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FDA's Proposed Rules to Address Inaccurate Orange Book Use Codes May Shorten Approval Timelines for Select 505(b)(2) and Generic Drugs

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Introduction & Background

Drug Approval and Patent Listing Process

Before being allowed to market a new drug¹ in the U.S., branded drug manufacturers must submit a new drug application (NDA) to the U.S. Food and Drug Administration (FDA), and the FDA must approve the NDA.^{2,3} After NDA approval, branded drug manufacturers typically timely submit for listing⁴ in the Orange Book⁵ applicable U.S. patents having claims covering the approved drug, its formulation(s), and methods of use, all as approved by the FDA.

When Orange Book listing method of treatment U.S. patents, the branded drug manufacturer must fill in a use code in FDA Form 3542,⁶ and submit the form to the FDA. Without attempting to determine the scope or accuracy of the use code in relation to the patent's claims, the FDA

¹ The scope of this article includes small molecules but does not extend to larger molecules (*e.g.*, proteins) derived from a biological source *i.e.*, biological products or biologics. *See, e.g.*, 21 C.F.R. § 600.3(h).

² *See, e.g.*, 21 U.S.C. § 355(a). “No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.”

³ As used herein, an NDA means a 505(b)(1) or 505(b)(2) application as defined in the Federal Food, Drug, and Cosmetic Act (FDCA). Biologics manufacturers submit a Biologics License Application (BLA) instead of an NDA.

⁴ To be timely listed, U.S. patents in force at the point of NDA approval must be Orange Book listed within 30 days of approval. *See, e.g.*, 21 C.F.R. § 314.53(c)(2)(R)(ii). “Within 30 days after the date of approval of its application or supplement, the applicant shall submit FDA Form 3542 for each patent that claims the drug substance (active ingredient), drug product (formulation and composition), or approved method of use . . .”

For U.S. patents issuing after NDA approval, “. . . the applicant shall submit to FDA the required patent information within 30 days of the date of issuance of the patent.” 21 C.F.R. § 214.53(d)(2).

⁵ Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, *FDA*, available electronically at: <http://www.accessdata.fda.gov/scripts/cder/ob/>, last accessed May 12, 2015.

⁶ FDA Form 3542 is available electronically at: <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048345.pdf>, last accessed May 12, 2015.

then publishes relevant information in the Orange Book, including the patent number, expiration date, and use code(s).

Generic and 505(b)(2) Drug Approval: Clearing Orange-Book Listed Patents

A generic manufacturer seeking to market a generic version of a branded drug must submit and gain FDA approval of an abbreviated new drug application (ANDA).⁷ Similarly, a 505(b)(2) applicant seeking to market its drug must submit and gain FDA approval of a paper NDA. For a section viii filing where only method claims are Orange Book listed, FDA cannot approve any section viii filing that would infringe an in-force Orange Book listed patent.⁸ Thus, in its ANDA or paper NDA, the generic manufacturer or 505(b)(2) applicant, not relying on section viii, and facing Orange Book listed patents, must assure FDA that its drug: 1) will not be marketed until the branded Orange Book listed patent(s) expire;⁹ or 2) will not infringe any of the brand's Orange Book listed patent(s), or provide detailed reasons why the Orange Book listed patent(s) are invalid or unenforceable.¹⁰

Section viii statements

When a branded drug has been approved for multiple uses, and the brand's remaining Orange Book listed patents cover only some of these approved uses, a generic or 505(b)(2) applicant may attempt to avoid a paragraph III or IV certification by submitting a section viii statement to FDA. The section viii statement, also known as a labeling carve-out, provides that the generic or 505(b)(2) applicant will market its drug only for method(s) not covered by any brand Orange Book listed patents. Generics and 505(b)(2) applicants submitting a section viii statement will also propose a modified label which does not include (e.g., carves out) approved uses covered by still-in-force Orange Book listed branded patents. When the FDA approves the ANDA or 505(b)(2) application, the generic or 505(b)(2) manufacturer can place its drug on the market for the FDA approved uses not covered by the brand's Orange Book listed patents.

⁷ See, e.g., section 505(j)(a)(A)(vii)(III) of the FDCA.

⁸ See, e.g., Drug Price Competition and Patent Term Restoration Act of 1984, Public Law 98-417.

