

Report to Congress

# The Listing of Patent Information in the Orange Book

Submitted Under Section 2(e) of the  
Orange Book Transparency Act of 2020



**U.S. FOOD & DRUG**  
ADMINISTRATION

## Executive Summary

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On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (Hatch-Waxman Amendments). The Hatch-Waxman Amendments require the U.S. Food and Drug Administration (FDA or Agency) to, among other things, make publicly available, with monthly supplements, a list of approved drug products. FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* publication (commonly known as the Orange Book) and this publication's monthly Cumulative Supplements satisfy this requirement. The Orange Book identifies drug products approved by FDA under section 505(c) and 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The *Addendum* to the Orange Book identifies drugs that have qualified under the FD&C Act for periods of exclusivity and provides patent information concerning certain approved drug products listed in the Orange Book.

The FD&C Act requires new drug application (NDA) applicants<sup>1</sup> to file with their application “the patent number and expiration date of 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” (1) “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 (2) “claims a method of using such drug for which approval is sought or has been granted in the application” (section 505(b)(1)(A)(viii) of the FD&C Act (21 U.S.C. 355(b)(1)(A)(viii)); see also 21 CFR 314.53). After approval of an NDA (including certain types of supplements to an NDA) but within certain time frames prescribed in the FD&C Act and FDA's implementing regulations, NDA holders<sup>2</sup> must submit required patent information for listing in the Orange Book (see section 505(c)(2) of the FD&C Act and 21 CFR 314.53). The FD&C Act requires FDA to regularly revise the Orange Book to include, among other things, patent information submitted under section 505(c)(2) of the FD&C Act (see section 505(j)(7)(A)(iii) of the FD&C Act). FDA serves a ministerial role with regard to the listing of patent information.

Both (1) an NDA submitted pursuant to section 505(b)(2) of the FD&C Act (a 505(b)(2) application) that relies, at least in part, on FDA's finding of safety and/or effectiveness for a listed drug and (2) an abbreviated new drug application (ANDA) must include an appropriate patent certification or statement for each patent that claims either the listed drug(s) relied upon or the reference listed drug (RLD), respectively, or a method of using such listed drug and for which information is required to be filed under section 505(b) or 505(c) of the FD&C Act. The timing of approval for a 505(b)(2) application and an ANDA (including a petitioned ANDA<sup>3</sup>) is subject to certain patent and exclusivity protections.

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<sup>1</sup> An *NDA applicant* is any person who submits an NDA to obtain FDA's approval of a new drug.

<sup>2</sup> An *NDA holder* is the applicant that owns an approved NDA.

<sup>3</sup> A *petitioned ANDA* is a type of ANDA for a 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 petition submitted under section 505(j)(2)(C) of the FD&C Act (suitability petition), that studies are not necessary to establish the safety and effectiveness of the proposed drug product. A petitioned ANDA is generally expected to provide the same therapeutic effect as the listed drug that was relied on as the basis of the suitability petition.

On January 5, 2021, the President signed into law the Orange Book Transparency Act (OBTA) of 2020 (Pub. L. 116-290). Section 2(e) of the OBTA requires the Agency (1) to solicit public comments regarding the types of patent information that should be included in, or removed from, the Orange Book and (2) to transmit to Congress, by January 5, 2022, a summary of the comments received and any actions the Agency is considering taking in response to these comments. This report to Congress fulfills both requirements of section 2(e) of the OBTA.

Prior to the enactment of the OBTA, FDA had solicited comments—through a *Federal Register* public docket established on June 1, 2020—on patent listing issues.<sup>4</sup> FDA reopened that docket on October 16, 2020, and again, after enactment of the OBTA, on March 16, 2021. FDA received 24 comments, preceding and subsequent to the enactment of the OBTA, in response to the public docket regarding the listing of patent information in the Orange Book. Each comment contained input on one or more issues related to the listing of patent information in the Orange Book. The comments expressed a variety of different and sometimes competing views on the types of patents and other information that should be included in, or removed from, the Orange Book.

In response to these public comments, FDA will create a multidisciplinary working group within the Agency. This working group will evaluate whether additional clarity is needed regarding the types of patents, patent information, or other patent-related information that should be included in, or removed from, the Orange Book, consistent with the current statutory requirements for patent listing in the FD&C Act. Additionally, as part of an Agency-wide effort to modernize the Orange Book, improve transparency, and provide useful information to regulated industry and the public, FDA will consider, in evaluating whether further improvements to the Orange Book should be made, the comments that provided additional insight into how stakeholders and the public have been utilizing the Orange Book.

The OBTA requires that the Government Accountability Office submit a related report to Congress not later than 2 years after enactment of the OBTA that may help inform the Agency's thinking on a number of these issues and, as such, FDA will review this report once it is available.

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<sup>4</sup> See “Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments” (85 FR 33169, Docket No. FDA-2020-N-1127 (June 1, 2020)).

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## I. Introduction

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On January 5, 2021, the President signed into law the Orange Book Transparency Act (OBTA) of 2020 (Pub. L. 116-290).

The OBTA amends section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and, among other things, (1) revises the requirements for submission of patent information by new drug application (NDA) applicants<sup>5</sup> and (2) by clarifying the types of patent and exclusivity-related information to be listed in FDA’s *Approved Drug Products With Therapeutic Equivalence Evaluations* publication (commonly known as the Orange Book or “the list”), including when certain patent information must be removed from the Orange Book. These revisions were generally consistent with existing regulations and practices of the U.S. Food and Drug Administration (FDA or Agency).

Section 2(e) of the OBTA requires that,

*[n]ot later than 1 year after the date of enactment of this Act, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs, shall—*

- (1) solicit public comment regarding the types of patent information that should be included on, or removed from, the list under section 507(j)(7) of the [FD&C] Act (21 U.S.C. 355(j)(7)); and*
- (2) transmit to Congress a summary of such comments and actions [FDA] is considering taking, if any, in response to public comment pursuant to paragraph (1) about the types of patent information that should be included or removed from such list.*

Prior to the enactment of the OBTA, FDA had solicited comments—through a public docket established on June 1, 2020—on patent listing issues.<sup>6</sup> FDA reopened that docket on October 16, 2020, and again, after enactment of the OBTA, on March 16, 2021. In total, FDA received 24 comments in response to this public docket. Each comment contained input on one or more issues related to the listing of patent information in the Orange Book. The comments expressed a variety of different and sometimes competing views on the types of patents and other information that should be included in, or removed from, the Orange Book.

In response to the directive in section 2(e) of the OBTA, FDA prepared the following report summarizing the public comments received regarding the types of patent information that should be included in, or removed from, the Orange Book under section 507(j)(7) of the FD&C Act. In

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<sup>5</sup> An *NDA applicant* is any person who submits an NDA to obtain FDA’s approval of a new drug.

<sup>6</sup> See “Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments” (85 FR 33169, Docket No. FDA-2020-N-1127 (June 1, 2020)).

addition, this report summarizes the actions FDA is considering taking in response to these public comments.

