

## Requirements, Benefits, and Possible Consequences of Listing Patents in FDA's Orange Book

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### Introduction

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act) amended patent law and drug law to facilitate pharmaceutical development and encourage the marketing of generic pharmaceuticals. Pub. L. No. 98-417, 98 Stat. 1585 (amending 21 U.S.C. § 355); see also H.R. Rep. No. 98-857, pt. 1, at 1 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647. While the Hatch-Waxman Act has been amended several times, the general framework remains the same. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066; 21st Century Cures Act of 2016, Pub. L. No. 114-255, 130 Stat. 1033. Under the Hatch-Waxman Act, the U.S. Food and Drug Administration (FDA) approves drug products through three types of applications: (1) new drug applications (NDAs), which must include full reports of nonclinical and clinical investigations showing that the proposed drug is safe and effective; (2) 505(b)(2) NDAs, which contain full reports of safety and effectiveness, where at least some of the information required for approval comes from studies by others; and (3) abbreviated new drug applications (ANDAs), which must contain information showing that the proposed drug, among other things, is bioequivalent to the reference drug.

NDAs must be accompanied by certain patent information, which the FDA then lists in its Approved Drug Products with Therapeutic Equivalence Evaluations publication (known as the Orange Book). Having patent information listed in the FDA's Orange Book provides benefits of possible regulatory stays under the Hatch-Waxman Act, which protect NDA holders from harm that could otherwise result from FDA approval of an infringing drug product. Not all patent information should be listed, however, and pharmaceutical companies should consider the statutory and regulatory requirements for listing, as well as the possible consequences of improper listing.

### Patent Information for Listing

#### Information That 'Must' Be Submitted

NDA applicants "shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1); see also 21 C.F.R. § 314.53(b)(1) (construing "drug" as "drug product"), (d)(1). If a patent issues after the NDA is filed but before it is approved, "the applicant shall amend the application to include the information." 21 U.S.C. § 355(b)(1); see also 21 C.F.R. § 314.53(d)(1) (providing a deadline of within 30 days of patent issuance). For patents issued after approval of the NDA, the NDA "holder shall file such information . . . not later than thirty days after the date the patent involved is issued." 21 U.S.C. § 355(c)(2); see also 21 C.F.R. § 314.53(d)(3).

The FDA publishes the submitted patent information in the Orange Book. 21 U.S.C. § 355(b)(1), (c)(2); 21 C.F.R. § 314.53(e). The FDA takes the position that it will not substantively review the correctness of patent information before publishing because the FDA interprets its role in listing patent information as “purely ministerial” and has explained that it “lacks both the resources and the expertise to police the correctness . . . of every patent listing submitted by an NDA holder.” *aaiPharma Inc. v. Thompson*, 296 F.3d 227, 237 (4th Cir. 2002); see also *United Food & Commercial Workers Unions & Emp’rs Midwest Health Benefits Fund v. Novartis Pharm. Corp.*, No. 15-cv-12732, 2017 BL 228218, at \*8 (D. Mass. June 30, 2017); *Teva Pharm., USA, Inc. v. Leavitt*, 548 F.3d 103, 106 (D.C. Cir. 2008); *Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1080 (D.C. Cir. 2001).

The FDA regulations indicate that patents whose information “must” be submitted “consist of drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents.” 21 C.F.R. § 314.53(b)(1). Drug substance patents include those “that claim the drug substance that is the subject of the pending or approved NDA or that claim a drug substance that is the same as the active ingredient that is the subject of the approved or pending NDA.” *Id.*; see also 67 Fed. Reg. 65,448, 65,452 (Oct. 24, 2002) explaining that an applicant “would determine whether the drug substance was the same as the active ingredient . . . by considering whether the drug substances can be expected to perform the same with respect to such characteristics as dissolution, solubility, and bioavailability”). “For patents that claim only a polymorph that is the same as the active ingredient described in the approved or pending NDA, the applicant must certify in the required FDA declaration form that the applicant has test data . . . demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA.” 21 C.F.R. § 314.53(b)(1).

