Orange Book
Questions and Answers
Guidance for Industry

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

July 2022
Generic Drugs

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https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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I. INTRODUCTION

This guidance is intended to assist interested parties (including prospective drug product applicants, drug product applicants, and approved application holders) in utilizing the *Approved Drug Products With Therapeutic Equivalence Evaluations* publication (the Orange Book).[2] This guidance provides answers to commonly asked questions that we have received from interested parties regarding the Orange Book.[3]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

The Orange Book identifies (1) drug products approved by FDA under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and (2) patent and exclusivity information related to approved drug products. In particular, the main criteria for the inclusion of a drug product in the Orange Book are that the drug product is the subject of an approved application and that FDA has not

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

[3] This guidance generally does not include topics addressed in the Orange Book Preface, the Frequently Asked Questions on The Orange Book, and the Frequently Asked Questions on Patents and Exclusivity web pages, which are available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm, https://www.fda.gov/Drugs/InformationOnDrugs/ucm114166.htm, and https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm, respectively.

determined the drug product to have been withdrawn from sale for safety or effectiveness reasons.[4]

The Orange Book is composed of four main parts:

(1) The Prescription Drug Product List, which is a list of approved marketed prescription drug products with therapeutic equivalence evaluations (which along with the OTC Drug Product List is referred to as the "Active Section");

(2) The OTC Drug Product List, which is a list of marketed over-the-counter (OTC) drug products that have been approved in new drug applications (NDAs) or abbreviated new drug applications (ANDAs) (which along with the Prescription Drug Product List is referred to as the "Active Section");

(3) The Drug Products with Approval under Section 505 of the FD&C Act Administered by the Center for Biologics Evaluation and Research List; and

(4) The Discontinued Drug Product List, which is a cumulative list of approved drug products that have never been marketed, are for exportation (e.g., only marketed outside the United States), are for military use, are not commercially distributed by a United States federal or state government entity, have been discontinued from marketing and FDA has not determined that they were withdrawn from sale for reasons of safety or effectiveness, or have had their approvals withdrawn for reasons other than safety or effectiveness subsequent to being discontinued from marketing (commonly referred to as the "Discontinued Section").

The Orange Book contains additional information, including three appendices and two addenda related to patents and exclusivity. The Orange Book website also has a number of additional resources that can assist stakeholders with using the Orange Book and related questions.[5]

In addition, the Orange Book contains therapeutic equivalence[6] evaluations for approved multisource prescription drug products, which are reflected for drug products in the Active Section.[7] These evaluations have been prepared to serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education on drug product selection and to foster containment of health care costs.[8]

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[4] See 21 CFR 314.161.

[5] Available at the Orange Book homepage at https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm.

[6] Approved drug products are therapeutic equivalents if they are pharmaceutical equivalents for which bioequivalence has been demonstrated, and they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling (21 CFR 314.3(b)).

[7] We note that those products with approved applications that are *single-source* (i.e., there is only one approved product available for that active ingredient, dosage form, route of administration, and strength) are also included in the Orange Book, but no therapeutic equivalence code is included with such products.

[8] Therapeutic equivalence evaluations in the Orange Book are not official FDA actions affecting the legal status of products under the FD&C Act. See, e.g., 45 FR 72582 at 72597 (October 31, 1980).

The coding system for therapeutic equivalence evaluations is designed (1) to allow users to determine quickly whether the Agency has determined that a particular approved drug product (e.g., a particular strength, dosage form, and route of administration of an approved drug) is therapeutically equivalent to other pharmaceutically equivalent[9] drug products and (2) to provide additional information to users on the basis of FDA's evaluations; the first item (i.e., therapeutic equivalence) is reflected in the first letter of the therapeutic equivalence code, and the second item (i.e., additional information) is reflected in the second letter of the code.

As noted in the Introduction, this guidance provides answers to questions that have been received by the FDA staff that publishes and manages the Orange Book. The questions and answers in this guidance cover the following topics:

- General inquiries about the content and format of the Orange Book
- Petitioned ANDAs
- The movement of drug products between the Active and Discontinued Sections of the Orange Book
- Patent listings

III. QUESTIONS AND ANSWERS

A. General Inquiries About the Content and Format of the Orange Book

Q1. Which applications are not listed in the Orange Book?