Additionally, section 2(f) of the OBTA requires that the Government Accountability Office (GAO) submit a report to Congress, as follows:

- (1) *IN GENERAL.—Not later than 2 years after the date of enactment of this Act, the Comptroller General of the United States (referred to in this section as the “Comptroller General”) shall submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives a report on the patents included in the list published under section 505(j)(7) of the [FD&C] Act (21 U.S.C. 355(j)(7)) that claim an active ingredient or formulation of a drug in combination with a device that is used for delivery of such drug, including an analysis of such patents and their claims.*
- (2) *CONTENT.—The Comptroller General shall include in the report under paragraph (1)—*
  - (A) *data on— (i) the number of patents included in the list published under section 505(j)(7) of the [FD&C] Act (21 U.S.C. 355(j)(7)) that claim the active ingredient or formulation of a drug in combination with a device that is used for delivery of the drug, and that together claim the finished dosage form of the drug; and (ii) the number of claims with respect to each patent included in the list published under such section 505(j)(7) that claim a device that is used for the delivery of the drug, but do not claim such device in combination with an active ingredient or formulation of a drug;*
  - (B) *an analysis of the listing of patents described in subparagraph (A)(ii), including the timing of listing such patents in relation to patents described in subparagraph (A)(i), and the effect listing the patents described in subparagraph (A)(ii) has on market entry of one or more drugs approved under section 505(j) of the [FD&C] Act as compared to the effect of not listing the patents described in subparagraph (A)(ii); and*
  - (C) *recommendations about which kinds of patents relating to devices described in subparagraph (A)(i) should be submitted to the Secretary of Health and Human Services for inclusion on the list under section 505(j)(7) of the [FD&C] Act and which patents should not be required to be so submitted in order to reduce barriers to approval and market entry.*

## II. Background

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### A. The Orange Book

On May 31, 1978, in response to requests from state health agencies for FDA's assistance in administering their laws relating to the substitution of drug products, the Commissioner of Food and Drugs sent a letter to officials of each state announcing FDA's intent to provide not only a list of all prescription drug products that had been approved for safety and effectiveness by FDA but also therapeutic equivalence (TE)<sup>7</sup> determinations for multisource prescription products. This list was distributed to the public as a proposal in January 1979 (see 44 FR 2932 (January 12, 1979)). This proposed list, which later became known as the Orange Book, included only prescription drug products that had been approved by FDA and were marketed at the time of publication. On October 31, 1980, FDA published a final version of the list (45 FR 72582), which was the first Orange Book.

On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (Hatch-Waxman Amendments). The Hatch-Waxman Amendments require FDA to, among other things, make publicly available, with monthly supplements, a list of approved drug products. The Orange Book and its monthly Cumulative Supplements satisfy this requirement.

The Orange Book identifies drug products approved by FDA under section 505(c) and 505(j) of the FD&C Act. The main criterion for the inclusion of a product in the Orange Book is that it has an NDA or abbreviated new drug application (ANDA) that has been approved and that has not been withdrawn for safety or effectiveness reasons or determined by FDA to have been withdrawn for safety or effectiveness reasons.

#### *1. Composition of the Orange Book*

The Orange Book is composed of the following 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 that is also in the Orange Book, 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 NDAs or ANDAs (which, along with the Prescription Drug Product List, is referred to as the "Active Section");

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<sup>7</sup> Approved drug products are *therapeutic equivalents* if they are pharmaceutical equivalents for which bioequivalence has been demonstrated and if 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)).

- (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 (commonly referred to as the “Discontinued Section”), 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 U.S. federal or state governmental 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.

The Orange Book contains additional information, including in three appendices and an addendum related to patents and exclusivity. In particular, the *Addendum* to the Orange Book identifies drugs that have qualified under the FD&C Act for periods of exclusivity and provides patent information concerning certain approved drug products listed in the Orange Book. The Orange Book website also has a number of additional resources that can assist stakeholders with using the Orange Book and answer related questions.<sup>8</sup>

In addition, the Orange Book contains TE evaluations for approved multisource prescription drug products, which are reflected, for drug products, in the Active Section. 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 healthcare costs.<sup>9</sup>

## 2. *Submission and Listing of Patent Information*

The FD&C Act has established requirements for FDA, NDA applicants, and NDA holders<sup>10</sup> related to the submission of patent information and the listing of patent information in the Orange Book. The FD&C Act requires NDA applicants to file with their application “the patent number and expiration date of 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” (1) “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 (2) “claims a method of using such drug for which approval is sought or has been granted in the application” (see section 505(b)(1)(A)(viii) of the FD&C Act; see also 21 CFR 314.53). An NDA applicant is required to amend its application to include this information if a patent that claims such drug or a method of using such drug is issued

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<sup>8</sup> The Orange Book home page is available at <https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm>.

<sup>9</sup> TE 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). Drug 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 TE code is included with such products.

<sup>10</sup> An *NDA holder* is the applicant that owns an approved NDA.



after the filing date but before approval of the application” (section 505(b)(1)(b) of the FD&C Act (21 U.S.C. 355(b)(1)(A)(viii)); see also 21 CFR 314.53). After approval of an NDA (including certain types of supplements to an NDA) but within certain time frames prescribed in the FD&C Act and FDA’s implementing regulations, NDA holders must submit the required information on any patent that meets the criteria for submission with an application, except that a patent claiming a method of using such drug may only be submitted if it claims a use approved in the NDA. Also, an NDA holder is required to submit information on certain patents that are issued after its application is approved (see section 505(c)(2) of the FD&C Act and 21 CFR 314.53). The FD&C Act requires FDA to regularly revise the Orange Book to include, among other things, patent information submitted under section 505(c)(2) of the FD&C Act (see section 505(j)(7) of the FD&C Act). FDA serves a ministerial role with regard to the listing of patent information (see, e.g., “Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not be Infringed” final rule, 68 FR 36676 at 36683 (June 18, 2003) (“Indeed, the requirement of prompt publication (“upon submission”), combined with the 30-day time frame for updating the Orange Book, are strong evidence that Congress did not intend us to undertake anything other than a ministerial action.”)).

### 3. *Facilitate Implementation of the Hatch-Waxman Amendments*

Since enactment of the Hatch-Waxman Amendments, FDA has provided recommendations and issued regulations pertaining to the patent listing requirements of the FD&C Act to facilitate implementation of these amendments. Below is a brief summary of those efforts.

#### a. Letters to Industry

FDA has provided NDA applicants and NDA holders with advice on how to comply with certain requirements, including the new requirements for submission of patent information, via letters to industry. These letters have demonstrated how FDA’s thinking on the appropriateness of the listing of certain patents has evolved. For example, shortly after enactment of the Hatch-Waxman Amendments, the Agency indicated that formulation patents were not covered by the FD&C Act and therefore should not be submitted for listing in the Orange Book. However, in 1985, FDA reconsidered its original position and stated that it intended to list composition patents, including formulation patents, claiming the drug for which the NDA was submitted and for which a claim of patent infringement could reasonably be asserted in the event of unlicensed manufacture, use, or sale of the drug.

#### b. Rulemakings

In 1989, FDA issued a proposed rule to implement the Hatch-Waxman Amendments, detailing the types of patents that FDA regarded as covered by the requirements in section 505(b)(1) and 505(c)(2) of the FD&C Act. In particular, FDA proposed that to comply with section 505(b)(1) and 505(c)(2) of the FD&C Act, NDA applicants would be required to submit information on drug (ingredient) patents, drug product (formulation and composition) patents, and method-of-

use patents (see “Abbreviated New Drug Application Regulations” proposed rule, 54 FR 28872 at 28918 (July 10, 1989)). The proposed rule excluded process patents from the types of patents required to be submitted. When FDA issued a final rule in 1992, FDA declined to finalize patent listing and certain other requirements and stated that because the Agency would be issuing final regulations governing patent certification and exclusivity at a future date, FDA was revising or deleting cross-references to those provisions and, when possible, replacing them with statutory citations (see “Abbreviated New Drug Application Regulations” final rule, 57 FR 17950 at 17951 (April 28, 1992)).