⁹ See, e.g., 21 U.S.C. § 355(b)(2)(A)(iii) (e.g., a certification under this statutory provision is called a paragraph III certification).

¹⁰ See, e.g., 21 U.S.C. § 355(b)(2)(A)(iv) (e.g., a certification under this statutory provision is called a paragraph IV certification).

Orange Book Listed Patents and Use Codes can Delay Generic (and 505(b)(2)) Drug Market Entry

Orange Book patent listing(s) can and have delayed the market entry of generic (and 505(b)(2)) drugs. In one case, the brand manufacturer Orange Book listed a new patent whose claims covered neither the approved drug nor any approved method of using the drug. Because FDA accepts and publishes use codes at face value, FDA did not approve the generic's ANDA. The generic manufacturer subsequently sued to delete the improper Orange Book listing, but the Federal Circuit held that the law did not allow such a right of action.

Correcting Inaccurate Orange Book Listed Patents and Use Codes via Counterclaiming in Litigation

Congress took a first step in addressing correction of inaccurate Orange Book listings and use codes in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (the Act). The Act, on its face, allows *e.g.*, ANDA filers who are sued for patent infringement by branded manufacturers to “assert a counterclaim seeking an order requiring the [brand] to correct or delete patent information submitted by the [brand] . . . on the ground that the [Orange Book listed] patent does not claim either . . . the drug for which the [brand's NDA] was approved; or . . . an approved method of using the drug.”¹¹

In *Caraco*,¹² the Supreme Court confirmed Congress's intent in passing the Act. Generic manufacturer Caraco filed an ANDA seeking to market a generic version of repaglinide, a diabetes drug. FDA had previously approved three different uses of repaglinide for: 1) treatment of diabetes with repaglinide alone, 2) treatment of diabetes with repaglinide in combination with metformin, and 3) treatment of diabetes with repaglinide in combination with thiazolidinediones.¹³ At the time of Caraco's ANDA submission, Novo Nordisk (Novo), the maker of repaglinide, held a patent for the use of repaglinide with metformin for the treatment of diabetes.¹⁴ Novo also held a composition of matter patent for repaglinide.¹⁵

When Caraco submitted its ANDA, Caraco assured the FDA that it would not market its generic drug until Novo's composition of matter patent had expired. At that time, Novo's use code for its method of treatment patent was defined as “Use of repaglinide in combination with

¹¹ 21 U.S.C. § 355(j)(5)(C)(ii)(I).

¹² *Caraco Pharm. Labs., Ltd. V. Novo Nordisk*, 132 S.Ct 1670 (2012).

¹³ *Id.* at 1678.

¹⁴ *Id.*

¹⁵ *Id.* at 1679.

metformin to lower blood glucose.”¹⁶ FDA advised Caraco that if it carved out use of repaglinide in combination with metformin with a section viii statement, FDA would allow Caraco to market its generic drug for the other two FDA approved uses.¹⁷ Caraco therefore submitted a section viii statement with proposed labeling carving out diabetes treatment by repaglinide in combination with metformin.¹⁸

Before FDA could approve Caraco’s ANDA, Novo broadened the above use code to describe a “method for improving glycemic control in adults with type 2 diabetes.”¹⁹ The FDA interpreted the new use code to protect all three approved methods of using repaglinide to treat diabetes, so Caraco’s proposed label overlapped with Novo’s new use code. The FDA then informed Caraco that it could no longer use the proposed section viii carve out to gain marketing approval because the use code and proposed label overlapped.²⁰

In a resulting paragraph IV litigation between Caraco and Novo, Caraco counterclaimed seeking an order requiring Novo to correct its use code “on the ground that [Novo’s method of treatment patent] does not claim” two of the approved methods of using repaglinide – alone or in combination with thiazolidinediones.²¹ The District Court granted summary judgment to Caraco.²² The Federal Circuit reversed, holding that “Caraco lacked ‘a statutory basis’ to assert a counterclaim.”²³ The Federal Circuit reasoned that the statutory phrase ‘an approved method of using the drug’ should refer to any approved method, and because Novo’s patented use of repaglinide in combination with metformin was an approved method, the counterclaim was unavailable.²⁴ The Supreme Court reversed the Federal Circuit and remanded, holding that “Caraco may bring a counterclaim seeking to ‘correct’ Novo’s use code ‘on the ground that’ [Novo’s method of treatment patent] ‘does not claim . . . an approved method of using the drug’ – indeed, does not claim two.”²⁵

¹⁶ *Id.*

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ *Id.*

²⁰ *Id.*

²¹ *Id.*

²² *Id.*

²³ *Id.*

²⁴ *Id.*

²⁵ *Id.* at 1688.