A1. The Orange Book does not include: (1) approved drug products that were discontinued either before the first edition in October 1980 or discontinued between 1980 and 1987, prior to the identification of discontinued products; (2) drug products that have a tentative approval;[10] (3) drug products marketed before 1962 for which a Drug Efficacy Study

[9] Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where the residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates (21 CFR 314.3(b)). They may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, within certain limits, labeling (Orange Book Preface at vii).

[10] *Tentative approval* is notification that an NDA or ANDA otherwise meets the requirements for approval under the FD&C Act, but cannot be approved because there is a 7-year period of orphan exclusivity for a listed drug under section 527 of the FD&C Act and § 316.31 of this chapter, or that a 505(b)(2) application or ANDA otherwise meets the requirements for approval under the FD&C Act, but cannot be approved until the conditions in

Implementation review has not been completed; (4) biological products licensed by FDA under the Public Health Service Act (42 U.S.C. 262);[11, 12] (5) marketed drug products that are not the subject of an approved NDA or ANDA (e.g., under OTC monograph); and (6) drug products compounded by a pharmacy pursuant to section 503A of the FD&C Act and drug products compounded by an outsourcing facility pursuant to section 503B of the FD&C Act. Approved drug products are removed from the Orange Book when, for example, an approval is withdrawn under section 505(e)(1) through (5) or 505(j)(6) of the FD&C Act,[13] when FDA has determined that the drug product was withdrawn from sale for reasons of safety or effectiveness,[14] or when the status of an approval is converted from final approval to tentative approval. In addition, certain products such as authorized generic drug products[15] and re-labeled drug products[16] are not separately identified in the Orange Book.

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§ 314.107(b)(1)(iii), (b)(3), or (c) are met; because there is a period of exclusivity for the listed drug under § 314.108; because there is a period of exclusivity for the listed drug under section 505A of the FD&C Act; because there is a period of exclusivity for the listed drug under section 505E of the FD&C Act; or because a court order pursuant to 35 U.S.C. 271(e)(4)(A) orders that the NDA or ANDA may be approved no earlier than the date specified. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval letter after any necessary additional review of the NDA or ANDA (21 CFR 314.3(b)).

[11] See the *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations* available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm.

[12] The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) required that, on March 23, 2020, an approved application for a biological product under section 505 of the FD&C Act be deemed to be a license for the biological product (i.e., an approved biologics license application (BLA)) under section 351 of the Public Health Service Act (PHS Act) (see section 7002(e)(4)(A) of the BPCI Act; see also section 7002(e)(4)(B)). As a result, on March 23, 2020, subject to a limited exception described in section 7002(e)(4)(B) of the BPCI Act, FDA removed from the Orange Book the listings for "biological products" that had been approved in applications under section 505 of the FD&C Act because these products are no longer "listed drugs."

[13] See section 505(e) and 505(j)(6) of the FD&C Act.

[14] 21 CFR 314.161.

[15] An *authorized generic drug* 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)). Because an authorized generic drug (which may or may not have a proprietary name) is marketed under the brand name drug product's NDA, the authorized generic drug is not separately listed in the Orange Book as it is already encompassed within the NDA listing under which it is marketed. The relevant NDA will be listed in the Active Section of the Orange Book when an authorized generic is marketed. FDA publishes a list of reported authorized generics and updates that list quarterly, which is available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/fda-listing-authorized-generics.

[16] A "labeler" engages in manufacturing, repacking, relabeling, or private-label distribution of the drug product. Products listed in the Orange Book are identified by the names of the holders of approved applications, rather than by the names of the manufacturers themselves, whereas FDA's National Drug Code Directory (https://www.accessdata.fda.gov/scripts/cder/ndc/index.cfm) identifies the labelers of such drug products.

Q2. Can I access the current data files for the Orange Book? How are data provided?