In 1994, FDA finalized the regulations governing certain patent and exclusivity provisions of the Hatch-Waxman Amendments, including patent listing requirements (see “Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions” final rule, 59 FR 50338 (October 3, 1994)). In response to a comment suggesting that clarification was needed on whether patent information on manufacturing processes is appropriate for submission to FDA, the preamble to the final rule reiterated that the regulation at 21 CFR 314.53(b) clearly states that information on process patents should not be submitted to FDA (59 FR 50338 at 50345 (October 3, 1994)).

In 2002, FDA issued a proposed rule in response to (1) disputes over whether certain listed patents met the regulatory requirements for listing in the Orange Book and (2) a request from the Federal Trade Commission to issue a regulation or guidance clarifying whether an NDA holder can list various types of patents in the Orange Book (see “Applications for FDA Approval to Market a New Drug: Patent Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not be Infringed” proposed rule, 67 FR 65448 at 65449 (October 24, 2002)). The proposed rule addressed (1) the types of patents that must and must not be listed, including, among others, certain patents that claim methods of use; (2) the patent certification statement that NDA applicants must submit as part of an NDA or a supplement to an NDA; and (3) the 30-month stay of approval for a 505(b)(2) application or an ANDA set out in the Hatch-Waxman Amendments (see also section 505(c)(3)(C) and 505(j)(5)(B)(iii) of the FD&C Act). In addition to proposing to clarify that NDA holders and NDA applicants must not submit information on patents that claim methods of use that are not approved for the listed drug or are not the subject of the pending application, respectively, the proposed regulation at 21 CFR 314.53(a) proposed to prohibit the listing of information on patents claiming packaging, patents claiming metabolites, and patents claiming intermediates (67 FR 65448 at 65451 (October 24, 2002)). The proposed rule, however, proposed to require NDA applicants and NDA holders to submit information on product-by-process patents (i.e., patents that claim a product by using or listing process steps to wholly or partially define the claimed product) and patents that claimed a drug substance even when the patented drug substance was a different form than the drug substance that was the subject of the pending or approved NDA as long as the drug substances were the same (67 FR 65448 at 65452 (October 24, 2002)).

FDA issued the final rule on patent listing requirements, with certain revisions, on June 18, 2003. The final rule revised FDA’s regulations to (1) incorporate the proposals described above with certain revisions; (2) prohibit the submission of patents claiming packaging, intermediates, or

metabolites; (3) require the submission of certain patents claiming a different polymorphic form of the active ingredient described in the NDA; and (4) add a requirement that for submission of polymorph patents, the NDA holder must have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA (see 68 FR 36676 at 36677 (June 18, 2003)).<sup>11</sup> The preamble to the final rule addressed comments on the types of patents that must and must not be submitted, including comments stating that patents claiming devices or containers that are either “integral” to the drug product or require prior FDA approval should be submitted and listed (68 FR 36676 at 36680). The comments described a distinction between packaging and devices such as metered dose inhalers and transdermal patches, which are drug delivery systems used and approved in combination with a drug. In response to the comment, FDA (1) agreed that patents claiming a package or container must not be submitted and (2) clarified that such packaging and containers are distinct from the drug product and thus fall outside of the requirements for patent submission (68 FR 36676 at 36680 (June 18, 2003)). FDA did not expressly address device-related patents associated with NDAs but clarified the rule to require submission of patents that claim the drug product as defined in FDA’s regulation at 21 CFR 314.3(b), which defines a *drug product* as “a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.” FDA explained that the “key factor” in determining whether the patent must or must not be submitted for listing is whether the patent claims the finished dosage form of the approved drug product. Patents must not be submitted for bottles or containers and other packaging, as these are not “dosage forms” (68 FR 36676 at 36680 (June 18, 2003)).

In 2015, FDA proposed regulations to implement portions of Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) (Pub. L. 108-173), which amended provisions of the FD&C Act that govern the approval of 505(b)(2) applications and ANDAs (MMA proposed rule) (“Abbreviated New Drug Applications and 505(b)(2) Applications” proposed rule, 80 FR 6802 (February 6, 2015)). Also in the MMA proposed rule, FDA recommended to amend certain regulations, including regulations regarding the submission of patent information, to facilitate the compliance with and efficient enforcement of the FD&C Act.

The MMA final rule, which was issued in 2016, among other actions, revised and streamlined the requirements for submission of patent information on (1) patents that claim the drug substance and/or drug product and meet the requirements for patent listing on that basis, (2) drug substance patents that claim only a polymorph of the active ingredient, and (3) certain NDA supplements (“Abbreviated New Drug Applications and 505(b)(2) Applications” final rule, 81 FR 69580 (October 6, 2016)). For example, in the MMA final rule, FDA clarified that an applicant need only satisfy the requirements for patent listing set forth in section 505(b)(1) and 505(c)(2) of the FD&C Act and, subject to the requirements for the submission of method-of-use

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<sup>11</sup> The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Pub. L. 108-173) superseded certain provisions of the 2003 final rule related to 30-month stays of approval; these superseded provisions were subsequently revoked by a technical amendment (see “Application of 30-Month Stays on Approval of ANDAs and Certain NDAs Containing a Certification That a Patent Claiming the Drug Is Invalid or Will Not Be Infringed” technical amendment (69 FR 11309 (March 10, 2004))).

patent information, need not identify each basis on which the patent claims the drug (see 81 FR 69580 at 69596 (October 6, 2016)). Accordingly, if a patent is eligible for listing as claiming both the drug substance and the drug product, an applicant would only be required to identify one of these two bases for listing (see 21 CFR 314.53(c)(2)(i)(S) and 314.53(c)(2)(ii)(T)). In addition, this MMA final rule codified FDA's longstanding position that the NDA holder's description of the patented method of use required for publication must contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval (see 21 CFR 314.53(c)(2)(ii)(P)(3)). For example, the rule requires that if the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, then the applicant must describe only the specific approved method of use claimed by the 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 product (see 21 CFR 314.53(c)(2)(ii)(P)(3)).

## **B. Patent Certifications and Exclusivities – Timing of Approval of 505(b)(2) Applications and ANDAs**

The timing of approval for a 505(b)(2) application and an ANDA (including a petitioned ANDA<sup>12</sup>) is subject to certain patent and exclusivity protections.

A 505(b)(2) application and ANDA must include an appropriate patent certification or statement for each patent that claims the listed drug(s) relied upon or the reference listed drug (RLD), respectively, or a method of using such drug and for which information is required to be filed under section 505(b) or 505(c) of the FD&C Act. The 505(b)(2) or ANDA applicant must submit one or more of the following certifications or statements:

- That such patent information has not been filed (a paragraph I certification);
- That such patent has expired (a paragraph II certification);
- The date on which such patent will expire (a paragraph III certification);
- That such patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the 505(b)(2) application or ANDA is submitted (a paragraph IV certification);

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<sup>12</sup> A *petitioned ANDA* is a type of ANDA for a drug product that differs from the the reference listed drug 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 petition submitted under section 505(j)(2)(C) of the FD&C Act (suitability petition), that studies are not necessary to establish the safety and effectiveness of the proposed drug product. A petitioned ANDA is generally expected to provide the same therapeutic effect as the listed drug that was relied on as the basis of the suitability petition.

- That there are no patents that claim the listed drug(s) or that claim a use of such drug (a “no relevant patents” statement, which is submitted instead of a patent certification); or
- That a method-of-use patent does not claim a use for which the 505(b)(2) or ANDA applicant is seeking approval (a 505(b)(2)(B) or 505(j)(2)(A)(viii) statement).