FDA's New Proposed Rules

While e.g., a generic can make a counterclaim in litigation, FDA has now proposed a mechanism to resolve disputed Orange Book listing use claims outside of the courtroom. Prompted by e.g., the Caraco case, FDA recently issued proposed new rules e.g., 1) outlining a mechanism for generic and 505(b)(2) drug manufacturers to challenge use code accuracy of Orange Book listed patents at the FDA; and 2) clarifying when use codes are considered late listed. , The FDA states that its proposed rules are “intended to reduce unnecessary litigation, reduce delays in the approval of 505(b)(2) applications and ANDAs that are otherwise ready to be approved, and provide business certainty to both brand name and generic drug manufacturers.”

Proposed New Mechanism for a Generic or 505(b)(2) Drug Applicant to Challenge Orange Book Listed Method of Treatment Patent Use Codes at the FDA

A key provision of FDA's proposed rules is a new method of treatment Orange Book listed patent use code challenge mechanism. Specifically, FDA proposes to amend 11 C.F.R. § 314.53(f) to add a novel accuracy challenge procedure for e.g., Orange Book listed method of treatment patent use codes.

“If any person disputes the accuracy or relevance of patent information submitted to the FDA . . . and published by the FDA [in the Orange Book] . . . that person must first notify FDA in a written or electronic communication . . . that states the grounds for disagreement.” FDA will then “request that the NDA holder confirm the correctness of the patent information within 30 days.”

For listed patents that claim an approved method of using the drug product, “FDA will request that the NDA holder confirm the correctness of the use code in the Orange Book, and provide information on the specific approved use claimed that allows the FDA to make a determination . . .” Unless the NDA holder withdraws or amends the patent information “in response to FDA's request . . . FDA will not change the patent information in [the Orange Book].”

If FDA, however, concludes there is “insufficient information to make a determination . . . and the NDA holder has confirmed the correctness of its description of the specific approved use claimed by the patent . . . the [FDA] will review the proposed labeling for the 505(b)(2) or ANDA with deference to the 505(b)(2) or ANDA applicant's interpretation of the scope of the patent.”

Under the proposed challenge mechanism, unless the NDA holder can adequately demonstrate to FDA that the Orange Book listed patent claims support its use code's scope, FDA will be able to interpret the use code in a manner favorable to generic (and 505(b)(2)) applicants. In this scenario, assuming all other requirements are met, FDA will approve the ANDA or 505(b)(2) application. The approval would come in spite of a use code that overlaps with the proposed labeling.

Late Listings

Mindful of the facts in *Caraco*, FDA has also proposed new rules that will diminish the ability of branded manufacturers to meaningfully broaden use codes late in the ANDA and 505(b)(2) submission processes. FDA's proposed rules will treat an NDA holder's (brand's) amendments to the description of the FDA approved methods of use as being untimely if:

- The amendment is submitted more than 30 days after patent issuance and it is not related to a corresponding change in approved product labeling; or
- The amendment is submitted more than 30 days after a corresponding change in approved product labeling.

As described in the proposed rules, “. . . an untimely filed method-of-use patent does not require a patent certification or [section viii] statement and would not delay approval of a pending . . . ANDA.” Similarly, “. . . if an amendment to change the patent use code is submitted more than 30 days after a corresponding change in approved product labeling, the amendment lacks a clear temporal link to the specific section(s) of approved product labeling claimed by the patent, and the patent information is untimely filed.”

Conclusion

If enacted, the FDA's new rules for challenging Orange Book patent use codes will likely result in:

- increased Orange Book listed method-of-treatment use code challenges at the FDA;
- increased rates of select ANDA and 505(b)(2) application allowances;
- decreased times for select ANDA and 505(b)(2) application allowances; and
- decreased inaccurate Orange Book listed patent use codes.

Branded manufacturers, and ANDA and 505(b)(2) applicants, should prepare now for the institution of these new rules.

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