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March 2023

GENERIC DRUGS

Stakeholder Views on Improving FDA's Information on Patents

Accessible Version

GAO-23-105477

GAO Highlights

Highlights of GAO-23-105477, a report to congressional committees

March 2023

GENERIC DRUGS

Stakeholder Views on Improving FDA's Information on Patents

Why GAO Did This Study

The process of developing and bringing a new drug to the market can be long and costly. Patent protections for new drugs provide opportunities for drug sponsors to recoup their costs by limiting competition for specified periods of time. While these protections can encourage research and development into innovative therapies, they can also increase costs for consumers and health insurers by keeping cheaper alternatives off the market. The U.S. has established policies to provide incentives to develop new brand name drugs while also creating opportunities for other companies to manufacture generic products, which are generally less expensive, once applicable patents expire or patent disputes have been resolved.

The Orange Book Transparency Act of 2020 includes a provision for GAO to review Orange Book patent listings for drug-device combination products, including the implications of these listings for generic products. In this report, GAO describes stakeholder views on (1) how Orange Book patent listings affect the entry of generic drug-device combination products into the market, (2) FDA's role overseeing the Orange Book, and (3) proposals for improving Orange Book patent listings.

GAO analyzed FDA documentation, reviewed published literature, and interviewed federal agency officials and 15 stakeholders, including experts, representatives of brand and generic drug companies, and advocacy groups representing patient interests.

View GAO-23-105477. For more information, contact John Dicken at (202) 512-7114 or dickenj@gao.gov.

What GAO Found

The Food and Drug Administration (FDA) is required to publish information on patents for approved brand name drugs in a publication known as the Orange Book. FDA regulations describe to brand name drug companies (sponsors) the patent information that should be submitted for listing in the Orange Book. FDA then publishes this information with a generally minimal review. This information can help generic drug sponsors determine when to seek FDA approval for the product they want to market. Listing patents in the Orange Book can also help brand name sponsors facing generic competition by providing additional time to resolve patent disputes before a generic product enters the market. Some research has raised questions about whether certain patent practices may delay generic competition, particularly for products that comprise a drug and a device, known as a drug-device combination product.

Stakeholders GAO interviewed provided varying views on how Orange Book patent listings may affect the entry into the U.S. market of generic drug-device combination products and FDA's role in overseeing patent listings.

- **Effect on generic market entry**. All 15 of the stakeholders GAO interviewed agreed that the Orange Book may help generic drug sponsors identify relevant patents when making product development decisions. However, there was not consensus on whether the patent information listed in the Orange Book may delay entry of generic drug-device combination products into the market. Some stakeholders and research suggested other factors—such as brand name sponsors being able to obtain patents for minor changes to a product—may have a greater effect on market entry of these products.
- **FDA's role in overseeing the Orange Book**. Thirteen of the 15 stakeholders GAO spoke with commented on FDA's role in overseeing the Orange Book. Of these 13, six stated that FDA's current role is sufficient, and FDA should not also be evaluating patents in the Orange Book for validity or quality. The other seven stated that FDA should have a more active role to ensure the patent information in the Orange Book meets listing requirements—for example, by substantively reviewing patent scope to ensure patents meet listing requirements.
- **Proposals for improving patent listings**. Stakeholders identified 13 different proposals. Among other things, 13 of the 15 stakeholders agreed it would be helpful for FDA to clarify which device-related patents should be listed in the Orange Book. However, they identified widely varied criteria for which device-related patents were appropriate to list.

FDA is planning to establish a multidisciplinary workgroup to evaluate whether additional clarity is needed regarding patent information that should be included in the Orange Book. While FDA officials said that resource challenges had prevented them from developing workgroup timelines or identifying its members, they hoped to make these decisions soon.

The Department of Health and Human Services provided technical comments on a draft copy of this report, which GAO incorporated as appropriate.

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Abbreviations

FDA	Food and Drug Administration

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U.S. GOVERNMENT ACCOUNTABILITY OFFICE
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March 15, 2023

The Honorable Bernard Sanders
Chair
The Honorable Bill Cassidy, M.D.
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Cathy McMorris Rodgers
Chair
The Honorable Frank Pallone, Jr.
Ranking Member
Committee on Energy and Commerce
House of Representatives

The process of developing and bringing a new drug to the market can be long and costly. Patent protections for new drugs provide opportunities for drug developers, also known as sponsors, to recoup their costs by limiting competition for specified periods of time. While these protections can encourage research and development into innovative therapies, they can also increase costs for consumers and health insurers by keeping cheaper alternatives off the market. Therefore, the U.S. has established a legal framework to provide incentives to develop new brand name drugs while also creating opportunities for other companies to manufacture generic drugs, which are therapeutically equivalent to the brand-name drug but generally are less expensive, once applicable patents expire.[1]

The Food and Drug Administration (FDA) and others have raised questions about whether certain patent practices by brand name sponsors may prolong patent protections, prevent generics from entering the market, and maintain higher prices. Researchers have noted that this may be especially true for certain drug-device combination products,

[1]See, e.g., Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Amendments. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355(j)). For the purpose of our report, brand name drugs are those drug products that have been approved for safety and effectiveness under section 505(c) of the Federal Food, Drug, and Cosmetic Act and typically have patent protection. 21 U.S.C. § 355(c). A generic drug is approved by the Food and Drug Administration as therapeutically equivalent to the corresponding brand name drug that works in the same way and is expected to provide the same clinical benefit; generic drugs are generally marketed under a nonproprietary name.

which are comprised of a drug used with a device.[2] These researchers are concerned that brand name sponsors are patenting incremental changes to devices that produce little to no additional therapeutic benefit to patients while preventing generic competition. Some researchers have linked these patent practices with high prices for certain drug-device combination products. In 2016, the House Committee on Oversight and Government Reform convened a hearing about the increasing price of a common drug-device combination product for the treatment of allergic reactions.[3] The product's price had increased by 400 percent since 2007, despite having an active ingredient (epinephrine) that was developed a century ago and is no longer protected by a patent. The committee noted its concern that the brand name sponsor had continued to receive protection against generic competition. This was in part due to the additional patents it received for modifications to the drug's associated device—an auto-injector—in 2009.

FDA is required to publish certain patent information received from brand name sponsors as part of a publically available list of approved drug products, known as the Orange Book.[4] Information about patents in the Orange Book can help generic drug sponsors make decisions about when to seek FDA approval to manufacture and market their product. Generic drug sponsors are also required to address the patents listed in the Orange Book for the brand name drug in their applications, and the legal framework for generic drug applications provides them a mechanism for challenging the validity of listed patents before their applications are approved. If such a challenge is successful, they may be able to market a generic drug before the patent term expires.

FDA has previously explained that the relevant statute does not establish anything other than what it has termed a "ministerial" role for FDA in

[2]See, for example, M.R. Patel, V.G. Press, L.B. Gerald, T. Barnes, K. Blake K, L.K. Brown, et al., "Improving the Affordability of Prescription Medications for People with Chronic Respiratory Disease," *American Journal of Respiratory Critical Care Medicine*, vol. 198, no. 11 (2018): 1367–74.

[3]*Reviewing the Rising Price of EpiPens, Before the House Committee on Oversight and Government Reform*, 114th Cong., Sept. 21, 2016.

[4]FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* publication is commonly known as the Orange Book. The Orange Book identifies drug products approved by FDA under sections 505(c) and 505(j) of the Federal Food, Drug, and Cosmetic Act. It includes information on certain approved drug products, including patents, active ingredients, and therapeutic equivalence evaluations. 21 U.S.C. § 355(j)(7)(A).

listing patents in the Orange Book.[5] That is, the law instructs FDA to list patent information that sponsors submit as part of their drug applications and does not establish any review or evaluation role for FDA regarding the listing of patents. Therefore, according to FDA, the agency has an administrative role in publishing the patent information submitted by brand name sponsors, but does not independently evaluate it for accuracy or appropriateness, other than to ensure that submission instructions have been followed.

The Orange Book Transparency Act of 2020 includes a provision for us to review Orange Book patent listings for drug-device combination products, including the implications of these listings for generic drugs.[6] In this report, we describe

(1) stakeholder views on how Orange Book patent listings may affect the entry of generic drug-device combination products into the U.S. market;

(2) stakeholder views on FDA's role in listing patents in the Orange Book; and

(3) stakeholder views on changes that could be made to improve the listing of patents in the Orange Book.

To address these objectives, we examined information from a variety of sources, including a review of federal law.[7] We also conducted a literature search and review of studies on device-related patents and their effect on the market entry of generic drug-device combination products. (See app. I for more information on how we conducted the literature review and a list of publications.) We reviewed stakeholders' responses to FDA's formal request for input on the listing of patent information in the Orange Book, which included stakeholder perspectives on how listing certain device-related patents affected the entry of generic drugs into the market, FDA's

[5]See, for example, FDA, *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 Fed. Reg. 36,680 (June 18, 2003).

[6]Pub. L. No. 116-290, § 2(f), 134 Stat. 4889, 4891–92 (2021).

[7]We were unable to obtain a list of all drug-device combination products in the Orange Book because FDA does not separately identify drug-device combination products for which device-related patents may be listed in the Orange Book.

role in listing patents in the Orange Book, and changes that should be made to improve patent listings.[8]

We also interviewed 15 selected stakeholders to obtain their views on how different patents listed in the Orange Book may affect the entry of generic drug-device combination products into the market, the strengths and weaknesses of listing different types of patents in the Orange Book, FDA's role, and proposals to improve patent listings. We selected stakeholders to provide a broad range of perspectives, including national associations representing brand and generic drug sponsors, experts with knowledge of these topics, and advocacy organizations representing patient interests. Among these 15 stakeholders, we reached out to a non-generalizable, judgmental sample of three brand name and three generic drug sponsors that marketed drug-device combination products and who were willing to speak to us on this topic. Although we included a broad range of stakeholders in our review, there may be additional perspectives that we did not capture. We also interviewed FDA officials and officials from the U.S. Patent and Trademark Office on their views on these topics. In addition, we sent FDA a summary of the proposals suggested to us by stakeholders during our interviews; we asked FDA to identify strengths and weaknesses for each proposal.

We conducted this performance audit from December 2021 to March 2023 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

Patent and Drug Approval Process

FDA and the U.S. Patent and Trademark Office are responsible for administering different laws applicable to the drug development process.

- The U.S. Patent and Trademark Office reviews patent applications, including from drug sponsors. If the office grants a patent, other drug

[8]See FDA, *Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments*, 85 Fed. Reg. 33,169 (June 1, 2020).

sponsors are excluded from making, using, or selling the patented formula during the life of the patent, which generally lasts 20 years.

- FDA is responsible for ensuring that both brand and generic drugs marketed in the U.S. are safe and effective. To obtain approval to market a drug, sponsors submit a drug application containing information on the drug components and composition and the manufacturing process and location. Brand name drug sponsors submit data on the drug's safety and effectiveness. For generic drugs, sponsors submit data demonstrating therapeutic equivalence to an approved brand name drug. This includes showing that the generic drug has the same active ingredient, strength, dosage form, and route of administration. A generic drug also must have the same conditions of use and the same labeling as the brand name drug, except for certain permissible labeling differences. In addition to the patent protections granted by the U.S. Patent and Trademark Office, some approved drugs may also be eligible for certain periods of market exclusivity, which may delay FDA's approval of competing drug products.[9] Generic drug sponsors may seek and obtain FDA approval to market their product after applicable patents and periods of market exclusivity for the brand name drug have expired or have been otherwise resolved.[10]

While brand name sponsors typically apply for patents early in the drug development process, they can seek patents for new innovations at any point. For example, early in the drug development process, drug sponsors may apply for patents on the active ingredient or a new combination of known ingredients and may also apply for patents on other aspects of the drug, such as a method of using it or its formulation and composition. Brand name sponsors may also apply for new patents after their drug is marketed. These later patents may be for modifications to the drug

[9]Market exclusivity begins only upon FDA approval of a drug, whereas patents can be issued or expire at any time regardless of a drug's approval status. Patents and periods of market exclusivity may or may not run concurrently, depending on the circumstances.