An applicant that submits a paragraph IV certification is required to give notice of the paragraph IV certification to the NDA holder for the listed drug(s) relied upon or RLD and to each owner of the patent that is the subject of the certification. Notice of a paragraph IV certification subjects the 505(b)(2) or ANDA applicant to the risk that it will be sued for patent infringement. If the NDA holder or patent owner initiates a patent infringement action within 45 days after receiving notice of the paragraph IV certification, there generally will be a statutory 30-month stay of approval of the 505(b)(2) application or ANDA while the patent infringement litigation is pending (see section 505(c)(3)(C) and 505(j)(5)(B)(iii) of the FD&C Act).

If a patent is timely listed in the Orange Book after a 505(b)(2) application or ANDA is submitted but before it is approved, the applicant generally must amend its application and provide an appropriate patent certification or statement to the newly listed patent, but a 30-month stay of approval will not be available (see section 505(c)(3)(C) and 505(j)(5)(B)(iii) of the FD&C Act).

### **C. Risk Evaluation and Mitigation Strategies**

The Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. 110-85) created section 505-1 of the FD&C Act (21 U.S.C. 355-1), which authorizes FDA to require a risk evaluation and mitigation strategy (REMS) if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks. A *REMS* is a required risk management strategy that employs tools beyond prescribing information to ensure that the benefits of a drug outweigh its risks. A REMS may require inclusion of a Medication Guide and/or a patient package insert to provide risk information to patients (see section 505-1(e)(2) of the FD&C Act) and/or a communication plan to disseminate risk information to healthcare providers (see section 505-1(e)(3) of the FD&C Act). A REMS may also include certain packaging and disposal requirements under section 505-1(e)(4) of the FD&C Act. In addition, FDA may require certain elements to assure safe use (ETASU) when such elements are necessary to mitigate specific serious risks associated with a drug (see section 505-1(f) of the FD&C Act). ETASU may include, for example, requirements that healthcare providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe-use conditions. When a REMS with ETASU is required for the RLD, section 505-1(i)(1)(C) of the FD&C Act, as amended by the Further Consolidated Appropriations Act, 2020 (Pub. L. 116-94), requires that the holder of an ANDA approved under section 505(j) of the FD&C Act use either a “single, shared system” with the RLD holder for the ETASU or a “different, comparable aspect” of the ETASU. FDA is aware that some NDA holders have obtained patents claiming the way one or more of their REMS requirements have been implemented and that this can impact the ability of

a prospective generic applicant to form a single, shared system with the NDA holder. The prospect of NDA holders obtaining patents for REMS was also contemplated by Congress in the FDAAA, which, prior to the amendments made to section 505–1 of the FD&C Act by the Further Consolidated Appropriations Act, 2020, (1) required the RLD and ANDA holders to use a single, shared system for the ETASU unless FDA waived the requirement and (2) provided that one of the grounds for which FDA could waive the single, shared system requirement would be if an aspect of the ETASU was claimed by a patent and the ANDA applicant certified that it sought a license to that aspect and was unable to obtain one (see 21 U.S.C. 355–1(i)(1)(B)(ii), 2012 ed.). FDA notes that section 505–1(f)(8) of the FD&C Act provides that no holder of an approved covered application shall use any ETASU to block or delay the approval of an application under section 505(b)(2) or 505(j) of the FD&C Act or to prevent application of such element to a drug that is the subject of an ANDA.

#### **D. FDA’s Solicitation of Public Comments Regarding Patent Listing in the Orange Book**

Prior to the enactment of the OBTA, FDA published, on June 1, 2020, a *Federal Register* notice entitled “Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments” (85 FR 33169, Docket No. FDA-2020-N-1127). This notice announced the establishment of a public docket and solicited comments on not only the types of patents currently listed in the Orange Book but also the impact that any change to current patent listing practices may have on drug product development. Comments were due by August 31, 2020. The notice included questions related to the following five topics: (1) general questions, (2) drug product patents, (3) method-of-use patents, (4) REMS-related patents, and (5) patents for digital applications. The Agency received 16 comment letters in response to this solicitation.

This docket was reopened for a second comment period from October 16 to November 16, 2020. The Agency received four comment letters in response to this second solicitation.

Section 2(e) of the OBTA, which the President signed into law on January 5, 2021, requires the Agency (1) to solicit public comments regarding the types of patent information that should be included in, or removed from, the Orange Book and (2) to transmit to Congress, by January 5, 2022, a summary of the comments received and any actions the Agency is considering taking in response to these comments.

To ensure that commenters had an opportunity to consider patent listing issues in light of the OBTA, FDA reopened the comment period for the public docket for a third time for a period of 30 days—from March 16 to April 15, 2021—to allow interested persons time to submit any additional comments regarding the types of patent information that should be included in, or removed from, the Orange Book. The Agency received four comments in response to this third solicitation.

This report to Congress includes a summary of the 24 comments FDA received in the public docket, preceding and subsequent to the enactment of the OBTA (i.e., on June 1, 2020, and

reopened on October 16, 2020, and March 16, 2021), regarding the types of patent information that should be included in, or removed from, the Orange Book.

### **III. Summary of the Public Docket Comments Received**

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As mentioned above, FDA received 24 comments in the *Federal Register* public docket; each comment contained input on one or more patent issues. FDA received comments from academia, pharmaceutical industry associations, brand and generic drug manufacturers, biopharmaceutical research companies, consulting firms, law firms, intellectual property and drug pricing advocacy groups, biotechnology and trade organizations, information services companies, a pharmacist, and a patient. Several comments included general remarks regarding FDA's authority and involvement with patents and exclusivities without focusing on particular patent information that should be included in, or removed from, the Orange Book.

In sections IIIA through IIIE of this report, the specific comments received are organized under the following five categories: (1) general questions, (2) drug product patents, (3) method-of-use patents, (4) REMS-related patents, and (5) patents for digital applications; these categories are based on the questions posed in FDA's June 1, 2020, *Federal Register* notice that first established the public docket.

The below summary of the comments received is not intended to express a view on these comments, including whether such comments accurately described current statutory or regulatory requirements. In addition, FDA received off-topic comments on issues expressing political views; those comments are not summarized here as they are not relevant to the types of patent information that should be included in, or removed from, the Orange Book.

The public docket comments, which are listed based on the particular *Federal Register* solicitation in which they were received, are available at the following websites:

- First solicitation (June 1, 2020): <https://www.regulations.gov/document/FDA-2020-N-1127-0001/comment>
- Second solicitation (October 16, 2020): <https://www.regulations.gov/document/FDA-2020-N-1127-0019/comment>
- Third solicitation (March 16, 2021): <https://www.regulations.gov/document/FDA-2020-N-1127-0024/comment>

#### **A. General Questions**

Comments in this category responded to the following five questions:

1. Do 505(b)(2) and ANDA applicants currently encounter any challenges because certain types or categories of patents are not listed in FDA's Orange Book?
2. Given the general increasing complexity of products approved in an NDA (e.g., drug-device combination products, complex delivery systems, associated digital applications), are there any aspects of FDA's interpretation of the statutory requirement for NDA holders to submit information on a patent that claims the drug or a method of using such drug that are not sufficiently clear? If there is a lack of clarity, how could this be resolved?
3. How would NDA holders and prospective 505(b)(2) and ANDA applicants weigh any advantages that may result from listing of additional types or categories of patent in the Orange Book against the potential need to submit additional patent certifications that could result in a delay of approval of a 505(b)(2) application or ANDA?
4. If you think FDA should clarify the type of patents that must be listed in the Orange Book, what factors should FDA consider in implementing this clarification? For example, should FDA consider specific factors in evaluating the timeliness of patent information submitted after such clarification?
5. Are there other issues related to the listing of patent information that we should consider?