A2. Yes. The Orange Book Data Files contain current Orange Book data for approved drug products and unexpired patent and exclusivity data, which are updated as outlined in Question 4. They are available in a compressed ZIP file under "Additional Resources."

Q3. When is the Orange Book updated? What information is included in the updates?

A3. The information in the Orange Book is updated in two ways—on its website and in print publications that are also available as downloadable PDFs. Website updates occur on a daily, semimonthly, monthly, and annual basis. Print updates occur on a monthly and annual basis. We are striving to have more regular updates to the Orange Book and have recently added semimonthly website updates to its schedule.

- The daily website updates generally occur (on business days) in the afternoon, Eastern Standard Time, and consist of patent information and new generic drug approvals.

- The semimonthly website updates generally occur twice each month on a Monday. They consist of new drug approvals, ownership changes, market status updates, and various types of changes to drug listing information (e.g., changes related to therapeutic equivalence codes, trade names, and reference listed drug (RLD)[17] or reference standard designation, among others), which have occurred in the *current month*.[18]

- The monthly data files updates, the monthly website updates, and the monthly print updates, entitled Cumulative Supplement (CS), generally occur at the end of the second week of each month and consist of all changes to the Orange Book which occurred in the *prior month*.[19]

- The print annual edition of the Orange Book, which is posted on the website, generally occurs in January and consists of a full copy of the Orange Book, including the Orange Book Preface, drug product lists, addendum, and appendices.[20]

Q4. When are newly approved NDA drug products listed in the Orange Book?

A4. Newly approved NDA drug products will generally appear in the Active Section of the Orange Book in the month following their approval, and will remain there unless the

[17] The *reference listed drug* 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))

[18] This schedule is current as of the publication of this guidance, but subject to change in the future.

[19] Since these publications are titled by month (i.e., "March CS") the changes may be limited to those that occurred in that specific month only.

[20] The annual print publication (and corresponding website update) of the Orange Book memorializes the state of drug products from the prior year.

NDA holder notifies FDA that the drug product will not be available for sale within 180 days of approval.[21] If the NDA holder notifies FDA that it does not intend to market upon approval, the NDA drug product will, in the month following such approval, appear in the Discontinued Section. See Question 4 above for additional information on updates to the Orange Book.

Q5. Do the daily updates to the Orange Book occur at a specific time of day?

A5. Daily updates to the Orange Book website are generally posted (on business days) in the afternoon, Eastern Standard Time. For example, approval actions taken on ANDAs made in the morning will generally be reflected in that afternoon's update. Similarly, patent information from newly submitted Forms FDA 3542 received early in the day will generally be reflected in that afternoon's update (if received later in the morning or in the afternoon, this information will generally be reflected in the daily updates for the next business day).

Q6. Are the marketing reports required under section 506I of the FD&C Act available to the public?[22]

A6. No. Consistent with section 506I(f) of the FD&C Act, FDA does not publish copies of marketing reports submitted to the Agency, but updates the Orange Book, as appropriate, as the reports are reviewed and processed.

Q7. Is it possible to obtain previous editions of the Orange Book or an Orange Book Data File from FDA?

A7. Requests for previous editions of the Orange Book or an Orange Book Data File[23] should be made under the Freedom of Information Act. Requests should be submitted either online via https://www.accessdata.fda.gov/scripts/foi/FOIRequest/index.cfm or in writing to FDA's Freedom of Information Staff at the following address:

Food and Drug Administration
Division of Freedom of Information
Office of the Executive Secretariat, OC
5630 Fishers Ln., Rm. 1035

[21] See section 506I(b) of the FD&C Act. If an NDA holder intends to market the drug product within 180 days of approval, no such notification should be submitted to the Agency.

[22] The FDA Reauthorization Act of 2017, Public Law 115-52 (Aug. 18, 2017) (FDARA) added section 506I to the FD&C Act, which imposes certain reporting requirements on NDA and ANDA holders regarding the marketing status of approved drug products. Specifically, the three required marketing status notifications set forth in section 506I of the FD&C Act are the following: notifications of the withdrawal of approved drugs from sale, notifications of approved drugs not being available for sale, and one-time reports on the marketing status of approved drugs.