[10]Under section 505(b)(2) of the Federal Food Drug & Cosmetics Act, applications for new drug products may rely, at least in part, on investigations that were not conducted by the sponsor. 21 U.S.C. § 355(b)(2) (2021). For example, such an application may rely on FDA's finding of safety or effectiveness for an approved product or on published literature in addition to studies conducted by the sponsor. A 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for an approved product listed in the Orange Book must include an appropriate patent certification or statement for each listed patent. Accordingly, FDA officials said the patent listing issues discussed in this report also generally are relevant to certain 505(b)(2) applications.

product or for new uses.[11] Our prior work found that some drug sponsors seek to extend patent protections for existing drugs to extend revenue generation by delaying or limiting the effect of generic competition. Strategies used by brand name sponsors are sometimes referred to as "evergreening."[12]

Listing Patents in the Orange Book

FDA's Orange Book provides both the public and generic drug sponsors with patent and other basic information about approved brand name drugs. As part of the drug approval process, brand name sponsors are required to complete patent declaration forms for certain patents claiming their product.[13] This includes drug substance (active ingredient) patents, drug product (formulation or composition) patents, and method-of-use patents. The forms require specific information on each patent's claims, such as the scope of the activity protected by the patent and its expiration date. For method-of-use patents, FDA requires brand name sponsors to include a description of the specific approved method of use claimed by the patent, which becomes the use code listed in the Orange Book.[14] After a brand name product has been approved, FDA publishes its patent information in the Orange Book.

Requirements for listing patents in the Orange Book have evolved over time. Between 1994 and 2016, FDA published three final rules that further described or revised patent listing requirements.

- In the 1994 final rule, FDA described the requirements for the submission of patent information to the agency, patent certification

[11]A drug sponsor must obtain FDA approval to make any changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product that may relate to safety or effectiveness. 21 C.F.R. § 314.70 (2021).

[12]See GAO, *Drug Industry: Profits, Research and Development Spending, and Merger and Acquisition Deals*, GAO-18-40 (Washington, D.C.: Nov. 17, 2017). Evergreening refers to when brand name sponsors obtain new patents on secondary features of a drug as earlier patents expire, which may extend patent protection past the original 20-year term. Later-filed patents may delay or prevent the entry of generic drugs into the market.

[13]See 21 U.S.C. § 355(b)(1)(A)(viii), (c)(2); 21 C.F.R. § 314.53 (2021). Form FDA 3542a is required to be submitted with new drug applications, amendments, or supplements, and Form FDA 3542 is required to be submitted within 30 days of product approval. Only information in Form FDA 3542 is listed in the Orange Book.

[14]Use codes are brief descriptions of the approved method of use claimed by the patent and should correspond to the method of use described on the drug product's labeling.

requirements for generic drug sponsors, and requirements for patent certification notices.[15]

- In the 2003 final rule, FDA clarified that certain patents should not be listed in the Orange Book—for example, patents claiming a drug package or container.[16] FDA noted that some comments on the proposed rule said that "devices or containers that are integral" to the product should be listed. In response, FDA stated that the key factor in determining whether to list a patent is whether the patent claims the finished dosage form of the approved drug product.
- In the 2016 final rule, FDA adopted a requirement that a brand name drug sponsor's description of its patented method of use included in the Orange Book must contain adequate information to allow a generic drug sponsor to determine whether an opportunity exists to obtain approval to market a generic drug for uses not covered by existing patents.[17]

Generic Drug Sponsors' Use of Orange Book Patent Listings

Generic drug sponsors may use the patent information in the Orange Book to make decisions regarding whether to pursue developing and seeking approval of an application to FDA for approval of that drug. As part of the application, the generic drug sponsor must make a certification for each patent listed in the Orange Book for the relevant brand name drug.[18] There are four types of certifications.

- **Paragraph I certification.** A relevant patent exists that claims the brand name drug or method of using the drug, but no patent information has been filed in the Orange Book for the drug. In this

[15]FDA, *Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions*, 59 Fed. Reg. 50,338 (Oct. 3, 1994).

[16]FDA, *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*, 68 Fed. Reg. 36,676 (June 18, 2003) (codified in relevant part at 21 C.F.R. § 314.53(b) (2021)).

[17]FDA, *Abbreviated New Drug Applications and 505(b)(2) Applications*, 81 Fed. Reg. 69,580 (Oct. 6, 2016).

[18]The approved drug product to which a new generic drug is compared is known as a reference listed drug. For the purposes of this report, we use the term "brand name drug."

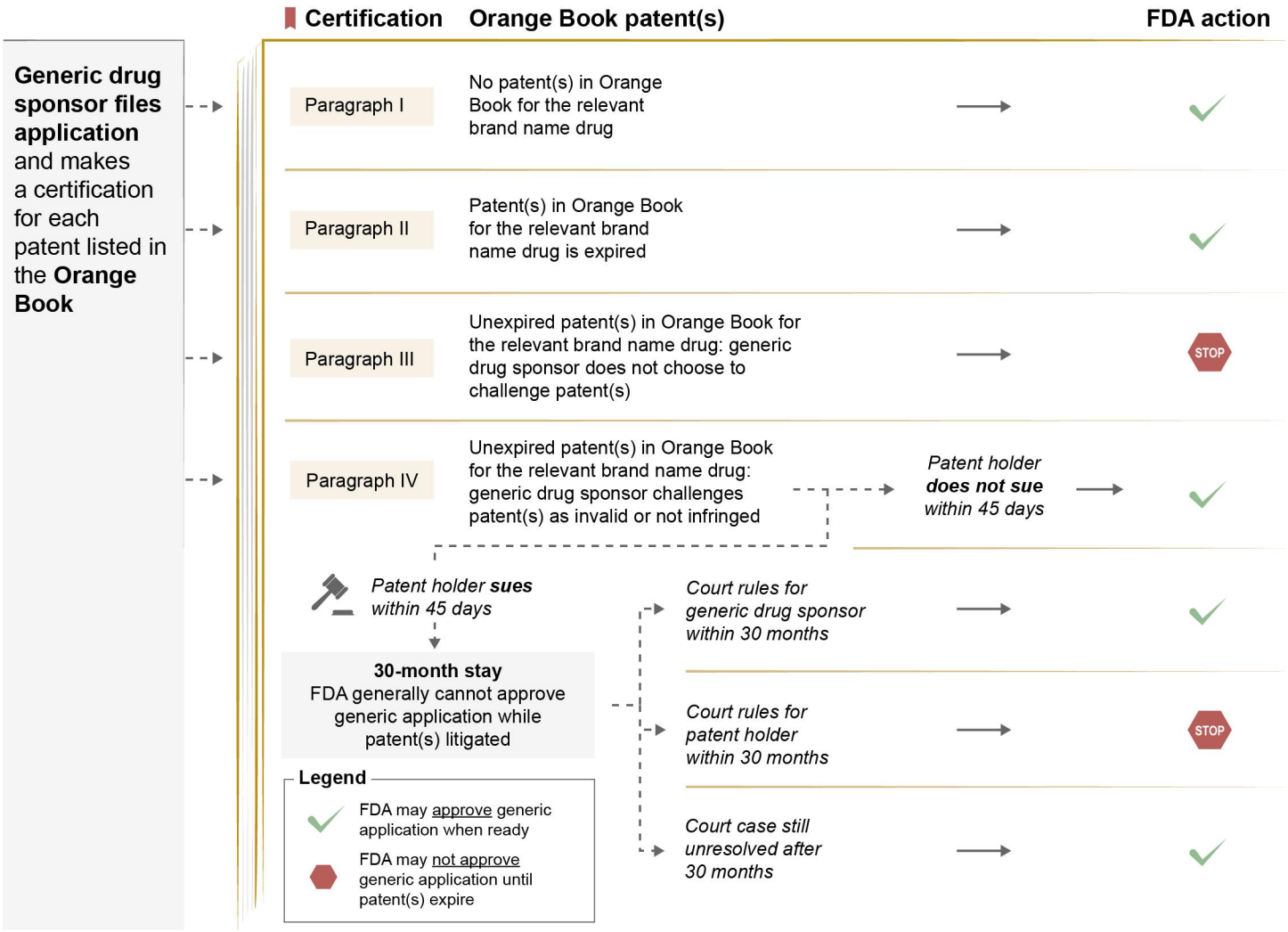
case, FDA can approve the application for the generic drug when it completes its review.

- **Paragraph II certification.** The patent listed in the Orange Book for the brand name drug is expired. In this case, FDA can approve the application for the generic drug when it completes its review.
- **Paragraph III certification.** The patent listed for the brand name drug in the Orange Book that will expire on a certain date, and the generic drug sponsor will wait for approval until that date. In this case, FDA may not approve the application for the generic drug until the patents expire.
- **Paragraph IV certification.** The generic drug sponsor challenges the patent listed in the Orange Book as invalid, unenforceable, or not infringed by the manufacture, use, or sale of the proposed generic drug. When FDA may approve the application in this case depends on several factors, including whether the patent holder chooses to sue for patent infringement within 45 days of the applicant providing notice to the brand name sponsor.[19]

Figure 1 demonstrates how these four different certifications relate to potential FDA actions.

[19]Paragraph II, III, and IV certifications are based on what patents are listed in the Orange Book. Brand name sponsors may also sue generic drug sponsors for patent infringement for patents not listed in the Orange Book.

Figure 1: Generic Drug Application Certifications



Source: GAO analysis of relevant federal laws. | GAO-23-105477

Text of Figure 1: Generic Drug Application Certifications

Generic Drug sponsor files application and makes a certification for each patent listed in the Orange Book.

1) **Paragraph 1**

   a) No patent(s) in Orange Book for the relevant brand name drug

   b) FDA may approve generic application when ready

2) **Paragraph 2**

   a) Patent(s) in Orange Book for the relevant brand name drug is expired

   b) FDA may approve generic application when ready

3) **Paragraph 3**

   a) Unexpired patent(s) in Orange Book for the relevant brand name drug: generic drug sponsor does not choose to challenge patent(s)

   b) FDA **may not** approve generic application until patent(s) expire

4) **Paragraph 4**

   a) Unexpired patent(s) in Orange Book for the relevant brand name drug: generic drug sponsor challenges patent(s) as invalid or not infringed

   b) Patent holder does not sue within 45 days

      i) FDA may approve generic application when ready

   c) Patent holder sues within 45 days

      i) 30-mont stay FDA generally cannot approve generic application while patent(s) litigated

         (1) Court rules for generic drug sponsor within 30 months

            (a) FDA may approve generic application when ready

         (2) Court rules for patent holder within 30 months

            (a) FDA may not approve generic application until patent(s) expire

         (3) Court case still unresolved after 30 months

            (a) FDA may approve generic application when ready

Source: GAO analysis of relevant federal laws. | GAO-23-105477

Notes: The Food and Drug Administration's (FDA) *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book, includes information for certain approved drug products, including patents and therapeutic equivalence evaluations. A generic drug

sponsor may also seek to enter the market prior to certain drug patents expiring by omitting the patented methods of use from the generic drug's labeling. Such labeling is commonly referred to as a "skinny label."

