June 5, 2020

FDA's Efforts to Modernize the Orange Book

On June 1, 2020, the U.S. Food and Drug Administration (FDA) published a series of Federal Register notices addressing the agency's efforts to modernize and provide clarity on key issues concerning FDA's "Approved Drug Products with Therapeutic Equivalents" publication, commonly known as the *Orange Book*. Specifically, FDA announced it has opened two public dockets to seek comments on enhancements that can be made to the *Orange Book*'s patent listing and therapeutic equivalence information and also issued a new draft guidance document, entitled "*Orange Book*: Questions and Answers Guidance for Industry." These efforts, according to the agency, are intended to facilitate generic competition, promote patient access, and improve the economics of developing generic medicines.

Orange Book Background

The Drug Price Competition and Patent Restoration Act of 1984, commonly known as the Hatch-Waxman Act, sought to encourage generic drug development by establishing an abbreviated approval pathway for generic drugs and creating a framework for challenging brand-name drug manufacturer's patents. The *Orange Book* plays a critical role in FDA's implementation of the Hatch-Waxman Act, as it provides a public compendium of drugs approved under the Federal Food Drug and Cosmetic Act and contains key information on marketing status, therapeutic equivalence, and relevant patents and exclusivity periods. The *Orange Book* is an important resource for stakeholders across the industry. For example, the *Orange Book* contains therapeutic equivalence evaluations for all prescription drugs, and prescribers and pharmacists rely on this information in making generic substitution decisions. Additionally, the *Orange Book*'s patent listing information provides information on the drug substance, drug product, and method-of-use patents that apply to a particular reference listed drug (i.e., the innovator drug), and this information helps generic drug manufacturers assess the patent claims that could potentially block entry of their generic product. The patent listing information is also critical to the 30-month stay, a touchstone of the Hatch-Waxman framework. If an innovator manufacturer lists a patent in the Orange Book, the generic manufacturer certifies that the patent is invalid, unenforceable, or will not be infringed, and the innovator manufacturer initiates patent litigation, an automatic 30-month stay goes into effect, during which time FDA cannot approve the generic application unless the patent litigation is resolved or other events occur.

While FDA has made a number of updates to the *Orange Book* over the years, the agency's recent Federal Register notices signal the agency is considering significant changes that could impact both brand and generic manufacturers.

Public Docket on Patent Listing

As discussed, one of the key features of the *Orange Book* is the patent listing information. In particular, innovator manufacturers must submit any patents that claim "the drug or a method of using the drug … to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product."[1] While FDA requires brand manufacturers to list drug substance, drug product, and method-of-use patents, these broad categories leave areas of uncertainty regarding what patents can be listed. For example, the patent-listing regulations do not expressly address whether patents covering devices for drug-device combination products, patents related to digital tools, or patents associated with risk evaluation and mitigation strategies (REMS) may be listed in the *Orange Book*, and FDA has not provided clarity on appropriate listing practices despite numerous requests from industry.[2]

[1] 21 CFR § 314.53(b).

[2] *See, e.g.*, Request for Advisory Opinion by Novo Nordisk Inc., Docket No. FDA-2012-A-1169 (Nov. 26, 2012); Request for Advisory Opinion by Forest Laboratories, Inc., Docket No. FDA-2011-A-0363 (May 12, 2011); Request for Advisory Opinion by

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The agency now appears ready to consider these issues and others, requesting that stakeholders provide input on a variety of issues, including:

- Whether the advantages of including additional categories of patent information in the *Orange Book*, such as device-related patents or REMS patents, are outweighed by the need to submit additional patent certification and resulting delays in approval;
- When it is justifiable to include device-related patents in the *Orange Book, e.g.*, when the device-related patent discloses the drug's active ingredient, the device-related patent claims a device that is "integral" to the administration of a drug for a combination product, or the device-related patent claims a method of use described in the drug labeling;
- Factors for determining whether a device-related patent should be considered a drug product patent or method-of-use patent;
- Whether patents related to the implementation of a REMS requirement should be included in the *Orange Book*; and
- Considerations for including patents for digital software applications associated with approved drugs in the *Orange Book*.

FDA acknowledges that the inclusion of additional categories of patents in the *Orange Book* would have important consequences. While patent listing information helps generic applicants assess the extent of patent coverage for a particular innovator product, it also creates the potential to delay generic entry due to a 30-month stay of FDA approval. FDA and generic manufacturers have therefore expressed concern that "over-listing" by innovator manufacturers could have anticompetitive effects, and FDA has emphasized that it will balance competing interests of the innovator and generic industries in considering whether to include additional types or categories of patent information in the *Orange Book*.

Public Docket on Therapeutic Equivalence Information

While the first Federal Register notice emphasizes questions related to patent listing, FDA's second notice casts a broader net, seeking general information regarding the current use of the *Orange Book* and suggestions for improvements to make it more accessible and useful to consumers, health care professionals, and drug developers. In particular, the second notice targets changes that can be made to the *Orange Book*'s therapeutic equivalence information, which, among other things, classifies as "A" -rated the products that FDA has deemed therapeutically equivalent to a reference drug, and as "B" -rated the products that are *not* therapeutically equivalent. Many state generic substitution laws incorporate these *Orange Book* ratings and require or permit substitution of generic drugs that are listed with "A" ratings, making the therapeutic equivalence information critical to the drug delivery system.

FDA is seeking feedback on therapeutic equivalence information and has established a public docket to solicit comments on the following issues, among others:

- Types of people or entities that use the *Orange Book* and the reasons for using it;
- Suggestions for making therapeutic equivalence information more user-friendly or specifically tailored to meet the needs of people or entities using this information;
- Whether and how therapeutic equivalence information promotes drug competition; and

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AstraZeneca, Docket No. FDA-2007-A-0099 (formerly 2007A-0261) (June 21, 2007)]; Request for Advisory Opinion by AstraZeneca, Docket No. FDA-2006-A-0063 (formerly 2006-0318) (Aug. 10, 2006); Request for Advisory Opinion by GlaxoSmithKline, Docket No. FDA-2011-A-0363 (Jan. 10, 2005).

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- Information or features that would make the *Orange Book* more useful, or any other information FDA should consider.

Orange Book Q&A Guidance

In addition to the public dockets, FDA announced the publication of a new draft guidance document providing responses to common *Orange Book* questions. The draft guidance provides technical, process-related information related to four broad categories: (i) general content and format inquiries, (ii) petitioned ANDAs, (iii) movements of drug products between the active and discontinued sections, and (iv) patent listing. Notably, the draft guidance does not offer novel legal interpretations and does not address significant open questions related to patent listing or any other topic. For example, while the draft guidance describes the processes for ensuring patent information is timely filed, submitting a request to remove a patent from the *Orange Book*, and engaging in patent-listing disputes, it does not address the circumstances under which certain patents (*e.g.*, device-related patents) may be listed. The draft guidance, when considered in light of the public dockets described above, nevertheless underscores the agency's commitment to provide clarity on outstanding issues.

Conclusion

FDA's recent Federal Register notices seek input on ways to leverage the *Orange Book*'s patent listing and therapeutic equivalence information to facilitate generic competition. These changes could have a material impact on both brand and generic drug manufacturers as changes to the patent listing could affect both patent litigation and timing of generic entry, while changes to the therapeutic equivalence code could impact generic substitution.

FDA will be accepting comments to these public dockets until August 31, 2020. If you have questions or would like assistance drafting comments for the public dockets, please contact any member of Ropes & Gray's FDA regulatory practice or your usual Ropes & Gray advisor. Ropes & Gray will continue to monitor developments related to Hatch-Waxman and the *Orange Book*.

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