within 180 days of the date of approval of a drug, no notification under this section (i.e., the notification that a drug is not available for sale under section 506I(b) of the FD&C Act) to FDA is required.

If an NDA or ANDA holder intends to commence commercial marketing of a drug for which the holder has previously submitted a notification that the drug was not available for sale, FDA recommends that the NDA or ANDA holder notify FDA 30-60 days before the anticipated launch date, which generally is the date the drug product will be introduced or delivered for introduction into interstate commerce, but no later than the date commercial marketing is commenced, in a letter to the applicable NDA or ANDA file through the electronic gateway to ensure that appropriate changes can be made in the Orange Book. The notification should prominently identify the submission as an "**ADMINISTRATIVE CHANGE / NOTIFICATION OF COMMERCIAL MARKETING.**"