Generic drug sponsors must wait until patents for the brand name drug expire to obtain approval to market a generic drug, unless the sponsor successfully challenges those patents listed in the Orange Book and obtains approval to market more quickly or does not seek approval for a patented use. Generic drug sponsors can initiate a patent challenge through a paragraph IV certification or other processes, as follows.

- **Paragraph IV certification.** A paragraph IV certification indicates to FDA and the brand name sponsor that the generic drug sponsor is challenging a patent listed for the brand name drug. The brand name sponsor then has the option to sue the generic drug sponsor for patent infringement. If that lawsuit occurs within 45 days of notice to the brand name sponsor, FDA generally cannot approve the generic drug application for 30 months (often called a 30-month stay) or until a judgment is entered by the court. If the generic drug sponsor is successful in the litigation, it may bring its drug to market with FDA approval. To incentivize earlier generic competition, the first generic drug sponsor to submit a substantially complete application with a paragraph IV certification can be eligible for a 180-day exclusivity period in which generally no other generic competitor can enter the market.[20] Therefore, a paragraph IV certification is often used by drug sponsors seeking to market the first generic.
- **Patent Trial and Appeal Board.** Within the U.S. Patent and Trademark Office, the Patent Trial and Appeals Board conducts trials that permit parties to challenge the patentability of claims in issued patents.[21] The board offers an alternative to the federal courts to resolve patent disputes. The board is generally required to issue final written decisions on its proceedings within 1 year of the date that the trial begins. Brand name sponsors must notify FDA if any patent claim has been canceled or invalidated by a final decision from the board

[20]There can be more than one first generic applicant—for example, if multiple generic drug sponsors submit their applications with paragraph IV certifications on the same day—in which case the generic drug sponsors can potentially share the 180-day exclusivity period.

[21]The Patent Trial and Appeal Board was established in 2012 under the Leahy-Smith American Invents Act. Pub. Law. No. 112-29, § 7, 125 Stat. 284, 313 (2011) (codified in relevant part at 35 U.S.C. § 6). The board also hears appeals from patent applicants who received adverse decisions from patent examiners.

and request that the patent listing be amended or withdrawn, as appropriate.[22]

- **Patent listing dispute process.** Generic drug sponsors may also submit a statement of dispute with FDA if they dispute the accuracy or relevance of patent information published in the Orange Book, or believe that a brand name sponsor has failed to submit required patent information.[23] FDA then sends this statement to the applicable brand name sponsor, which must then either confirm the patent information is correct and include the signed verification required by the regulations, acknowledge the patent information is incorrect and amend the information, or withdraw the information. Only if the brand name sponsor does the latter will FDA change the patent information in the Orange Book.

Generic drug sponsors may also seek to enter the market prior to certain drug patents expiring by omitting the patented methods of use from the generic drug's labeling. When a patent is only listed as claiming certain approved methods of use, a generic drug sponsor may be able to avoid patent infringement by omitting the patented methods of use from the generic drug's labeling and submitting a section viii statement in its generic drug application.[24] The statement acknowledges that while patent information for a specific method of use has been submitted to FDA, the patent at issue does not claim a use for which the applicant seeks approval.[25]

Generic drug sponsors rely on use codes, which briefly describe the drug's FDA-approved methods of use covered by a patent, to decide how to address method-of-use patents listed in the Orange Book. For example, a brand name drug may be approved for treating multiple

[22]21 U.S.C. § 355(j)(7)(D). Specifically, where any listed patent claim has been canceled or invalidated by the Patent Trial and Appeal Board or a court, and the brand name sponsor determines that the patent no longer meets listing requirements, the sponsor must notify FDA within 14 days of the decision and request that such patent be amended or withdrawn in accordance with the decision.

[23]21 C.F.R. § 314.53(f)(1) (2021).

[24]21 U.S.C. § 355(j)(2)(A)(viii). When a patent is only listed as claiming certain approved methods of use, a generic drug sponsor may be able to avoid patent infringement by omitting the patented methods of use from the generic drug's labeling and submitting a section viii statement in its generic drug application, commonly referred to as a "skinny label".

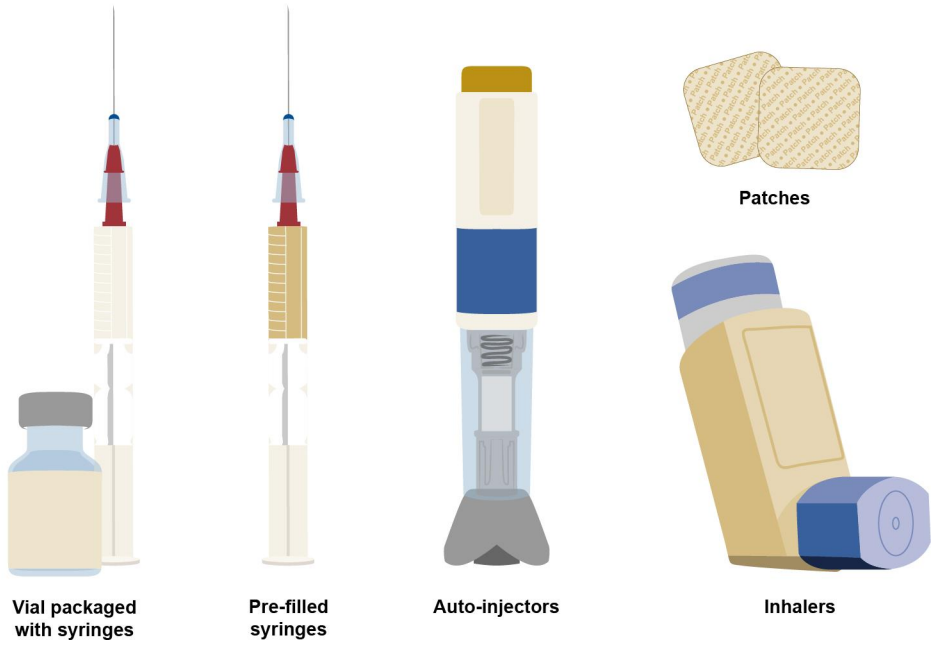
[25]If the generic drug labeling does include an indication or other condition of use that is claimed by a method-of-use patent, the application must include a paragraph II, III, or IV certification with respect to that patent. 21 C.F.R. § 314.94(a)(12)(iii) (2021).

conditions, which are listed in its drug labeling. Although the brand name sponsor may have patented these different uses, some of the patents may have expired. If so, the use codes in the Orange Book would only describe the uses with unexpired patents, which may cover only a few of the conditions that the drug may treat. This indicates to the generic drug sponsor that it could potentially seek to enter the market by excluding the patented methods of use from its product labeling. Instead, the generic drug's labeling would indicate that the generic drug is approved for the brand name drug's uses that are no longer patented. Such labeling is commonly referred to as a "skinny label." FDA determines whether a generic drug application will be rendered less safe or effective by omitting the patented information from the labeling (in which case the generic drug sponsor would not be approved with the proposed skinny label).

Drug-Device Combination Products

Drug-device combination products are products composed of a drug and a device that, for example, are combined to produce a single product (such as a pre-filled syringe), packaged together, or used together to deliver a drug to the patient. These products are highly varied and include pre-filled syringes, auto-injectors, patches, and inhalers. (See fig. 2.)

Figure 2: Examples of Different Types of Drug-Device Combination Products



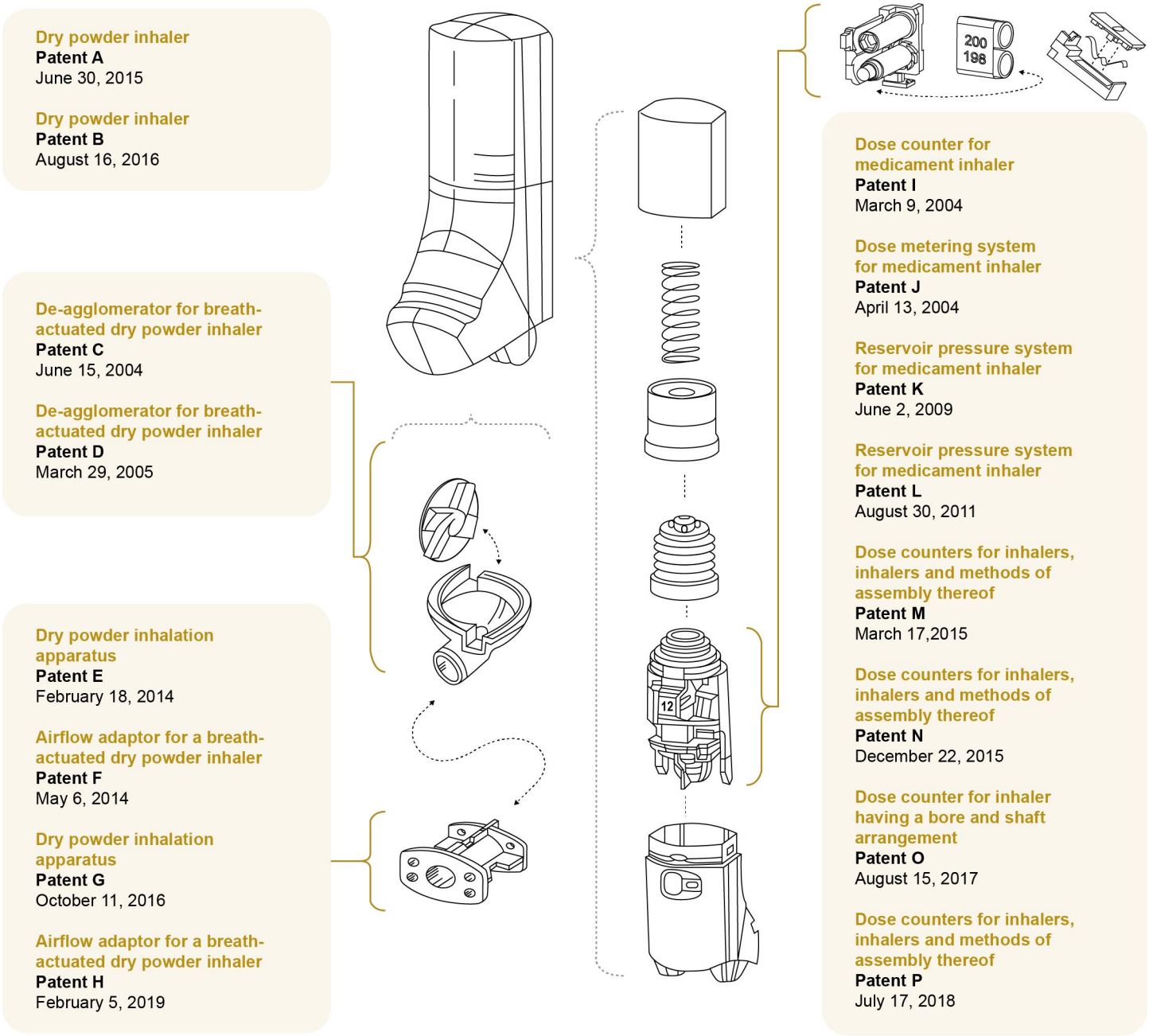
Source: GAO presentation of FDA information. | GAO-23-105477

Brand name sponsors can obtain patents on both the drug and device parts of their drug-device combination products and might include these patents for listing in the Orange Book. Device-related patents for drug-device combination products listed in the Orange Book may claim the active ingredient, drug formulation, a new method of use, or a component of the FDA-approved product such as a dose counter on an inhaler, which measures the amount of medication delivered to the patient.[26] (See fig. 3.) Brand name sponsors can modify the drug or device and obtain additional patents for those changes. These additional patents can also be listed in the Orange Book if they meet the listing requirements. Some researchers have stated that it may be easier to modify and obtain patents on devices than for drugs.[27]

[26]Drug-device combination products include a broad range of products; this report focuses on patents for drug-device combination products that are listed in the Orange Book.