[23] Available at the Orange Book homepage at https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm.

Rockville, MD 20857.[24]

B. Petitioned ANDAs

Q8. A petitioned ANDA[25] drug product is listed in the Orange Book without a therapeutic equivalence code. What is its RLD? Should a therapeutic equivalence code be assigned to that ANDA?

A8. For a petitioned ANDA, the RLD should be the listed drug referenced in the approved suitability petition.[26] The first petitioned ANDA approved will not be pharmaceutically equivalent to the RLD and thus no therapeutic equivalence code would be assigned to it. However, after the first petitioned ANDA is approved, FDA generally will assign therapeutic equivalence codes to all ANDAs that contain the same petitioned differences from the RLD (i.e., in dosage form, route of administration, strength, or active ingredient (in a drug product with more than one active ingredient)) as the first petitioned ANDA to reflect whether these petitioned ANDAs are therapeutically equivalent to one another.

C. The Movement of Drug Products Between the Active and Discontinued Sections of the Orange Book

Q9. Are only those drug products for which approval of the application has been withdrawn (i.e., the approval of the drug product application has been withdrawn by FDA) considered *withdrawn from sale* by FDA?

A9. No. A drug product considered withdrawn from sale is not limited to the withdrawal of approval of a drug product application. The Agency has previously indicated that withdrawal from sale is not limited to a permanent withdrawal of a product but can include drug products for which "any decision to discontinue marketing"[27] has been made. In particular, FDA previously explained its interpretation that a drug is considered

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[24] Recommendations on submitting a Freedom of Information Act request are provided on FDA's How to Make a FOIA Request web page, available at https://www.fda.gov/RegulatoryInformation/FOI/HowtoMakeaFOIARequest/default.htm.

[25] A *petitioned ANDA* is a type of ANDA for a proposed drug product that differs from the RLD in its dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient) and for which FDA has determined, in response to a suitability petition submitted under section 505(j)(2)(C) of the FD&C Act, that clinical studies are not necessary to establish the safety and effectiveness of that proposed drug product. See also the proposed rule entitled "Abbreviated New Drug Applications and 505(b)(2) Applications," published February 6, 2015 (80 FR 6802 at 6806). For more on petitioned ANDAs, see the guidances for industry *Referencing Approved Drug Products in ANDA Submissions* (October 2020) and *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019). 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.

[26] 21 CFR 314.94(a)(3)(i).

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

to have been "withdrawn from sale" for purposes of section 505(j)(5) and 505(j)(6)(C) of the FD&C Act 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.[28]

Likewise, FDA has considered a drug product to have been withdrawn from sale if the NDA or ANDA holder has notified FDA that the drug product is not being marketed.

Those drug products in the Discontinued Section for which a determination has been made that the products were not withdrawn for safety or effectiveness reasons and the determination has been published in a Notice in the *Federal Register* have been annotated with a footnote following the product strength: "**Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**". However, this notation may not appear for all such determinations published in Notices in the *Federal Register*. For example, the Orange Book does not reflect determinations published in Notices in the *Federal Register* before 1995.

Q10. How should an NDA or ANDA holder notify FDA, under section 506I of the FD&C Act, that a drug product is or will be withdrawn from sale?

A10. The NDA or ANDA holder should submit a notification of withdrawal from sale in a letter to the applicable NDA or ANDA file[29] through the electronic submissions gateway.[30] The notification should prominently identify the submission as an "ADMINISTRATIVE CHANGE / NOT AVAILABLE FOR SALE."[31]

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[28] See the proposed rule "Abbreviated New Drug Application Regulations," published July 10, 1989 (54 FR 28872 at 28907). For more information on recommendations related to accurate reporting of marketing status, see the guidance for industry *Marketing Status Notifications Under Section 506I of the Federal Food, Drug, and Cosmetic Act; Content and Format* (August 2020).