The comments received in response to this first general set of questions covered a range of topics, and commenters also expressed a range of perspectives on these topics. For example, a variety of comments provide input on (1) whether the current requirements related to the listing of patent information in the Orange Book should be clarified or modified and (2) on the types of patents commenters considered appropriate for listing or the benefits or drawbacks of different patent listing approaches. One comment appears to support the current listing requirements and indicates that FDA should not create additional types or categories of patents eligible to be listed in the Orange Book.

Another comment generally supports the listing of any patent that claims an FDA-approved drug product, which the comment asserts includes the product's integrated and essential constituent parts, and suggests that both NDA holders and prospective applicants for follow-on products (including products submitted in ANDAs and 505(b)(2) applications) would benefit from an inclusive patent listing framework that enables orderly pre-launch litigation regarding the validity, enforceability, or applicability of any patent that might delay or otherwise inhibit the prompt entry of FDA-approved follow-on drug products.

However, another comment appears to support a more restrictive patent listing framework, stating that the Orange Book was originally developed to list drug patents and contending that expansion to include medical device and digital application patents, among other patents, deviates substantially from one of the Orange Book's central premises: to establish clearly



defined bounds of market exclusivity, further generic competition, and lower prices. Another comment states that, consistent with the holding and reasoning of the First Circuit in *In re: Lantus Direct Purchaser Antitrust Litig.*, 284 F.Supp.3d 91 (1st Cir. 2018), FDA should prohibit device and component patents from being listed in FDA’s Orange Book and only list drug and method-of-use patents. Another comment suggests patents other than those which claim the drug or an approved method of using the drug are currently listed in the Orange Book and recommends that FDA delist most secondary and all tertiary patents from the Orange Book, especially those patents that do not “claim the drug” or “methods of using the drug.”

One comment contends that allowing companies to include additional patents in the Orange Book would extend their monopoly over critical drugs.

Other comments propose various modifications to the current listing requirements that could change the categories of patents listed and either limit or expand the number of patents listed. For example, one comment recommends more limited listing requirements, proposing that only patents protecting innovations that improve health and have been demonstrated to do so through clinical testing should be rewarded with the benefits of “patent linkage.” The comment suggests that this proposal would be achieved by creating a new field in the Orange Book to distinguish health-contributing patents (which would enjoy added protection through “patent linkage”) from non-contributing patents (which would not).

Another comment suggests that if FDA considered an extra component (e.g., an electronic device) in making a TE determination, the patent information listed in the Orange Book should include the relevant patents—including software, device, drug, or any other patents—that claim the drug with the component considered for the TE determination. Another comment notes the uncertainty and potential that digital health technologies hold and indicates that future therapeutics will continue to integrate features and technologies that are complex and not contemplated by traditional features limited solely to active ingredients, formulations, and methods of use; the comment therefore urges the continued evaluation of the Orange Book’s (1) practices in this area and (2) policies that encourage disclosure of patent information, as the commenter believes such disclosure better serves all relevant stakeholders and encourages industry competition.

One commenter had not encountered any problems regarding certain types or categories of patents not being listed in the Orange Book. However, another comment notes challenges with NDA holders bringing litigation against 505(b)(2) and ANDA applicants with regard to patents that have not been listed in the Orange Book. That commenter specifically notes that litigation for non-Orange Book-listed patents can occur at a different time than the litigation contemplated under the Hatch-Waxman Amendments for Orange Book-listed patents and can lead to delayed launches of substitutable generics. This same commenter, though, states that there has been an increase in the listing of ineligible patents in the Orange Book and notes that this adds unnecessary costs and barriers to the approval of generic competitors.

Some comments address whether aspects of FDA’s interpretation of the statutory or regulatory requirements related to patent listing are sufficiently clear. One comment suggests that there are

aspects of FDA’s statutory interpretations regarding the types of patents for complex products that are and are not subject to listing in the Orange Book that would benefit from greater clarity. Another comment states that the rules for patents claiming drug-device combination products are not clear and suggests, to avoid errors or abuse, implementing a referee process by which FDA enforces the rules about which patents must be listed. Another comment states that FDA should clarify that patents that claim a device or component of a device that are encompassed within (i.e., part of) an NDA-approved drug-device combination product are required to be listed, including patents with claims covering an entire delivery device or a component part of a delivery device that are encompassed within the NDA. Another comment asserts that recent litigation on “skinny labels”<sup>13</sup> suggests that courts are willing to place undue emphasis on method-of-use patents (citing *GlaxoSmithKline LLC v. Teva Pharmaceuticals USA, Inc.*<sup>14</sup>) and then suggests that FDA should take a position in the Orange Book on the assertability of certain method-of-use patents against ANDAs with “skinny labels.”

Another comment suggests that, given the general increasing complexity of products approved in NDAs, there is a lack of clarity with respect to FDA’s practices for listing certain products in the Orange Book and for making therapeutic equivalence evaluations for these products. In addition, this comment suggests (1) that the Orange Book should list products with components such as a sensor, electronic device, or digital application separately from the drug product alone if there is a difference in clinical outcome associated with the additional component and (2) that FDA should provide clarity on its criteria for making TE evaluations for products with components like these relative to the drug product without such a component.

Other comments discuss the timelines for implementing any clarification to the types of patents that must be listed in the Orange Book. One comment indicates that if FDA does clarify that additional types of patents must be listed in the Orange Book, this clarification should allow applicants a sufficient time period to file a supplemental listing request. Two comments similarly suggest that if FDA seeks to clarify its regulatory requirements in future rulemaking proceedings, any new patent listing rules should apply only prospectively. Another comment states that FDA should provide a time frame for listing patents that are only listed due to new clarifications consistent with its timely listing requirement, i.e., within 30 days of the effective date of the clarification. The same comment states that for patents already listed that would be delisted following clarification, the patent listing dispute process could be sufficiently used and, for patents not currently listed that would become eligible for listing after clarification, a window of not more than 180 days during which patents already issued as of the date of clarification may be listed.

Several comments provide input on what information is disclosed in the Orange Book about listed patents and other subjects and offer various views on what additional information either should be made available by FDA or should be required to be disclosed by the holders of the listed drugs. For example, one comment suggests that FDA should identify which patents are late-listed. Another comment suggests adding the following fields to the Orange Book:

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<sup>13</sup> The commenter describes a “skinny label” as ANDA labeling that intentionally excludes patented indications.

<sup>14</sup> 976 F.3d 1347 (Fed. Cir. 2020). The Federal Circuit has since withdrawn this opinion and issued a new panel opinion on August 5, 2021. See 7 F.4th 1320 (Fed. Cir. 2021).

paragraph IV information, National Drug Code (NDC) information, Drugs@FDA information, submission dates for original applications, 505(b)(2) designations, orphan drug information, and descriptions of exclusivity and patent codes. Relatedly, another comment suggests that when an ANDA containing a paragraph IV certification is received, FDA should notate the NDA Orange Book listing to identify the NDA and strength for which the ANDA was submitted.

Additionally, the commenter recommends that FDA identify the parts of the NDA labeling that are protected by method-of-use patents listed in the Orange Book to make labeling carve-outs easier for ANDA applicants. Another comment suggests that for each product protected by patents or a regulatory exclusivity, FDA should require applicants to provide periodic information about the number of units sold and the sales revenue.

One comment suggests that FDA should publish the number of patents ever listed for a specific product in the searchable electronic Orange Book database, including patents that have expired and have been delisted from the current edition. Another comment suggests that FDA should either (1) retain a list of expired patents in the Orange Book but clearly state that these patents have expired or (2) periodically publish a separate list with every patent ever listed in the Orange Book (including those that have expired); further, this comment indicates this list should be made available in a database that can be searchable by end-users and also in data files with an open format.