[27]See, for example, T. Stemler, "Minor Advances, Major Consequences: Hatch-Waxman Administers Exclusivity for Drug Delivery Devices," *Mitchell Hamline Law Review*, vol. 46, no. 3 (2020): 655-688.

Figure 3: Example Showing a Drug-Device Combination Product for which Several Patents Are Listed in the Orange Book



Source: GAO presentation of patents listed in the Orange Book, U.S. Patent and Trademark Office. | GAO-23-105477

Text of Figure 3: Example Showing a Drug-Device Combination Product for which Several Patents Are Listed in the Orange Book

- Dry powder inhaler
  Patent A
  June 30, 2015
- Dry powder inhaler
  Patent B
  August 16, 2016
- De-agglomerator for breath-actuated dry powder inhaler
  Patent C
  June 15, 2004
- De-agglomerator for breath-actuated dry powder inhaler
  Patent D
  March 29, 2005
- Dry powder inhalation apparatus
  Patent E
  February 18, 2014
- Airflow adaptor for a breath-actuated dry powder inhaler
  Patent F
  May 6, 2014
- Dry powder inhalation apparatus
  Patent G
  October 11, 2016
- Airflow adaptor for a breath-actuated dry powder inhaler
  Patent H
  February 5, 2019
- Dose counter for medicament inhaler
  Patent I
  March 9, 2004
- Dose metering system for medicament inhaler
  Patent J
  April 13, 2004
- Reservoir pressure system for medicament inhaler
  Patent K
  June 2, 2009
- Reservoir pressure system for medicament inhaler
  Patent L
  August 30, 2011

- Dose counters for inhalers, inhalers and methods of assembly thereof
  Patent M
  March 17,2015
- Dose counters for inhalers, inhalers and methods of assembly thereof
  Patent N
  December 22, 2015
- Dose counter for inhaler having a bore and shaft arrangement
  Patent O
  August 15, 2017
- Dose counters for inhalers, inhalers and methods of assembly thereof
  Patent P
  July 17, 2018

Source: GAO presentation of patents listed in the Orange Book, U.S. Patent and Trademark Office. | GAO-23-105477

Notes: FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book, includes information for certain approved drug products, including patents and therapeutic equivalence evaluations. The figure is meant to illustrate patents a brand name drug sponsor obtained for an inhaler and identified for listing in the Orange Book. It does not necessarily include all patents obtained for the inhaler. Certain patents, such as those related to the manufacturing process or packaging of a drug-device combination product, are to be excluded from listing in the Orange Book. Dates in the figure refer to when the U.S. Patent and Trademark Office granted the patent.

Stakeholder Views Varied on How Orange Book Patent Listings Affect Generic Drug-Device Combination Products

Stakeholders expressed a variety of views on how the Orange Book patent listings affect the entry of generic products into the U.S. market. However, some stakeholders and research suggested factors other than the Orange Book may have a greater effect on market entry of these products.

Stakeholders Had Varied Views on How Elements of the Orange Book Affect the Market Entry of Generic Products

Brand name and generic drug sponsors, experts, advocacy groups, and national associations we interviewed expressed a variety of views on how the Orange Book patent listings affect the entry of generic products into the U.S. market. Specifically, views varied on how and whether the Orange Book's information on relevant patents, device-related patent listings, and use codes affect the entry of generic products.

Information on Relevant Patents

All 15 of our stakeholders agreed that the Orange Book may help generic drug sponsors identify relevant patents when making product development decisions and identified multiple benefits. Specifically, stakeholders from a range of different groups said that the Orange Book patent listings do the following.

- Inform generic drug sponsors of the key patents brand name sponsors may enforce through litigation, which may help generic drug sponsors decide how and when to enter the market with a generic product (10 stakeholders).
- Help generic drug sponsors know which patents to challenge through paragraph IV certifications. Successful challenges can result in a generic drug sponsor having the opportunity to be the first generic product on the market, and therefore, receive the benefit of a 180-day exclusivity period (six stakeholders).
- Help generic drug sponsors determine how to design or innovate to avoid infringing on patents, because the Orange Book listing provides information on all the key patents for a brand name product (five stakeholders).
- Help generic drug sponsors resolve patent disputes early, prior to the entry of their generic products onto the market (four stakeholders).
- May prevent generic drug sponsors from being caught up in unexpected, costly litigation, because the Orange Book patent listings reduce the likelihood that a generic drug sponsor may fail to identify a relevant patent prior to bringing a generic product to the market (three stakeholders).

However, eight stakeholders (generic drug sponsors, advocacy organizations, and experts) highlighted the fact that the Orange Book does not provide information on all patents related to a brand name product that may be important to consider prior to marketing a generic product. Certain patents, such as those on the drug manufacturing process, cannot be listed in the Orange Book. As a result, four of these stakeholders said generic drug sponsors may use other resources, such

as patent attorneys, to help them identify and assess all the patents for an approved product.[28]

FDA officials told us the patent information in the Orange Book helps generic drug sponsors make decisions about when to enter the market with their products, but the information is limited based on what brand name sponsors submit for listing. FDA officials noted that generic drug sponsors are able to use other resources to identify other patents that could be enforced by brand name sponsors. These other resources could help reduce generic drug sponsors' time spent on products that may not be marketable, according to officials. Although the Orange Book is not comprehensive, FDA officials said that it can still provide useful information on relevant patents that generic drug sponsors should consider before seeking approval for a generic product. In addition, officials said the Orange Book includes information that is not found in other resources, such as the date that FDA received patent information from the brand name sponsor for listing in the Orange Book, which informs whether a 30-month stay may be available in the context of a particular application.

Device-Related Patent Listings

There was not consensus among our 15 stakeholders on how or which device-related patent listings in the Orange Book could either delay or facilitate the entry of generic drug-device combination products into the market. Five of our 15 stakeholders thought that listing at least some types of device-related patents could delay the entry of generic drug-device combination products into the market.

- Three stakeholders (two generic drug sponsors and an advocacy organization) said that listing device-related patents that (1) do not claim the active ingredient or drug formulation or (2) are not for devices uniquely tailored for certain drugs can unnecessarily delay the entry of generic drug-device combination products into the market.[29]

[28]Seven of our 15 stakeholders did not identify any factors that limit the Orange Book's ability to provide information on relevant patents to generic drug sponsors.

[29]Device-related patents for drug-device combination products listed in the Orange Book may claim the drug substance (active ingredient), drug product (formulation or composition), or method of use. When discussing their views on device-related patent listings, some stakeholders specifically discussed a particular type of drug product patent (drug formulation patents).

These stakeholders explained that these patents are typically related to a device component or a common device—like a syringe—that can be used with multiple active ingredients and is not necessarily tailored for delivering the specific drug.[30] As a result, listing these patents in the Orange Book may require generic drug sponsors to challenge them to enter the market, even though the device component is not unique to the particular drug. Challenging the patents can delay the entry of generic drug-device combination products into the market through an unnecessary 30-month stay, according to these stakeholders.[31]

- Two stakeholders (an expert and advocacy organization) thought that any device-related patents listed in the Orange Book can unnecessarily delay the entry of generic drug-device combination products into the market. One of these stakeholders noted that device-related patents can lead to unnecessary 30-month stays, which could delay the entry of generic drug-device combination products.

In contrast, nine stakeholders (three brand name sponsors, a generic drug sponsor, three national associations, and two experts) said listing any device-related patent that claimed an FDA-approved product or a component of an approved product (not just the active ingredient or drug formulation) can facilitate the entry of generic drug-device combination products into the market. These stakeholders thought that listing these patents in the Orange Book provides important information on relevant patents, as explained above. One of these stakeholders also said that litigation for Orange Book listed patents is more efficient because most litigation is typically resolved within the 30-month stay, which is usually faster than litigation for non-Orange Book listed patents. However, two stakeholders (a national association and a generic drug sponsor) said

[30]A component of a drug-device combination product may include specific mechanical features of a device, such as a dose counter for an inhaler.

[31]One generic drug sponsor also said that there are cases where a generic drug sponsor may want to market a generic product at risk of infringing patents not listed in the Orange Book because it may have a strong case against such patents. As a result, this stakeholder explained that if there are other nonspecific device-related patents listed in the Orange Book, sponsors will not be able to market their generic product using other certifications (i.e., under paragraphs I, II, or III), in spite of having a potentially strong case against other patents.

that litigation for non-Orange Book patents takes about as long as the 30-month stay.[32]

In addition, some of these stakeholders identified factors that limit any delays caused by listing device-related patents.

- Four stakeholders (a national association, two brand name sponsors, and a generic drug sponsor) noted that patents listed in the Orange Book no longer significantly delay the entry of generic products into the market due to changes in the law that prevent brand name sponsors from obtaining consecutive 30-month stays for products.[33] As a result of these changes, there can be no more than one 30-month stay of approval of a generic drug application.
- Four stakeholders (a national association, a brand name sponsor, a generic drug sponsor, and an expert) said that it is unlikely device-related patents cause additional delays because there are usually other patents that also trigger the 30-month stay. These stakeholders said it is rare for a brand name drug-device combination products to have only device-related patents listed in the Orange Book. In a generic drug application, a generic drug sponsor must make a paragraph II, III, or IV certification for each patent listed in the Orange Book. According to these stakeholders, there are usually other patents, in addition to the device-related patents, for which the generic drug sponsor makes a paragraph IV certification and triggers the 30-month stay. One of these stakeholders said this makes it difficult to know what kind of patents are delaying the entry of generic products into the market.

FDA officials told us they do not have enough information to assess how device-related patent listings affect the entry of generic drug-device combination products into the market. They noted that FDA does not separately track device-related patents listed in the Orange Book, and brand name sponsors are not required to submit information to FDA identifying which patents are related to the device part of a drug-device

[32]In a 2002 report that discussed 30-month stays, the Federal Trade Commission also concluded that the 30-month stay typically approximated the duration of a patent lawsuit and the average time FDA needed to review and approve a generic drug. See Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (July 2002).

[33]See Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, § 1101, 117 Stat. 2066, 2448 (2003) (codified at 21 U.S.C. § 355(j)(5)(B)(iii)). See also 81 Fed. Reg. 69,580 (Oct. 6, 2016) (codified in relevant part at 21 C.F.R. 314.107(b)(3)(i) (2021)).

combination product. In addition, they noted that FDA's role in overseeing the Orange Book does not include analyzing device-related patent listings.

Use Codes

Some of the 15 stakeholders we spoke with said that ambiguous or overly broad use codes listed in the Orange Book delayed the entry of generic products into the market, while other stakeholders did not identify this as a problem or have a perspective to share.[34] The concerns identified were not specific to drug-device combination products, but may include them.