[29] This guidance includes recommendations for the submission of documentation directly to an NDA or ANDA file, even if such documentation is intended for the Division of Orange Book Publication and Regulatory Assessment. Submissions to the application files are triaged and distributed, including to the Division of Orange Book Publication and Regulatory Assessment, as appropriate. Submissions directly to the Division of Orange Book Publication and Regulatory Assessment are not recommended unless specifically directed (see, for example, Question 18).

[30] 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.

[31] See guidance for industry *Marketing Status Notifications Under Section 506I of the Federal Food, Drug, and Cosmetic Act; Content and Format* (August 2020).

NDA and ANDA holders are required to provide a written notification to FDA 180 days prior to withdrawing an approved drug product from sale.[32] If it is not practicable to submit the notification 180 days before withdrawing the drug product from sale, that submission should be made "as soon as practicable, but not later than the date of withdrawal" from sale.[33,34]

Q11. How and when should an NDA or ANDA holder request that an application be moved from the Discontinued Section of the Orange Book to the Active Section?

A11. Prior to requesting that an application be moved from the Discontinued Section to the Active Section, the application holder should determine whether the submission of a supplement under 21 CFR 314.70 or 314.97 is required prior to or at the time of introduction of the drug product into the marketplace.

If a prior approval supplement under 21 CFR 314.70(b) is required:

- The application holder should notify FDA 1 to 2 months prior to the anticipated approval of the supplement that the application holder is seeking market entry or re-entry via submission to the application file identified as an "ADMINISTRATIVE CHANGE / NOTIFICATION OF COMMERCIAL MARKETING."

- The product will generally be moved from the Discontinued Section to the Active Section upon approval of the supplement in a subsequent monthly cumulative supplement.

If a Changes Being Effected supplement under 21 CFR 314.70(c) is required:

- The application holder should determine the anticipated launch date, which is generally the date the drug product is put into the marketplace for distribution.

- The application holder should notify FDA that the application holder is seeking market entry or re-entry approximately 1 to 2 months before the anticipated launch date via submission to the application file identified as an "ADMINISTRATIVE CHANGE / NOTIFICATION OF COMMERCIAL MARKETING."

- The product will generally be moved from the Discontinued Section to the Active Section upon the anticipated launch date in a subsequent monthly cumulative supplement.

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

[33] Ibid.

[34] This notification addresses only the requirement in section 506I(a) of the FD&C Act; additional notifications may be required when a drug product is withdrawn from sale, for example, under section 506C(a) of the FD&C Act.

Q12. When will a move of a drug product to or from the Discontinued Section be reflected in the Orange Book?

A12. A move to or from the Discontinued Section will generally be reflected in a future Orange Book monthly cumulative supplement update. See Question 4 above for additional information on updates to the Orange Book.[35]

D. Patent Listings

1. Listing Patents

Q13. How does an NDA holder ensure that Form FDA 3542 (Patent Information Submitted Upon and After Approval of an NDA or Supplement)[36] is timely filed?

A13. An NDA holder must submit information for each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and that claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent, or claims a method of using such drug for which approval has been granted in the application.[37] The NDA holder must submit this patent information to the NDA on a Form FDA 3542.[38] FDA publishes this patent information in the Orange Book. This patent information must be submitted not later than 30 days after the date of approval of the NDA.[39] If such a patent is issued after the date of approval of the application, the NDA holder must submit a Form FDA 3542 not later than 30 days after the date of issuance of the patent.[40]

With respect to any errors or omissions that FDA identifies in a Form FDA 3542, section 314.53(c)(2)(ii) provides:

> If the applicant submits the required patent information within the 30 days, but we notify an applicant that a declaration form is incomplete or shows that the patent is not eligible for listing, the applicant must submit an acceptable declaration form within 15 days of FDA notification to be considered timely filed.

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[35] We note that there may be user fee implications associated with moves to and from the Discontinued Section. See FDA's latest guidance on assessing user fees under PDUFA.

[36] The Form FDA 3542 is available at https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/ucm048345.pdf.