One comment suggests that FDA should add information about government disclosures on patents listed in the Orange Book and opines that the ideal approach would be to include this information in the list of data items that NDA applicants or NDA holders are required to provide under 21 CFR 314.50(h), 314.53, and 314.70(f). Another comment suggests that FDA should require disclosures about previous and current litigation, if any, for each patent listed in the Orange Book, including all legal events concerning each patent (e.g., disputes over infringement and validity, failure to disclose government rights as required under 35 U.S.C. 202(c)(6) and 37 CFR 1.77(b)(3), pending and past march-in requests, 28 U.S.C. 1498 cases, or inter partes' reviews at the United States Patent and Trademark Office).

A few comments asked for more Orange Book-related information to be made available for research purposes. One comment suggests that FDA should publish Orange Book data files with dates that would allow researchers to estimate the number of years a specific drug has been or will be under some form of exclusivity; this suggestion is aimed at furthering research regarding secondary patenting and helping answer questions relating to, for example, how long a drug is typically under some form of exclusivity or whether the trend has been changing recently. Another comment suggests that the forms that contain required patent information submitted to FDA by NDA applicants (i.e., Forms FDA 3542 and FDA 3542a) should be published on FDA's website, alongside existing Orange Book information, so that patent researchers can make use of the data more easily, more quickly understand the scope of patent protection on specific drugs, and more efficiently perform research on broader trends in pharmaceutical patenting.

FDA also received a few comments regarding other topics, including the forms used to submit patent information to FDA and the format used to display information in the electronic version of

the Orange Book. One comment contends that Form FDA 3542 and the usage of this form discourages the complete identification of patent information required by the statute and suggests that Form FDA 3542 may be improved in several ways to facilitate proper patent listing in the Orange Book.

## **B. Drug Product Patents**

Comments in this category responded to the following two questions:

1. Are there elements of FDA’s regulatory definition of drug product or dosage form in 21 CFR 314.3(b) that may be helpful to clarify to assist NDA holders in determining whether a patent claims the finished dosage form of an approved drug product?
2. What factors should FDA consider in providing any clarifications related to whether device-related patents need to be submitted for listing as a patent that claims the drug? For example, what are the advantages and disadvantages of requiring patents that claim a device constituent part of a combination product approved under section 505 of the FD&C Act to also claim and/or disclose the active ingredient or formulation of the approved drug product (or the drug product class) to fall within the type of patent information that is required to be submitted to FDA for listing in the Orange Book? Also, how, if at all, should this analysis be affected by considerations about whether the device or specific component of device claimed in the patent is “integral” (see 68 FR 36676 at 36680) to the administration of the drug?

In response to the first question, one comment generally suggests that FDA should clarify its interpretation of its 21 CFR 314.3(b) “drug product” and “dosage form” definitions as they relate to the listing of device patents. Another comment suggests that FDA should clarify the definitions for drug-device combination products, especially those with primarily a container-closure function, with a clarification as to which features of such devices are eligible for patent claims to be listed in the Orange Book.

Other comments provide input about whether device-related patents should be submitted for listing as a patent that claims the drug and whether FDA should consider clarifying this topic. One comment states that FDA should construe “patent which claims the drug” to mean any patent that (1) claims one or more articles used as a component of the drug product or (2) claims the composition of the drug product (e.g., a combination of such components or specific amounts, ratios, or configurations thereof).

One comment contends that patents should be listed in the Orange Book so long as (1) the patent at issue legitimately claims an integrated device component of an approved NDA product or a method of using such a constituent part and (2) FDA directly reviewed that integrated device component in connection with, and as a condition of approving, the listed NDA product.

Another comment suggests that all patents that (1) claim an integrated device component of an approved NDA product (or a method of using such an integrated device component) and (2) have the potential to block the marketing of an approved follow-on product should be listed in the Orange Book.

Multiple comments provide input on whether patents that claim a device constituent part of a combination product approved in an NDA should also be required to claim or disclose the active ingredient or formulation of the drug to be listed in the Orange Book. A number of these comments suggest that such patents should not be required to claim or disclose the active ingredient to be listed. For example, two comments suggest that FDA should clarify that a patent that claims a device or device component need not also claim or expressly call out the active ingredient in the drug to be considered a patent that “claims the drug” under section 505(b)(1) of the FD&C Act. One comment states that FDA should confirm that patents claiming the device constituent part of an NDA-approved drug-device combination product or a component thereof, including patents that do not disclose or claim the active ingredient or formulation of the approved drug product, meet the listing standard. A similar comment states that FDA should not construe section 505(b)(1) of the FD&C Act in a manner that limits the listing of patents that claim a device constituent part of a combination product only to those patents that expressly claim or recite a device or device component in combination with the drug’s active ingredient or formulation. Two comments suggest that FDA should define what constitutes a drug delivery system and make clear that patents that claim pre-filled drug delivery devices should be listed if the approved product is a drug-device combination product that encompasses that device, even if the patent does not claim or disclose the active ingredient, formulation, or finished dosage form.

One comment suggests (1) that while claiming the drug active ingredient should be sufficient to render a patent that claims a device or device component subject to listing, this claim should not be construed as a necessary factor and (2) that when a patent that claims a device or device component does not claim the device or device component in combination with the drug’s active ingredient, determining whether that patent is subject to listing should turn on whether the device as used with the drug product meets the Agency’s regulatory definition of a *combination product* as set forth at 21 CFR 3.2(e), even if the drug product is not specifically designated as such by FDA.

However, another comment suggests that a patent should claim either the “drug product” or “dosage form” of an NDA product for it to be listed in the Orange Book and not simply claim an element in the drug product or dosage form, e.g., a delivery device or packaging element. This comment requests that FDA clarify that listed patents need to include claims to the active ingredient in the drug product.

A few comments provide input on how the analysis of whether device-related patents should be submitted for listing could be affected by considerations about whether the device or specific component of the device claimed in the patent is “integral.” One comment suggests that defining “integral” would help clarify whether a patent should be listed or not and argues that if a patent claim covers any part of an NDA-approved drug product or the method of using that product that is “integral” to the approved product, then that patent should be listed. Two comments indicate

that FDA should accept device patents for listing in the Orange Book but only if the device constituent part of a drug product claimed in the patent is integral to the drug's delivery system and is reviewed and approved as part of the NDA; one of these commenters notes that this requirement not only limits the eligibility to patents that meet the applicable statutory and regulatory requirements but also reduces the potential for anti-competitive "game-playing" by brand companies.

### **C. Method-of-Use Patents**

Comments in this category responded to the following three questions:

1. What information should FDA consider regarding when a patent that claims a method of using a device constituent part, or only a component of a device constituent part, might or might not meet the statutory standard for submission by the NDA holder for listing in the Orange Book as a method-of-use patent? Should FDA consider whether: (1) The patent claims and/or discloses the active ingredient or formulation of the approved drug product (or the drug product class)?; (2) the device constituent part is described in certain sections of the listed drug labeling?; or (3) use of the device is described in labeling for the listed drug, but the device is not a constituent part of the drug product? Should FDA consider whether the drug product labeling states that the drug is only for use with the specific device? Should FDA also consider device labeling, for example whether the device labeling indicates the device is for use with the specific drug?
2. What information should FDA consider regarding whether there are circumstances in which a patent claiming the way an approved drug product is administered would meet the statutory standard for submission by the NDA holder for listing in the Orange Book as a drug product patent rather than a method-of-use patent?
3. What information should FDA consider regarding whether there are circumstances in which a method-of-use patent claiming the way an approved drug product is administered that is not described in FDA-approved product labeling would meet the statutory standard for listing in the Orange Book?