- Seven stakeholders (two generic drug sponsors, two national associations, two experts, and an advocacy organization) said generic drug sponsors experience confusion or unnecessary delays in entering the market due to overly broad or ambiguous use codes. Specifically, they said the use codes listed in the Orange Book do not always align with the information brand name sponsors include in other places, such as in method-of-use patents or FDA approved drug labeling. Generic drug sponsors may therefore be uncertain of their ability to submit an application with a skinny label.
- Five stakeholders (two brand name sponsors, a generic drug sponsor, a national association, and an advocacy organization) did not identify any challenges regarding ambiguous or overly broad use codes listed in the Orange Book. One of these stakeholders thought that the use codes were generally specific.
- Two stakeholders (experts) said they did not have enough knowledge on use codes to determine whether they affected the entry of generic products into the market.

FDA officials told us that ambiguous and overly broad use codes in the Orange Book may delay the entry of generic products into the market. They noted recent court cases that highlighted how ambiguous or overly

[34]One stakeholder (a brand name sponsor) did not provide perspectives on use codes when asked by GAO.

broad use codes could limit opportunities for generic drug sponsors to develop skinny labels for their products.[35]

Some Stakeholders and Research Suggested Factors Other than the Orange Book May Have a Greater Effect on Market Entry of Generic Drug-Device Combination Products

Some stakeholders, the U.S. Patent and Trademark Office, and six articles we reviewed identified factors related to practices of brand name sponsors that may affect the entry of generic drug-device combination products more than Orange Book patent listings.

Obtaining Secondary Patents

Four stakeholders (a generic drug sponsor, two experts, and an advocacy organization) said that the U.S. Patent and Trademark Office sometimes grants certain patents, such as those for minor changes to the drug, that create barriers for generic entry. They also said these patents play a larger role in delaying the entry of generic products into the market than Orange Book patent listings.[36] According to these stakeholders, certain patents for minor innovations unnecessarily extend patent protections to brand name sponsors of drug-device combination products.

Six articles we reviewed raised similar issues. These articles found that device-related patents delayed the entry of generic drug-device combination products into the market, due more to the protections provided to brand name sponsors for obtaining patents than because those patents were listed in the Orange Book. For example, one article

[35]For example, see *GlaxoSmithKline LLC v. Teva Pharmaceuticals USA, Inc.*, 7 F.4th 1320 (Fed. Cir. 2021). The court found that Teva infringed a method-of-use patent covering a GSK product, even though Teva had marketed its generic drug with a skinny label drafted by FDA based on use codes provided by GSK. In June 2022, Teva appealed this decision to the U.S. Supreme Court. Petition for Writ of Certiorari, *Teva Pharmaceuticals USA, Inc. v. GlaxoSmithKline LLC*, No. 23-37 (U.S. petition filed July 11, 2022).

[36]See GAO, *Intellectual Property: Patent Office Should Define Quality, Reassess Incentives, and Improve Clarity*, GAO-16-490 (Washington, D.C.: June 30, 2016). This report found, through a survey of patent examiners, that 70 percent of the population of patent examiners reported not having enough time to complete a thorough patent examination given a typical workload. The report also found that this and other factors created an environment where some issued patents may not meet patentability standards.

found that, of the 49 drug-device combination products the authors reviewed, 26 products had a device-related patent expiring later than patents on the active ingredient. These device-related patents added a median extension of 4.7 years to the drug-device combination products' patent protections.[37] Another article also noted that patents may play a larger role in delaying the entry of certain generic drug-device combination products than for others. Specifically, it found that patents delayed the market entry of generic drug-device combination products more for those that use inhalers than for those that use nebulizers (a type of drug delivery device for inhaled drugs used to treat asthma and other conditions), which the researchers partially attributed to differences in patent claims and brand name sponsors' strategies for defending them.[38]

Shifting Old Active Ingredients to New Devices

Two stakeholders (an expert and an advocacy organization) said that brand name sponsors may delay the entry of generic drug-device combination products when they shift old active ingredients to new devices and, in some cases, remove their older products from the market. For example, one advocacy organization said brand name sponsors may pull their old drug-device combination products with expired patents off the market once they develop and market new devices for the original active ingredient. This makes it difficult for the generic drug sponsor to

[37]R.B. Beall, J.W. Nickerson, W.A. Kaplan, and A. Attaran, "Is Patent 'Evergreening' Restricting Access to Medicine/Device Combination Products?" *PLoS One*, vol. 11, no. 2 (2016): e0148939.

[38]W.B. Feldman, D. Bloomfield, R. F. Beall, and A. S. Kesselheim, "Brand Name Market Exclusivity for Nebulizer Therapy to Treat Asthma and COPD," *Nature Biotechnology*, vol. 40, no. 9 (2022): 1319–1325.

The article describes how inhalers are generally packaged with the medication (as a single product or packaged together with the drug), while nebulizer devices are generally sold separately from the drugs that they deliver. According to the article, inhalers are generally more expensive as well. The researchers attribute the difference in the effect of patents on the brand name sponsors' strategies. Specifically, brand name sponsors of nebulizers may have weaker patent claims that are vulnerable to being challenged by generic drug sponsors and may use fewer resources to defend these patents than brand name sponsors of inhalers.

access the older device to conduct important tests to establish therapeutic equivalence for FDA approval, according to the stakeholder.[39]

FDA Coordination with U.S. Patent and Trademark Office

The Food and Drug Administration (FDA) and the U.S. Patent and Trademark Office have announced plans to better coordinate to improve each agency's processes, including sharing expertise that will allow the office to better assess applications for new patents. In September 2021, in response to an executive order, FDA sent a letter to the U.S. Patent and Trademark Office identifying concerns about the issuing of patents that hinder competition in the U.S. drug market and offering training and information that might help the office to better determine whether pharmaceutical products reflect a patentable invention. In July 2022, the U.S. Patent and Trademark Office responded to FDA, saying that it would take steps to protect against patenting of incremental and obvious changes to drugs, provide additional time and resources for examiners reviewing patent applications, and collaborate with FDA to develop new policies. In November 2022, the U.S. Patent and Trademark Office in collaboration with the FDA issued a Federal Register notice soliciting public comment on the issues and initiatives described in the exchange of letters between the two agencies and announcing a joint listening session for public comment.

Source: FDA and the U.S. Patent and Trademark Office. | GAO-23-105477

Officials from the U.S. Patent and Trademark Office also said that brand name sponsors may take advantage of state drug substitution laws when withdrawing and replacing their older products in the market. Specifically, officials said that some states prevent pharmacists from substituting a new product prescribed by a doctor with a generic of the older product unless it has been found to be bioequivalent to the new product, which an older generic may not be, even if it has the same active ingredient.[40]

Two articles we reviewed found that when brand name sponsors shift old ingredients to new devices, it may prevent generic competition. For example, one of these articles found that this practice led to a median of 28 years of protection from generic competition after initial FDA approval for brand name sponsors of 14 inhalers approved from 1986 to 2020.[41]

In a letter to the U.S. Patent and Trademark Office, FDA officials also discussed similar factors related to brand name sponsor practices that may affect the entry of generic products into the market. Specifically, officials raised questions about whether brand name sponsors may be obtaining patents for changes to a product or switching the market to new products that do not have much additional therapeutic benefit to patients, and therefore unnecessarily delay the entry of generic products.[42] FDA

[39]A generic drug is considered to be therapeutically equivalent to a brand name drug if it has the same active ingredient, route of administration, dosage form, and strength, and is bioequivalent to the brand name drug. To be bioequivalent, a generic drug generally needs to deliver the same amount of active ingredient in the same amount of time as the brand name drug.

[40]Changes to the device in the brand name drug-device combination product may sometimes require the generic drug sponsor to do additional testing of its product to receive FDA approval, according to FDA officials.

[41]W.B. Feldman, D. Bloomfield, R. F. Beall, and A. S. Kesselheim, "Patents and Regulatory Exclusivities On Inhalers For Asthma And COPD, 1986–2020," *Health Affairs*, vol.41, no. 6 (2022): 10-1377.

[42]In July 2021, President Biden issued an executive order on promoting competition in the American economy, which identified the underlying role of the patent system in delaying generic drug competition and directed FDA to write a letter to the U.S. Patent and Trademark Office to describe and enumerate its concerns about patent practices that may be delaying generic entry. See Exec. Order No. 14036, *Promoting Competition in the American Economy*, 86 Fed. Reg. 36987 (July 9, 2021).

plans to coordinate with the U.S. Patent and Trademark Office to review these questions further. (See side bar.)

Stakeholders Had Differing Views on the Effect of FDA's Role in Listing Patents in the Orange Book and the Sufficiency of Agency Guidance

FDA stated that the ministerial role it has taken makes it possible to quickly update information in the Orange Book, but limits the agency's ability to screen patent information submitted by brand name sponsors for listing in the Orange Book. Stakeholders we interviewed had differing views about the implications of FDA's role, including on the sufficiency of guidance provided to drug sponsors.

Stakeholder Views Differed on the Appropriateness and Effect of FDA's Role

FDA officials have stated that Congress did not intend it to undertake anything other than a "purely ministerial" role with respect to the listing of patents in the Orange Book. That is, the law instructs FDA to list patent information that sponsors submit as part of their drug applications and does not establish any review or evaluation role for FDA regarding the listing of patents. FDA's role has also been validated in several court cases.[43] In addition, FDA officials stated that they do not believe FDA has the necessary resources to evaluate the listings in the Orange Book. FDA officials said the brand name sponsor is responsible for evaluating whether a patent meets the requirements for listing, because doing so requires an interpretation of the claim, which can be the subject of litigation, they said.

Thirteen of the 15 stakeholders we spoke with expressed differing views about the appropriateness and effects of FDA's ministerial role in publishing patent listings in the Orange Book.[44] Of these 13 stakeholders, six (national associations, brand name sponsors, a generic drug sponsor,

[43]See, for example, *aai Pharma Inc.* v. *Thompson*, 296 F.3d 227, 242–43 (4th Cir. 2002) (holding that FDA's interpretation of its statutory responsibility for Orange Book listings as purely ministerial was reasonable), cert. denied, 538 U.S. 923 (2003); *Am. Bioscience, Inc.* v. *Thompson*, 269 F.3d 1077, 1084 (D.C. Cir. 2001) (noting FDA's longstanding policy to administer the Hatch-Waxman Amendments in a ministerial fashion).

[44]The remaining two stakeholders did not express an opinion about FDA's ministerial role.

and an expert) stated that FDA's ministerial role is appropriate for ensuring quality information in the Orange Book. Four of the six stakeholders said FDA lacks the resources or expertise to review the patents submitted by brand name sponsors. One of these stakeholders stated that, although FDA employs lawyers with patent law experience, the agency would need to greatly increase its number of professionals with relevant expertise if it were to conduct assessments of Orange Book listings. Another stakeholder noted that FDA could face legal action if it begins making determinations as to the appropriateness of patents listed in the Orange Book, as this expertise and authority lie with the U.S. Patent and Trademark Office. Another stakeholder noted that FDA's ministerial role has not resulted in a significant number of improper patent listings in the Orange Book.