[37] See section 505(b)(1)(A)(viii), 505(b)(1)(B), and 505(c)(2) of the FD&C Act; see also 21 CFR 314.53(b)(1). "Patent information that is not the type of patent information required by subsection (b)(1)(A)(viii) shall not be submitted under this paragraph." Section 505(c)(2) of the FD&C Act.

[38] 21 CFR 314.53(c)(2)(ii).

[39] See section 505(c)(2) of the FD&C Act and 21 CFR 314.53(c)(1), 21 CFR 314.53(c)(2)(ii).

[40] See section 505(c)(2) of the FD&C Act and 21 CFR 314.53(c)(1), 21 CFR 314.53(c)(2)(ii) and 21 CFR 314.53(d)(3).

Under the terms of the regulation, to be considered timely filed as of the date of the original submission of patent information, the NDA holder must submit an acceptable Form FDA 3542 within 15 days of FDA's original notification.[41] NDA holders should carefully read the instructions to Form FDA 3542 in correcting such deficiencies. Following the submission of a Form FDA 3542 that the Agency determines is acceptable, the patent information will be reflected in the Orange Book.

Q14. How does an NDA holder ensure that an amendment to the description of an approved method of use claimed by the patent is timely filed?

A14. An NDA holder's amendment to the description of an approved method(s) of use (MOU) claimed by the patent will be considered timely filed if it is submitted within 30 days of (1) patent issuance, (2) approval of a corresponding change to the drug product labeling, or (3) a decision by the U.S. Patent and Trademark Office or a Federal court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent.[42] Outside of these circumstances, and except as provided in the patent listing dispute regulations,[43] an amendment to the description of the approved MOU claimed by the patent will not be considered timely filed.[44]

Q15. How can an NDA holder submit a reissued patent to the Orange Book for listing?

A15. An NDA holder is required to request that the original patent be removed from the Orange Book once a patent is reissued[45] because, upon patent reissuance, the original patent is surrendered and ceases to have legal effect.[46] Consistent with our regulations for any request to withdraw a patent from the Orange Book, the original patent will remain listed in the Orange Book until FDA determines that no first applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent or after the 180-day exclusivity period of a first applicant based on that patent has expired or has been extinguished or relinquished.[47]

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[41] 21 CFR 314.53(c)(2)(ii).

[42] 21 CFR 314.94(a)(12)(vi) and 21 CFR 314.50(i)(4). For a decision by the U.S. Patent and Trademark Office or a Federal court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent, the amendment must contain a copy of that decision. 21 CFR 314.94(a)(12)(vi) and 21 CFR 314.50(i)(4).

[43] See 21 CFR 314.53(f)(1).

[44] 21 CFR 314.94(a)(12)(vi) and 21 CFR 314.50(i)(4).

[45] 21 CFR 314.53(f)(2)(i).

[46] See the final rule "Abbreviated New Drug Applications and 505(b)(2) Applications," published October 6, 2016 (81 FR 69580 at 69601), referencing 37 CFR 1.178(a).

[47] 21 CFR 314.53(f)(2)(i).

Q16. How does FDA receive and process a request from an NDA holder for removal of a patent or patent information from the Orange Book?

A16. If an NDA holder determines that a patent or patent claim no longer meets the statutory requirements for listing, the NDA holder must promptly notify FDA to amend or withdraw the patent information and request that the patent information be removed from the Orange Book.[48] Where any claim of a listed patent has been cancelled or invalidated pursuant to a final decision issued by the Patent Trial and Appeal Board (PTAB) of the United States Patent and Trademark Office or by a court, from which no appeal has been, or can be, taken, if the NDA holder determines that a patent or patent information no longer meets the statutory listing requirements, the NDA holder must notify FDA in writing within 14 days of the decision and request that such patent or patent information, as applicable, be amended or withdrawn in accordance with the decision and include information related to the patent cancellation or invalidation decision (including a copy of the decision).[49] As described above, FDA will remove a patent or patent information from the Orange Book if there is no first applicant eligible for 180-day exclusivity based on a paragraph IV certification to that patent or after the expiration, extinguishment, or relinquishment of any 180-day exclusivity period for a first applicant.[50]

An NDA holder may submit a withdrawal of a patent and request for removal of the patent from the Orange Book by letter to the NDA file.[51] The letter must contain the NDA number, each product to which the request applies, and the patent number.[52] A Form FDA 3542 is not required to be submitted for this request, but the NDA holder should clearly and prominently identify that it is seeking patent withdrawal and removal from the Orange Book under 21 CFR 314.53(f)(2)(iv).