A number of comments provide information that the commenters think FDA should consider regarding circumstances in which method-of-use patents that claim a method of using a device constituent part or a component of a device constituent part might or might not meet the standard for listing in the Orange Book. For example, one comment states that FDA should only permit method-of-use device patents to be listed if they claim an active ingredient of a drug product or the drug product itself. Another comment similarly indicates that these patents should be listed in the Orange Book if they claim an active ingredient of a drug product or the drug product itself and notes that the labeling of the drug should substantiate that the device is an integral part of the dosage form.

Another comment indicates that FDA should consider whether the patent claims cover the specific active pharmaceutical ingredient (API), API class, or formulation of the relevant drug product. The same comment said that patents claiming a method of using a device constituent part should only be listed if the claims present a novel “use case” (i.e., use of the drug with the patented device constituent part should be a different “use case” than use of the drug with a non-patented version of that device constituent part for the patent to be listed). The comment also states that a method-of-use patent should only be listed if the device is critical to the administration of the drug for a method of use described in the Indications section of the drug product’s labeling. Also, this comment notes that when use of the device is described in labeling for the listed drug but the device is not a constituent part of the drug product, listing of a patent related to a method-of-use for the device should only be considered if the drug product is also specifically referenced in the device labeling.

One comment suggests FDA should consider whether there is a difference in clinical outcomes in determining whether method-of-use patents that claim a method of using a device constituent part or a component of a device constituent part might meet the statutory standard for listing.

However, two comments interpret the FD&C Act and FDA’s implementing regulations to require listing of patents claiming a method of using a device constituent part or component thereof in an NDA-approved single-entity combination product if the patent could reasonably be asserted upon an unlicensed person engaging in the manufacture, use, or sale of the drug—regardless of whether the patent claims and/or discloses the active ingredient or formulation of the approved drug product (or the drug product class). Another comment indicates that a patent claiming a method of using a pre-filled drug delivery device or a component thereof (e.g., a patent claiming a method for determining the final dose of a drug contained in a cartridge in a pen-type injector through the configuration or operation of certain device components) should be subject to the patent listing requirement, even if the patent does not claim or disclose the active ingredient, formulation, or finished dosage form.

FDA also received input about the information the Agency should consider regarding whether there are circumstances in which a patent claiming the way an approved drug product is administered would meet the statutory standard for submission for listing as a drug product patent rather than a method-of-use patent. One comment states that when determining whether to list a patent as a drug patent or a method-of-use patent, FDA should consider whether the method of administration for the drug could make a clinical difference to all patients or to a defined subgroup of patients sufficient to be identified in the drug’s label. Another comment contends that FDA should be guided by how an applicant characterizes the patent in its Form FDA 3542 and suggests that if the Form FDA 3542 indicates that the patent claims one or more approved methods of using the drug product, the patent would qualify as a method-of-use patent, whereas if the Form FDA 3542 indicates that the patent claims an active ingredient or the approved drug product, the patent would qualify as a drug substance or a drug product patent, respectively.

In addition, some comments provide input in response to the second question about what

information FDA should consider regarding whether there are circumstances in which a method-of-use patent claiming the way an approved drug product is administered that is not described in FDA-approved product labeling would meet the statutory standard for listing in the Orange Book.<sup>15</sup> Several comments argue against listing method-of-use patents for a method of administration that is not described in approved product labeling. One comment contends that a method-of-use patent that claims the way a drug product is administered that is not described in the FDA-approved product labeling should not be included in the Orange Book because this type of patent is of a more general nature and not specific to the drug product or dosage form. Another comment states that patents covering methods of administration not related to a drug's indication should not be listed in the Orange Book because otherwise, an ANDA applicant would be forced to certify to patents on methods of use for which they are not seeking approval. Similarly, another comment argues that since the mode of delivery is part of the "Prescribing Information" of the labeling, if the way an approved drug product is administered is not referenced in the FDA-approved product labeling, then the way that the drug product is administered is not a part of the approved drug product and listing of the patent is not proper in this context. Another comment states that it would not be appropriate to authorize the listing of method-of-use patents that do not claim FDA-approved methods of administering a listed drug product and indicates that doing so would be impossible to square with the text and structure of the Hatch-Waxman Amendments and FDA's implementing regulations.

However, one comment contends that the NDA applicant, not FDA, must assess whether a method-of-use patent claiming the way an approved drug product is administered that is not described in FDA-approved product labeling would meet the statutory standard for listing in the Orange Book. Another comment notes that FDA's role in patent listing matters is purely ministerial and, accordingly, the statute and its corresponding regulations should govern in this and all circumstances.

#### **D. REMS-Related Patents**

Comments in this category responded to the following two questions:

1. What information should FDA consider regarding whether patents that claim how the sponsor has implemented a particular REMS requirement meet the statutory requirement for the type of patent information that is required to be submitted to FDA for listing in the Orange Book? What factors should be considered in making this determination?
2. Are there other issues related to patents that claim how the sponsor has implemented a particular REMS requirement that FDA should consider with regard to listing patent information in the Orange Book, including any potential

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<sup>15</sup> Certain comments were submitted to this docket before enactment of the OBTA. The OBTA amended section 505(c)(2) of the FD&C Act to state, in part: "a patent that is identified as claiming a method of using such drug shall be filed only if the patent claims a method of use approved in the application."



impact listing such patents in the Orange Book could have on development of REMS for generic versions of products? For example, does listing patent information in the Orange Book for such patents pose difficulties for ANDA applicants in developing a single, shared system REMS for that product?

As with the preceding categories, the comments received in this category reflected a range of different and sometimes competing views.

Some comments provide circumstances in which the commenters believe REMS-related patents should be listed in the Orange Book. For example, one comment indicates that REMS patents should be listed in the Orange Book as long as a claim of patent infringement could reasonably be asserted. Another comment states that patents are not, and should not be, excluded from eligibility for listing in the Orange Book solely on the ground that they relate to a REMS because the statute does not exclude patents otherwise meeting the listing criteria from listing based on the subject matter to which they relate. Another comment contends that the statute and corresponding regulations already identify the factors that govern whether a REMS-related patent must be listed and, because FDA has a ministerial role with respect to patent listing, states that the Agency should not develop an alternative framework beyond what is in the statute.

In contrast, multiple comments contend that REMS-related patents should not be listed in the Orange Book. One comment states that REMS requirements frequently concern such topics as the distribution of drug products or enhanced monitoring of adverse events and do not meet the statutory requirement for the type of patents that should be listed in the Orange Book. Similarly, another comment indicates that REMS are meant to provide additional safety measures to permit a drug to be marketed when the drug is associated with risks or adverse events to be managed and that REMS-related patents are not similar to categories of patents listable in the Orange Book. Another comment indicates that, given the well-documented history of brand application holders' misuse of the REMS requirements for anticompetitive purposes, there is a concern that REMS-related patents, if listed, would be particularly subject to abuse. The comment states that FDA should not list patents that claim one or more elements of a REMS because such patents do not claim the relevant drug or a method of using such drug. More generally, one comment suggests that REMS and patents should be handled separately and argues that REMS are for safety and patent listings are for critical patents that need to be challenged or expire before ANDA marketing. One comment suggests that FDA should delist REMS patents from the Orange Book and clarify that such patents should not be invoked as a roadblock to generic approval or market entry of important pharmaceutical products.

Other comments express views about the potential impact listing such patents in the Orange Book could have on the development of REMS for generic versions of products or on the approval of generic drugs. For example, one comment argues that listing REMS patents creates difficulties for ANDA applicants to develop a single, shared REMS with the RLD's NDA holder for that product because that NDA holder would likely claim that the ANDA applicant would need to obtain patent licenses as part of the discussion for that single, shared REMS. However, another comment contends that, in light of the enactment of the Further Consolidated Appropriations Act, 2020, any concerns regarding the impact of patent listing on the

development of REMS for generic versions of products are unfounded.