The other seven stakeholders (advocacy groups, generic drug sponsors, and experts) stated that FDA should take a more active role with regard to patents listed in the Orange Book. These stakeholders said that FDA should better enforce the Orange Book listing requirements, monitor patent listings for accuracy and timeliness, and be more active in patent disputes. One advocacy group noted that FDA could better ensure that listed patents meet the requirements for listing without going so far as to interpret patents or assess their validity. Specifically, this group said that FDA could better referee Orange Book listings by conducting an initial review to determine if the patent submissions meet listing requirements—a process that could trigger FDA to ask for clarification from brand name sponsors rather than relying on third parties to raise concerns through the courts. One expert suggested that FDA could work with the U.S. Patent and Trademark Office to review patents—particularly for drug-device combination products—to ensure they are suitable for Orange Book listing. A generic drug sponsor and an advocacy group also stated that FDA could take a more active role to ensure the use codes submitted by brand-name sponsors for their method-of-use patents align with the information on the drug's FDA-approved label.

Most Stakeholders Cited a Lack of Criteria for Orange Book Patent Listings

As we described above, FDA has issued three final rules—in 1994, 2003, and 2016—to provide clarity to address industry confusion about listing requirements for drug-device combination products and to improve the accuracy of use codes. However, 12 of the 15 stakeholders we interviewed reported that FDA's patent listing guidance has been

insufficient for determining which device-related patents should be listed in the Orange Book. These 12 stakeholders represented each category: brand name and generic drug sponsors, advocacy organizations, experts, and national associations. See table 1 for a sample of stakeholder comments related to FDA guidance on patent listings for drug-device combination products. In addition, beginning in 2005, four brand name sponsors submitted formal requests to FDA for clarification on which device-related patents to list in the Orange Book. (See text box.)

Table 1: Examples of Stakeholder Feedback Concerning Areas of Insufficient Guidance for Orange Book Patent Listings

Example of stakeholder feedback
An expert stated that the Food and Drug Administration's (FDA) guidance has evolved over time, but is still lacking. The stakeholder said that FDA has not weighed in on the role of device patents in the Orange Book, and the courts have recently done so in place of FDA.[a] The stakeholder added that it would be valuable if FDA could provide more guidance on patent listings to decrease the need for judicial involvement.
A national association said that the main concern among its members is the legal uncertainty around which device patents to list in the Orange Book, and that this is a source of frustration since the question has been pending for many years. The stakeholder added that some brand name sponsors are concerned that recent court rulings, in the absence of FDA guidance, have exposed them to anti-trust litigation.
A brand name sponsor stated that device patents are an area where there is uncertainty about which patents should be included, and that FDA has not provided any specific guidance on listing these patents.
A generic drug sponsor expressed the concern that, because of the lack of FDA guidance on patent listing, brand-name drug sponsors tend to list more patents than might be appropriate.
An advocacy organization stated that the lack of guidance on which device-related patents to include in the Orange Book provides brand name sponsors the ability to prolong their market exclusivities by listing patents that should not be included in the Orange Book.

Source: GAO interviews with key stakeholders. | GAO-23-105477

[a]See, for example, *In re: Lantus Direct Purchaser Antitrust Litig.*, 950 F.3d 1 (1st Cir. 2020) (holding that a brand name sponsor had improperly listed a patent in the Orange Book for a component of its injector pen because the component did not claim the drug ingredient or the device).

Drug Sponsors' 2005 Requests for FDA Guidance

For some drug sponsors, the Food and Drug Administration's (FDA) 2003 final rule, which provided clarification regarding which patents should be listed in the Orange Book, did not answer certain questions about which patents for drug-device combination products sponsors should submit to FDA. Over a period of years beginning in 2005, four brand name sponsors formally requested that the agency issue clarifying guidance in the form of an advisory opinion. The drug sponsors described in their petitions challenges with reconciling FDA's interpretation of what constitutes a drug product with FDA's industry guidance and the 2003 final rule. For example, prior FDA industry guidance for inhalers and nasal sprays considered protective packaging to be integral to the drug product. Although FDA commented in the 2003 rule that patents integral to the drug product should be listed in the Orange Book, the rule also stated that packaging and containers are distinct from the drug product and fall outside the requirements for patent submission. Additionally, three of the four brand name sponsors sought clarity regarding whether patents for pre-filled drug delivery devices should be listed even if those patents do not claim the drug product.

FDA responded to the four brand name sponsors in 2020, 15 years after the first request for an advisory opinion was submitted. In its response, FDA denied the drug sponsors' requests and stated that the topics raised by the four drug sponsors should be examined as part of a broader effort to seek comment on the subject of patent listings in the Orange Book. As part of its response, FDA invited each drug sponsor to submit comments to FDA's public docket through a Federal Register notice published on June 1, 2020.

Source: GAO analysis of drug sponsor and FDA correspondence. | GAO-23-105477

Stakeholders Proposed a Variety of Changes to Improve or Clarify Orange Book Patent Listings, and FDA Noted Limitations

Stakeholders identified 13 proposals that FDA or others could implement to improve the quality of Orange Book patent listings. (See app. II for the proposals.) In addition, most stakeholders said FDA should clarify which device-related patents should be listed in the Orange Book, but they had widely different suggestions on what the criteria should be for listing these patents. While FDA identified limitations to some of these proposals, it also noted that it expects to consider others.

Stakeholders Proposed Changes to Improve the Quality of Orange Book Patent Listings; FDA Identified Limitations for Some Proposals

Stakeholders we interviewed identified proposals that they thought could improve the quality of patent listings or help generic products enter the market. These 13 proposals varied greatly.[45] For example, one proposal related to having FDA provide additional information in the Orange Book on method-of-use patent claims to better assist generic drug sponsors in entering the market using skinny labels. Another proposal related to having an independent panel review patent listings to ensure they were appropriate and valid. These 13 proposals came from 14 of the 15 stakeholders we interviewed, including generic drug sponsors, advocacy organizations, and national associations, with some stakeholders supporting multiple proposals. (See app. II for a list of the thirteen changes proposed by stakeholders.)

FDA officials preliminarily reviewed these proposals at our request and identified multiple limitations to implementing them. Of the 13 proposals, FDA officials preliminarily identified limitations to 11 that would make them challenging to implement. These limitations included the time and

[45]Although we included a broad range of stakeholders in our review, there may be additional perspectives that we did not capture. With respect to those comments and proposals submitted in response to FDA's 2020 public docket, FDA officials noted the agency continues to consider these comments and proposals and that the preliminary feedback presented here is not complete and does not reflect the agency's views on their merits.

resources FDA would need to implement the change, potential for legal challenges, and FDA's limited role in overseeing patent listings.

FDA officials acknowledged that three of the 13 proposals are similar to or were raised in response to their 2020 request for public comments on the listing of patent information in the Orange Book.[46] Specifically, FDA officials acknowledged their awareness of the following proposals: (1) linking the Orange Book to other FDA data, (2) providing additional guidance on eligibility for listing device-related patents, and (3) having periodic, regular public meetings to discuss listing requirements.

FDA plans to consider whether additional changes need to be made to the Orange Book as part of its agency-wide efforts to modernize the Orange Book. In response to the public comments that FDA received, the agency is also establishing a multidisciplinary workgroup to review Orange Book patent listings.[47] FDA said this workgroup would evaluate whether additional clarity is needed regarding the types of patents, patent information, or other information that should be included in the Orange Book, or removed from it. As of December 2022, FDA officials had not determined which specific issues the workgroup may examine. In addition, FDA officials said competing priorities and resource challenges had prevented them from developing timelines for establishing the workgroup and identifying the workgroup's members, but noted that they hoped to make these decisions soon.

Stakeholders Identified a Variety of Criteria to Clarify Which Device-Related Patents Should Be Listed in the Orange Book; FDA May Consider If Guidance Is Needed

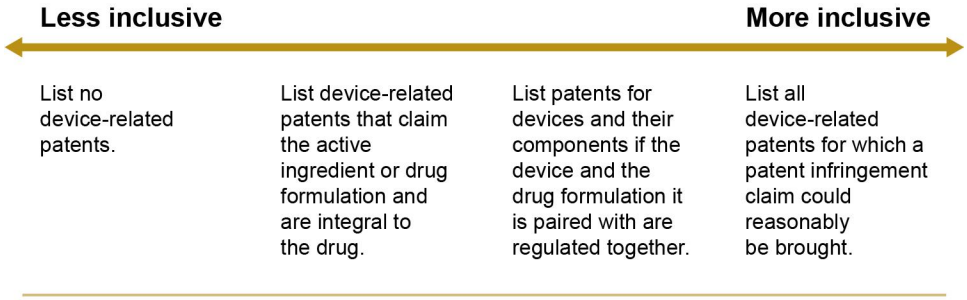
All of our stakeholders also identified a variety of criteria that they thought may clarify which device-related patents should be listed in the Orange Book. However, the listing criteria that stakeholders identified varied widely and were based on their differing perspectives of current FDA patent listing requirements, or how these patents may affect the entry of generic drug-device combination products into the market. (See fig. 4.) For example, stakeholders that identified more inclusive criteria believed

[46]See FDA, *Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments*, Docket No. FDA-2020-N-1127, 85 Fed. Reg. 33,169 (June 1, 2020).

[47]FDA announced in December 2021 that it would create a multidisciplinary workgroup in response to comments it obtained through a 2020 public docket.

that more device-related patents should be listed. They typically believed a more comprehensive listing of device-related patents could facilitate the entry of generic drug-device combination products into the market by providing generic drug sponsors with information on relevant patents that brand name sponsors may enforce. In contrast, stakeholders that identified less inclusive criteria believed that fewer device-related patents should be listed. They generally said that listing device-related patents delays the entry of generic drug-device combination products into the market because it could result in unnecessary 30-month stays or litigation. One stakeholder also did not think incremental device-related changes should receive the same protections from generic competition as other innovations.

Figure 4: Examples of the Variety of Criteria Stakeholders Identified to Clarify Device-Related Patent Listing Requirements in the Orange Book



Source: GAO summary of information provided by selected stakeholders. | GAO-23-105477

Text of Figure 4: Examples of the Variety of Criteria Stakeholders Identified to Clarify Device-Related Patent Listing Requirements in the Orange Book

Examples of Orange Book listing criteria proposed by stakeholders (from less inclusive to more inclusive:

- List no device-related patents.(Less inclusive)
- List device-related patents that claim the active ingredient or drug formulation and are integral to the drug.
- List patents for devices and their components if the device and the drug formulation it is paired with are regulated together.
- List all device-related patents for which a patent infringement claim could reasonably be brought. (More inclusive)

Source: GAO summary of information provided by selected stakeholders. | GAO-23-105477

Note: The Food and Drug Administration's (FDA) *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book, includes information for certain approved drug products, including patents and therapeutic equivalence evaluations. We did not do an independent assessment of the criteria proposed by stakeholders.

One article in our literature review raised topics similar to those raised by our stakeholders in describing the pros and cons for listing device-related patents in the Orange Book.[48] This article noted that while listing device-related patents in the Orange Book may benefit generic drug sponsors by providing information on relevant patents, the benefit may be minimal. The Orange Book does not have comprehensive information on patents, and FDA has excluded the listing of certain patents, such as those related to the manufacturing process of the drug. As a result, generic drug sponsors often use other resources in addition to the Orange Book to review all the relevant patents for a given product. The article explained that since these other resources also provide information to generic drug sponsors of relevant patents, any patent listing in the Orange Book may be redundant of information found through these other resources.