Q17. An NDA holder has requested that a patent be removed from the Orange Book. The patent remains in the Orange Book with a *delist request* flag. When will the patent be removed?

A17. A patent may remain listed for a certain period even if the NDA holder requests that it be removed because a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent.[53]

Until the patent is removed from the Orange Book — after any associated 180-day exclusivity has expired or has been extinguished or relinquished — ANDA applicants must submit or maintain appropriate certifications to the patent notwithstanding the NDA

[48] 21 CFR 314.53(f)(2)(i).

[49] Section 505(j)(7)(D) of the FD&C Act, as added by section 2(d) of the Orange Book Transparency Act of 2020.

[50] Section 505(j)(7)(D) of the FD&C Act and 21 CFR 314.53(f)(2)(i).

[51] 21 CFR 314.53(f)(2)(iv).

[52] Ibid.

[53] 21 CFR 314.53(f)(2)(i).

holder's request to remove the patent.[54] Applicants submitting a 505(b)(2) application are not required to certify to a patent when the delist request flag is set to *Y* in the Orange Book.[55]

2. Patent Listing Disputes

Q18. Can a patent listing be disputed?

A18. Yes. Section 314.53(f)(1) outlines a process through which a person other than the NDA holder can dispute the accuracy or relevance of patent information published in the Orange Book, as well as the process for the relevant NDA holder to respond to such disputes. If any person either "disputes the accuracy or relevance of patent information submitted to the Agency" and published by the Agency in the Orange Book or "believes that an NDA holder has failed to submit required patent information, that person must first notify the Agency in a written or electronic communication titled '314.53(f) Patent Listing Dispute.'"[56] The patent listing dispute may be sent to the Division of Orange Book Publication and Regulatory Assessment at orangebook@fda.hhs.gov.[57]

The patent listing dispute "must include a statement of dispute that describes the specific grounds for disagreement regarding the accuracy or relevance of patent information," which FDA will send to the applicable NDA holder.[58] Section 314.53(f)(1) states:

> For a dispute regarding the accuracy or relevance of patent information regarding an approved method of using the drug product, this statement of dispute must be only a narrative description (no more than 250 words) of the person's interpretation of the scope of the patent. This statement of dispute must only contain information for which the person consents to disclosure because FDA will send the text of the statement to the applicable NDA holder without review or redaction.

FDA will forward the dispute to the NDA holder as described in the regulation.

[54] 21 CFR 314.94(a)(12)(viii)(B).

[55] 21 CFR 314.50(i)(6)(ii)("A 505(b)(2) applicant is not required to provide or maintain a certification to a patent or patent information that remains listed only for purposes of a first applicant's 180-day exclusivity for its ANDA").

[56] 21 CFR 314.53(f)(1).

[57] Alternatively, the patent listing dispute may be submitted to the following address: Office of Generic Drugs, Central Document Room, 5901B Ammendale Road, Beltsville, MD 20705.

[58] 21 CFR 314.53(f)(1).

Q19. How does FDA provide notification to the public of whether a patent listing dispute has been submitted?

A19. For all patent listing disputes, FDA promptly posts information to a Patent Listing Dispute List website[59] indicating whether (1) a patent listing dispute has been submitted to FDA and (2) the NDA holder has timely responded to the patent listing dispute.[60] The Patent Listing Dispute List contains relevant drug product information and information on the disputed patent. This list is cumulative in nature and is organized by the drug product established name and patent number(s).

[59] The Orange Book Patent Listing Dispute List website is available at https://www.fda.gov/Drugs/InformationOnDrugs/ucm559235.htm.

[60] See 21 CFR 314.53(f)(1)(iii).