One comment contends that REMS innovation does not benefit patients or advance clinical care, and another comment indicates that listing REMS-related patents would harm competition and undermine the FDAAA, as REMS should not be used to block or delay a generic application. Similarly, another comment states that section 505-1(f)(8) of the FD&C Act mandates that holders of approved applications must not use any ETASU to block or delay approval of another application, and this comment also indicates that listing of patents pertaining to REMS with ETASU represents a barrier to approval that runs counter to this goal of the legislation. Another comment states that it would be a serious mistake to allow companies to file REMS-related patents in the Orange Book, which would result in 30-month stays of approval for ANDAs and provide NDA holders opportunities to improperly delay the entry of competition.

Other comments suggest areas for clarification by FDA regarding REMS-related patents. One comment suggests that FDA should clarify whether it considers “patents claiming safe methods of patient treatment or administration (e.g., marker-assisted methods for adjusting and administering drug doses)” to be patents that claim a REMS. Another comment states that FDA should clarify what it considers to be a patent that claims how an application holder has implemented a REMS and whether a patent should be listed should depend on whether the patent is deemed to claim “the drug” or “a method of using the drug,” not on special rules or prohibitions that hinge on whether a REMS is implemented or not.

Finally, one comment suggests that FDA should be listed as co-inventors on certain REMS patents as a condition of approval, thereby allowing FDA to “license” the REMS patent to any and all ANDA applicants.

## **E. Patents for Digital Applications**

Comments in this category responded to the following two questions:

1. If an approved drug product has an associated digital application (e.g., a mobile application that accepts and records information from an ingestible sensor in a drug product), what factors should be considered in determining whether a patent that claims an aspect of that digital application meets the standards for listing in the Orange Book?
2. Are there other issues related to patents for digital applications associated with approved drugs that should be considered with regard to listing patent information in the Orange Book?

FDA received a number of comments providing a range of views regarding the factors that should be considered in determining whether a patent that claims an aspect of a digital application associated with an approved drug product meets the standards for listing in the Orange Book.

One comment suggests listing patents only to the extent they claim integrated device constituent parts that FDA has expressly reviewed and approved as a condition of approval of the NDA, but further suggests such patents should not be listed to the extent they cover separable prescription drug-use-related software that is not accompanied by safety or efficacy claims. Another comment suggests listing patents for digital applications in the Orange Book under the following three specific scenarios: (1) when the mobile application is considered a medical device and the mobile application plays a critical role in the safety or efficacy of the product when administered for an approved indication; (2) when the functionality of the application could pose a risk to a patient's safety if the device were to not function as intended; and (3) when the application provides a patient-specific analysis, a patient-specific diagnosis, or treatment recommendations. Another comment contends that when a digital application (1) serves only to help patients self manage a disease or a condition without a specific treatment suggestion or (2) automates simple tasks for healthcare providers, patents for the application should not be listed in the Orange Book.

One comment states that if a patent claims a method of using an approved drug product in combination with an associated digital application, and this digital application is referenced in the approved drug labeling, then the patent should be listed in the Orange Book as long as a claim of patent infringement could reasonably be asserted.

One comment suggests that determining whether a patent that claims a digital application associated with an approved drug product should be subject to listing should turn on whether the patent for the digital application meets the statutory standard of claiming the drug or a method of using the drug; this comment also suggests that FDA should consider convening public workshops or meetings at which questions in this area could be discussed.

Another comment indicates that it is not possible to identify all the factors and issues the Agency should consider when determining whether patents on digital applications should be listed in the Orange Book at this time, given the nascent status of digital technologies, but suggests that patents claiming a digital application be listed in the Orange Book either when the digital application is approved as part of a combination product with the drug under an NDA or when the software is referenced by name in the drug labeling.

Commenters also raise other issues related to patents for digital applications and listing information about these patents and the associated approved drugs in the Orange Book. For example, one comment contends that patents on digital tools should not be listed in the Orange Book as a means of preventing generic entry of compounds that contain the same small molecule ingredient, asserting as an example, "a new 'digital' version of the blockbuster drug Abilify (aripiprazole) which includes an ingestible sensor, a smartphone application, and a wearable sensor." The commenter asserts that patents on these components should not be assertable against generic "non-digital" versions of the product.

Another comment suggests that FDA should create a separate section in the Orange Book for approvals that include digital applications and argues that failure to create this separation would

undercut the incentives created by Orange Book listing and lead to confusion at the pharmacy level that may allow pharmacists to substitute basic drug product formulations for products with smart components.

Two comments suggest that the Orange Book should reflect that approved smart products (which include the drug product formulation and smart components) are not therapeutically equivalent to non-digitally enhanced products that have the same drug product formulation (e.g., use a bioequivalent capsule or tablet).

#### **IV. The Actions FDA Is Considering in Response to the Public Comments**

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This section of the report provides information on the actions the Agency is considering taking in response to the public comments summarized above.

The Agency convened a working group in order to review the comments received and prepare this report. As noted in section III of this report, the comments received provided a variety of different and sometimes competing views on the types of patent information that should be included in, or removed from, the Orange Book. The diversity of viewpoints on these topics indicate a need to examine these issues more closely and suggests that there is not a consensus view around specific proposed changes that should be made to the types of patent information included in the Orange Book; rather, the comments suggested that there are a variety of equities and issues to be considered in examining this topic and that some of these issues are still evolving.

In response to the public comments summarized above, FDA will build upon the efforts of the working group that reviewed the comments and will create a multidisciplinary working group within the Agency to evaluate whether additional clarity is needed regarding the types of patent information that should be included on, or removed from, the Orange Book, consistent with the existing statutory requirements for patent listing in the FD&C Act.

In performing this evaluation, the Agency will consider the amendments to the FD&C Act included in the OBTA, the diversity of perspectives presented by stakeholders, and the Agency's ministerial role with respect to the listing of patent information. In considering what steps may be appropriate to take to provide additional clarity on the types of patent information that should be included in, or removed from, the Orange Book, FDA will also consider the comments received regarding factors FDA should consider in implementing any clarification.

Additionally, as part of an Agency-wide effort to modernize the Orange Book, improve transparency, and provide useful information to regulated industry and the public, FDA will consider the comments that provided additional insight into how stakeholders and the public have utilized the Orange Book and whether further improvements to the Orange Book should be made, including improvements that are not related to the types of patent information included in the Orange Book. Further, the Agency will continue to consider the more general comments received to the public docket that suggest modifications to the Orange Book beyond the types of

patent information that should be included in, or removed from, the Orange Book as part of this ongoing effort.

Lastly, FDA notes that the GAO report required to be completed within 2 years after the date of enactment of the OBTA may help inform the Agency's thinking on a number of these issues; as such, the GAO report will be reviewed by FDA once it is available.

## **V. Conclusion**

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- On January 5, 2021, the President signed into law the OBTA of 2020 (Pub. L. 116-290). Section 2(e) of the OBTA, in part, requires the Agency to solicit public comments regarding the types of patent information that should be included in, or removed from, the Orange Book. In response to this directive, FDA solicited public comments and received 24 comment letters in response to the public docket, each containing input on one or more issues related to the listing of patent information in the Orange Book.
- In response to the public comments, FDA will create a multidisciplinary working group within the Agency to evaluate, based on its review of the comments and changes to the statute in the OBTA, whether additional clarity is needed regarding the types of patent information that should be included in, or removed from, the Orange Book, consistent with the existing statutory requirements for patent listing in the FD&C Act.