FDA officials noted that one problem with more inclusive criteria is that it could worsen the issue of "patent thickets." This is when brand name sponsors submit patents for listing that do not extend the total patent term but may have the effect of intimidating and dissuading potential generic drug sponsors from seeking approval for a generic product. FDA officials said they have seen a significant increase in the total number of patents being submitted for listing in the Orange Book over the years, with 30 or 40 patents submitted for some new drug-device combination products like inhalers. FDA plans to consider whether additional clarity is needed regarding the types of patents that should be listed in the Orange Book as part of the agency's multidisciplinary workgroup. However, officials expected that developing and implementing any criteria would involve a significant amount of resources.

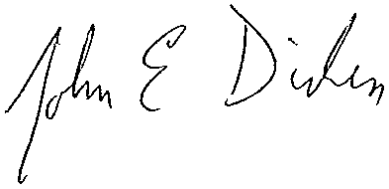
Agency Comments

The Department of Health and Human Services provided technical comments on a draft copy of this report, which we incorporated as appropriate.

[48]S. R. Kestle, P. E. Miller, and D. K. Mroz, "Should Drug-Delivery Device Patents Be Listed in the Orange Book?" *American Pharmaceutical Review* (July/August 2017).

We are sending copies of this report to the appropriate congressional committees, the Secretary of Health and Human Services, the Commissioner of the Food and Drug Administration, and other interested parties. In addition, the report is available at no charge on the GAO website at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or at dickenj@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix III.



John E. Dicken
Director, Health Care

Appendix I: Publications Addressing FDA's Orange Book, Market Entry of Generic Drug-Device Combination Products, and FDA's Oversight Role

The Food and Drug Administration (FDA) is required to publish information on patents for approved brand name drugs in a publication known as the Orange Book.[1] We conducted a literature review on the effects of the Orange Book and patents on the market entry of generic drug-device combination products. We identified literature published from January 2010 through September 2022 by searching research databases, including SCOPUS, PubMed, CINHAL and HeinOnline. Our literature search focused on finding scholarly materials, working papers, government reports, congressional materials, think tank, and trade articles. Also, we identified additional publications through citations in publications identified in the literature search, periodic scanning of websites of organizations that cover topics related to this objective, and referrals of articles from stakeholders to whom we spoke.

In total, we reviewed 67 publications and identified nine that were relevant to our review. Specifically, we determined that these nine were relevant because they addressed one or more factors related to how device-related patents may affect the entry of generic drug-device combination products or the effect of FDA's oversight role on the quality of patent information in the Orange Book. We did not conduct an independent review or assessment of data reported in these publications.

Beall, Reed F., Jason W. Nickerson, Warren A. Kaplan, and Amir Attaran. "Is Patent 'Evergreening' Restricting Access to Medicine/Device Combination Products?" *PLoS One*, vol. 11, no. 2 (2016).

[1]FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* publication is commonly known as the Orange Book. The Orange Book identifies drug products approved by FDA under sections 505(c) and 505(j) of the Federal Food, Drug, and Cosmetic Act. It includes information on certain approved drug products, including patents and therapeutic equivalence evaluations. 21 U.S.C. § 355(j)(7)(A).

Beall, Reed F., and Aaron S. Kesselheim. "Tertiary Patenting on Drug–Device Combination Products in the United States." *Nature Biotechnology*, vol. 36, no. 2 (2018): 142-145.

Eisenberg, Rebecca S., and Daniel A. Crane. "Patent Punting: How FDA and Anti-Trust Courts Undermine the Hatch-Waxman Act to Avoid Dealing with Patents." *Michigan Telecommunications and Technology Law Review*, vol. 21, no.2 (2015): 197-262.

Feldman, William B., Doni Bloomfield, Reed F. Beall, and Aaron S. Kesselheim. "Patents and Regulatory Exclusivities on Inhalers for Asthma and COPD, 1986–2020." *Health Affairs*, vol. 41, no. 6 (2022).

Feldman, William B., Doni Bloomfield, Reed F. Beall, and Aaron S. Kesselheim. "Brand Name Market Exclusivity for Nebulizer Therapy to Treat Asthma and COPD." *Nature Biotechnology*, vol. 40 (2022):1319–1325.

Kumar, Neeraj. "Listing of Drug Delivery Device Patents in the USFDA's Orange Book: What the Patent Drafters Can Learn from Lantus® soloSTAR® Device Lawsuit?" *Expert Opinion on Therapeutic Patents*, vol. 31, no. 12 (2021): 1075-1077.

Kestle, Sydney R., Paula E. Miller, and David K. Mroz. "Should Drug-Delivery Device Patents Be Listed in the Orange Book?" *American Pharmaceutical Review*, July/August 2017.

Sherkow, Jacob S., and Patricia J. Zettler. "EpiPen, Patents, and Life and Death." *New York University Law Review Online*, vol. 96 (2021): 164-180.

Stemler, Taylor. "Minor Advances, Major Consequences: Hatch-Waxman Administers Exclusivity for Drug Delivery Devices." *Mitchell Hamline Law Review*, vol. 46, no. 3 (2020): 655-688.

Appendix II: Thirteen Stakeholder Proposals to Improve Orange Book Patent Listings, and Responses from FDA

Stakeholders identified 13 proposals to either improve existing elements of the Orange Book, such as its ability to provide information on relevant patents, or address challenges they identified, such as the ambiguity regarding patent listing practices for device-related patents.[1] Food and Drug Administration (FDA) officials acknowledged they were aware of three of the proposals because they are similar to or were raised in response to the agency's 2020 request for public comment on the listing of patent information in the Orange Book.[2] FDA officials identified several limitations for implementing 11 of the 13 proposals that could mitigate their potential benefits. Below are summaries of stakeholder views on the proposals and preliminary considerations that FDA officials noted regarding the potential effects of these proposals.[3]

Link the Orange Book to other FDA data.

- **Stakeholder proposal.** One advocacy organization suggested that FDA should link the Orange Book to different FDA databases like the National Drug Code Directory or Drugs@FDA. Generic drug sponsors often use information from these other FDA databases to help them make product development decisions and determine whether it is feasible for them to enter the market. As a result, the advocacy organization thought that by linking these data sources to the Orange

[1]The Food and Drug Administration's (FDA) *Approved Drug Products with Therapeutic Equivalence Evaluations* publication is commonly known as the Orange Book. The Orange Book identifies drug products approved by FDA under sections 505(c) and 505(j) of the Federal Food, Drug, and Cosmetic Act. It includes different information on certain approved drug products, including patents and therapeutic equivalence evaluations. 21 U.S.C. § 355(j)(7)(A).

[2]See FDA, *Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments*, 85 Fed. Reg. 33,169 (June 1, 2020).

[3]Although we included a broad range of stakeholders in our review, there may be additional perspectives that we did not capture.

Book, it would make it easier for generic drug sponsors to access the information.

- **FDA officials' response.** FDA officials were not certain if the benefits of this proposal would outweigh its disadvantages. While officials said that linking the Orange Book to different databases could be beneficial to generic drug sponsors, it could also be labor intensive for the agency to implement, depending on the type and accessibility of the information to be linked. FDA officials also acknowledged that they were aware of this proposal because it was similar to a comment FDA received in response to its 2020 request for public comments on the listing of patent information in the Orange Book.

Create a separate resource identifying all drug product patents.

- **Stakeholder proposal.** An advocacy organization and expert suggested that FDA require brand name sponsors to list all the patents they have for a product in a resource that is separate from the Orange Book. Patents that are not currently listed in the Orange Book, like patents on the manufacturing process, could be included in this separate list. The advocacy organization said that the Orange Book plays an important role in promoting transparency, but it also links any listed patent to a potential 30-month stay. If brand name sponsors had to list all patents for a drug product in a resource that is separate from the Orange Book, it would still promote transparency while mitigating the potential for unnecessary delays to generic entry, according to this stakeholder.
- **FDA officials' response.** FDA officials said that there are significant time and resource constraints for this proposal that outweigh its benefits. According to officials, this new resource might be beneficial to generic drug sponsors if it is accurate because it would mitigate time spent reviewing patent information. However, if FDA had to create this separate list, it would divert a significant amount of agency resources from other work. It would also create a new burden on brand name sponsors since they would need to submit patent information for this new resource in addition to the Orange Book.

Provide more guidance on device-related patent listings.

- **Stakeholder proposal.** Thirteen stakeholders (brand name and generic drug sponsors, national associations, experts, and advocacy groups) suggested that FDA should provide guidance on which patents should be listed in the Orange Book for drug-device combination products. One stakeholder suggested that FDA should

use easy-to-apply criteria because the current requirements are unclear.[4] They said that the lack of additional guidance from FDA has led brand name sponsors to rely on judicial decisions to determine which patents to list in the Orange Book. This stakeholder said that it would be better to have FDA officials determine which patents should be listed in the Orange Book because of their expertise.

- **FDA officials' response.** FDA officials said it was unclear if the benefits of this proposal outweighed its disadvantages. They said additional guidance may provide clarity on which device-related patents should be listed in the Orange Book, but could also limit the patent information in the Orange Book, which could create more uncertainty for generic drug sponsors. This is because the additional guidance could exclude some relevant device-related patents from the Orange Book that could be infringed by new generic products. In addition, developing criteria and implementing any guidance would take a significant amount of the agency's resources. FDA officials also acknowledged that they were aware of this proposal because it was raised in response to FDA's 2020 request for public comments on the listing of patent information in the Orange Book.

Develop questions to assess eligibility for Orange Book listing.

- **Stakeholder proposal.** One national association suggested that FDA should create a set of questions that help brand name sponsors identify which device-related patents should be listed in the Orange Book. The stakeholder said these questions could be similar to those used in Form FDA 3542 to assess whether certain patents related to the active ingredient should be listed in the Orange Book.[5] According to the stakeholder, this would help brand name sponsors to comply with requirements and help generic drug sponsors by reducing the

[4]This stakeholder said that FDA should consider allowing device-related patents to be listed in the Orange Book if one or more of the following conditions applied: (1) the patent also claims the active ingredient or formulation of the approved drug; (2) the patent claims a device (or component of such a device) that is physically, chemically, or otherwise combined or mixed with a drug and produced as a single entity; (3) the patent claims a device (or component of such a device) that is packaged together in a single package with a drug or as a unit; or (4) the patent claims a device (or component of such a device) that is packaged separately from a drug but that is co-labeled for use with a drug and where both are required to achieve the intended use, indication, or effect.

[5]Brand name sponsors must submit patent information using the appropriate form. 21 C.F.R. § 314.53(d) (2021). This form, titled *Form FDA 3542: Patent Information Submitted Upon and After Approval of an NDA or Supplement*, contains yes or no questions to help brand name sponsors determine whether certain patents should be listed in the Orange Book.

possibility that listed patent information could unnecessarily delay FDA approval.

- **FDA officials' response.** FDA officials said it was unclear if the benefits of this proposal outweighed its disadvantages. A set of questions for brand name sponsors may provide additional clarity on which device-related patents should be listed in the Orange Book, but there could be increased uncertainty for generic drug sponsors if the questions lead to more limited information in the Orange Book. There may be relevant device-related patents not captured by the question set and therefore not listed in the Orange Book, which could increase generic drug sponsors' litigation risk, according to officials. In addition, implementing this proposal would take a significant amount of the agency's resources.

Conduct periodic public meetings.

- **Stakeholder proposal.** One national association suggested that FDA could convene periodic public meetings or workshops where stakeholders can discuss patent listing-related topics with the agency, such as the listing of device-related patents in the Orange Book. This could provide stakeholders a chance to raise any questions or areas of uncertainty regarding Orange Book patent listings. These meetings would be helpful in answering stakeholder questions on how to incorporate the increasing complexity of FDA-regulated products into Orange Book listing practices. The national association also said these meetings could also help FDA better understand the topic and identify areas that should be addressed through agency guidance to prevent systemic problems.
- **FDA officials' response.** FDA officials said it was unclear if the benefits of this proposal outweighed its disadvantages. FDA officials said convening periodic public meetings would be resource intensive for the agency and could divert work from other priorities. They also said that it was unclear how this proposal would improve patent listings. As a result, officials said they would likely explore other alternatives for soliciting regular feedback from stakeholders, such as through public comment periods. FDA officials also acknowledged that they were aware of this proposal because it was similar to a comment FDA received in response to its 2020 request for public comments on the listing of patent information in the Orange Book.

Require a crosswalk of use codes, drug labeling, and patent claims.

- **Stakeholder proposal.** One generic drug sponsor and officials from the U.S. Patent and Trademark Office suggested that FDA should require brand name sponsors to submit a crosswalk with Form FDA 3542 indicating how the product's labeling aligns with the method-of-use patent claims and use codes in the Orange Book. The use code is a brief description of a drug's method of use that is covered by the patent and included in the drug's labeling, which can help generic drug sponsors assess if they can enter the market using skinny labels.[6] It does not contain all the information on the patented method of use that brand name sponsors include in Form FDA 3542.[7] By making this information and the crosswalk public, it could lead to earlier dispute resolution regarding use codes, according to officials from the U.S. Patent and Trademark Office.
- **FDA officials' response.** FDA officials could not determine if the benefits of this proposal outweighed its disadvantages. They said a crosswalk may have limited use. In addition, they said that it would be resource-intensive for FDA to make all this information public, and that this could also lead to additional patent disputes regarding the scope of the patent. Moreover, FDA officials said they already evaluate how the drug labeling corresponds to the use code and whether a generic drug application can be approved with a skinny label, although they do not examine whether the patent claims listed in the form relate to the use code.

Include rationale for use code in Form FDA 3542.

- **Stakeholder proposal.** One generic drug sponsor said that FDA should require brand name sponsors to explain how the use codes listed in the Orange Book align with their product's labeling and method-of-use patent claims in Form FDA 3542 in situations where they may not perfectly align. The generic drug sponsor thought that

[6]When a patent is only for specific methods of use, a generic drug sponsor may be able to avoid patent infringement by omitting the patented methods of use from the generic drug's labeling and submitting a section viii statement in its generic drug application, commonly referred to as a "skinny label." A section viii statement refers to the skinny label option provided in section 505(j)(2)(A)(viii) of the Federal Food, Drug, and Cosmetic Act. See 21 U.S.C. § 355(j)(2)(A)(viii).

[7]For patents that claim a method of use, the brand name sponsor must submit information only on those patents that claim indications or other conditions of use for which approval has been granted. In addition, the sponsor must identify with specificity the sections and subsections of the approved labeling that describes the method(s) of use claimed by the patent. See 21 C.F.R. § 314.53(b)(1) and (c)(2)(i)(O) (2021).

this would better ensure the use code aligns with the method-of-use patent claims in Form FDA 3542.

- **FDA officials' response.** FDA officials did not think the benefits of this proposal would outweigh its disadvantages. According to officials, although the Form FDA 3542 does not direct brand name sponsors to provide their rationale for the use code, the form does direct brand name sponsors to include the patent claims that correlate with the drug labeling and use code. As a result, this information may help individuals understand how the use code aligns with the method-of-use patent claims and the product's labeling, according to officials.

Give deference to generic drug sponsors in use code disputes.

- **Stakeholder proposal.** One stakeholder suggested that FDA should defer to generic drug sponsors in their interpretation of use codes when there are disputes regarding the use code's relevance or accuracy. In a 2015 proposed rule discussing challenges to the accuracy or relevance of use codes, FDA proposed deferring to the generic drug sponsor's interpretation of the scope of the method-of-use patent when reviewing a proposed skinny label.[8] The rule focused on circumstances where the brand name sponsor confirms the accuracy of the information, fails to timely respond, or does not provide adequate clarity for FDA to determine whether the scope of a proposed skinny label would be appropriate based on the brand name sponsor's use code and approved labeling. According to the stakeholder, this would better ensure that brand name sponsors write clear use codes that align with the method-of-use patent claims and the approved drug labeling.
- **FDA officials' response.** FDA officials said it was unlikely the benefits of this proposal outweighed its disadvantages. Public comments submitted in response to the 2015 proposed rule contended that it would be inappropriate to defer to the generic drug sponsor's interpretation of the scope of a patent. A comment also asserted that this approach would encourage generic drug sponsors to routinely dispute method-of-use patent information in an attempt to receive deference on a narrow interpretation of the method-of-use patent. As a result, FDA officials said that they did not implement the proposed revision in the agency's final rule.

[8]80 Fed. Reg. 6,802, 6,804 (Feb. 6, 2015).

Modify regulations related to the removal of patents from the Orange Book based on Patent Trial and Appeal Board proceedings.

- **Stakeholder proposal.** One national association and officials from the U.S. Patent and Trademark Office suggested that FDA should better integrate the Patent Trial and Appeal Board's proceedings by modifying its regulations on when brand name sponsors must report to FDA on determinations of patentability to better reflect statutory changes made by the Orange Book Transparency Act of 2020.[9] FDA regulations require brand name sponsors to promptly notify FDA to amend or remove patent information from the Orange Book if the sponsor determines that a patent no longer meets the listing requirements, including if there has been a judicial finding that a listed patent is invalid.[10] Officials from the U.S. Patent and Trademark Office said the term "judicial" in the regulation implies that it only applies to district court proceedings, so FDA may want to consider reinterpreting its regulations to include the board's proceedings.
- **FDA officials' response.** FDA officials said that while the agency has not changed its regulations to incorporate the Patent Trial and Appeal Board proceedings, it has described how Patent Trial and Appeal Board proceedings affect Orange Book patent listings in its July 2022 final guidance on the Orange Book.[11]

Have FDA review patents before listing in the Orange Book.

- **Stakeholder proposal.** Two generic drug sponsors and an advocacy organization suggested that FDA should review patents that are to be listed in the Orange Book to ensure they meet the listing requirements. These stakeholders thought that this would prevent inappropriate patents from being listed in the Orange Book and enable drug sponsors to have confidence in the patent listings.

[9]The Orange Book Transparency Act of 2020 requires brand name sponsors to notify FDA if any claim of a patent has become canceled or invalidated by a final decision from the Patent Trial and Appeal Board. Specifically, where any listed patent claim has been canceled or invalidated by the Patent Trial and Appeal Board or a court, and the brand name sponsor determines that the patent no longer meets listing requirements, the sponsor must notify FDA within 14 days of the decision and request that such patent be amended or withdrawn in accordance with the decision. Pub. L. No. 116-290, § 2(d), 134 Stat. 4889, 4891 (codified at 21 U.S.C. § 355(j)(7)(D)).

[10]21 C.F.R. § 314.53(f)(2) (2021).

[11]FDA, *Orange Book: Questions and Answers Guidance to Industry* (July 2022).

- **FDA officials' response.** FDA officials did not think the benefits of this proposal outweighed its disadvantages. FDA officials said the agency does not substantively analyze patents for their appropriateness due to its limited role in overseeing the Orange Book. In addition, officials said that the patent dispute process already allows individuals to dispute the accuracy or relevance of patents listed in the Orange Book. FDA officials acknowledged that this process relies on the brand name sponsor to make the appropriate changes in the Orange Book.

Have an independent panel review patents before listing in the Orange Book.

- **Stakeholder proposal.** One advocacy organization suggested that an independent, external panel should review patents submitted by brand name sponsors for listing in the Orange Book to determine whether the patents meet the listing requirements. Based on this review, the panel would then make recommendations to FDA for which patents to list in the Orange Book. The advocacy organization said an independent panel would have the expertise needed to review the patent listings and would not have any potential conflicts of interest that could affect its recommendations.
- **FDA officials' response.** FDA officials could not determine whether this proposal's benefits would outweigh its disadvantages. They said the benefits of the panel were unclear and that legislative action may be needed to form a panel. In addition, FDA officials said a panel review would create an extra step in the listing process and would create delays in publishing patent information in the Orange Book. If the panel is providing recommendations, FDA officials were also unsure if the agency would have the authority to implement any recommendations made by the panel.

Create an alternative mechanism for removing Orange Book listed patents.

- **Stakeholder proposal.** One generic drug sponsor proposed that FDA should have an alternative mechanism for removing certain patents from the Orange Book when the patents' claims change as a result of judicial or administrative proceedings. Under the current patent listing dispute process, the patent holder must determine whether a patent should be removed from the Orange Book. However, under this proposal, FDA could have a mechanism for its removal that does not

rely on the patent holder to take action.[12] Having an alternative mechanism to facilitate the removal of inappropriate patents from the Orange Book could help fairly balance brand name and generic drug sponsor interests, according to this generic drug sponsor.

- **FDA officials' response.** FDA officials said it was unlikely that the benefits of this proposal outweighed its disadvantages. They said the benefits for this proposal are not clear and that the proposal is inconsistent with regulations and FDA's role in overseeing the Orange Book. In addition, FDA officials noted statutory changes made by the Orange Book Transparency Act of 2020 clarify when Patent Trial and Appeal Board proceedings would affect Orange Book listings and should help to address this issue.

Allow brand name sponsors to list patents only once.

- **Stakeholder proposal.** One advocacy organization suggested that brand name sponsors should not be able to list patents after their initial submission of Form FDA 3542 to FDA. The advocacy organization said that the listing of follow-on patents in the Orange Book may delay the resolution of patent litigation, which can subsequently delay FDA approval of a generic product. By limiting how frequently brand name sponsors can list patents in the Orange Book, the advocacy organization said it may reduce the number of listed patents and may encourage brand name sponsors to apply for and enforce their patents more quickly and efficiently.
- **FDA officials' response.** FDA officials could not determine if this proposal's benefits outweighed its disadvantages. They said that while this proposal could reduce the amount of time FDA takes to review Form FDA 3542, it could result in the omission of relevant patents from the Orange Book, which could increase litigation risk for generic sponsors. Moreover, FDA officials said that generic drug sponsors may wait until unlisted patents expire to enter the market due to this increased litigation risk. Officials also said that this proposal is inconsistent with federal law.

[12]The generic drug sponsor provided an example of how this process could be structured. It said if the patent no longer claims the drug product and its removal does not jeopardize a first generic filer's rights, the mechanism could allow the generic drug sponsor to submit a petition to FDA seeking removal of an invalid patent. FDA could review the petition and determine if the patent should be removed. If FDA agrees the patent should be removed, then the patent holder would need to respond within 30 days to appeal the decision in court.

Appendix III: GAO Contact and Staff Acknowledgments

GAO Contact

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Staff Acknowledgments

In addition to the contact named above, William Hadley (Assistant Director), Perry Parsons (Analyst-in-Charge), Deb Miller, Dhara Patel, and DeAndrea Porch contributed to this report. Also contributing were Sonia Chakrabarty, Joycelyn Cudjoe, Leia Dickerson, Kaitlin Farquharson, Sandra George, Laurie Pachter, Ethiene Salgado-Rodriguez, and Nicole Willis.

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