Drug product patents include those “that claim the drug product . . . that is described in the pending or approved NDA.” *Id.* (citing 21 C.F.R. § 314.3). FDA regulations define “drug product” as “a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.” *Id.* § 314.3(b). In interpreting the regulations, the FDA noted that dosage forms listed in the Orange Book include “metered aerosols, capsules, metered sprays, gels, and pre-filled drug delivery systems.” 68 Fed. Reg. 36,675, 36,680 (June 18, 2003).” The key factor is whether the patent being submitted claims the finished dosage form of the approved drug product.” *Id.*

Method-of-use patents include those “that claim indications or other conditions of use for which approval is sought or has been granted in the NDA.” 21 C.F.R. § 314.53(b)(1). “The applicant must separately identify each pending or approved method of use and related patent claim(s).” *Id.* FDA regulations indicate that “[f]or approved NDAs, the NDA holder’s description of the patented method of use . . . must describe only the approved method(s) of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.” *Id.* “If the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, the applicant must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.” *Id.* “For approved NDAs, the NDA holder submitting information on the method-of-use patent must identify with specificity the section(s) and subsection(s) of the approved labeling that describes the method(s) of use claimed by the patent submitted.” *Id.*

#### **Information That ‘Must Not’ Be Submitted**

The FDA regulations indicate that information on “[p]rocess patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates . . . must not be submitted to FDA.” *Id.* Additionally, information on patents that only claim unapproved uses of a drug should not be submitted. 68 Fed. Reg. at 36,681; see also 21 C.F.R. § 314.53(b), (c)(2).

Process patents include those that claim methods for making (i.e., chemically synthesizing) the drug. The FDA reasons that the drug alone is not claimed, so submission of the information is not permitted. 21 C.F.R. § 314.53(b)(1). Notably, product-by-process patents, which claim a product by describing or listing the process steps to define the claimed product, should be submitted to the FDA if they claim the drug product that is the subject of the NDA. 67 Fed. Reg. at 65,452 (Oct. 24, 2002); see also *In re Bridgeford*, 357 F.2d 679, 682 (C.C.P.A. 1966); *Cadence Pharm., Inc. v. Fresenius Kabi USA, LLC*, No. 13-cv-139 DMS(MDD), slip op. at 6-7 (S.D. Cal. June 5, 2014), Dkt. No. 251 (denying motion for summary judgment on counterclaim seeking a product-by-process claim to be delisted). To avoid potential confusion between process patents (which are not listed) and product-by-process patents (which should be listed), applicants are required to certify whether the patent being submitted is a product-by-process patent in which the product claimed is novel. 68 Fed. Reg. at 36,680.

Patents claiming a drug product's packaging or container may not be listed even though information regarding a drug's packaging or container is part of the NDA because the agency does not approve the packaging or container per se. 67 Fed. Reg. at 65,451; see 21

C.F.R. § 314.50(d)(1)(ii)(a). The packaging or container is distinct from the approved drug product and "thus fall[s] outside of the requirements for patent submission." 68 Fed. Reg. at 36,680. In contrast, drug-delivery systems, including "metered aerosols, capsules, metered sprays, gels, and pre-filled drug delivery systems," are drug products, as discussed above, and patents covering them should be listed. *Id.*; see also *In re Lantus Direct Purchaser Antitrust Litig.*, 284 F. Supp. 3d 91, 104 (D. Mass. Jan. 10, 2018) (finding that a prefilled injector pen approved as a drug delivery device for treating diabetes is not packaging and that patents covering the device may be listed in the Orange Book).

Patents claiming metabolites include those patents that claim the chemical compound formed from the active ingredient of a drug after being broken down by the body. 68 Fed. Reg. at 36,680. The FDA considers that patents claiming a metabolite should not be listed because they do not claim the approved drug as required by the listing statute. See *id.* (citing 67 Fed. Reg. at 65,451). Allowed, however, are patents claiming an approved method of using an approved drug to administer a metabolite. *Id.* Submission of such a patent would be allowed as long as the requirements for submission of method-of-use patents are met. *Id.*

Patents claiming intermediates include those that claim "materials that are produced during preparation of the active ingredient and are not present in the finished drug product." *Id.* The FDA considers intermediates as "in-process materials" rather than drug substances or components in the finished drug product. *Id.*; see also 21 C.F.R. § 210.3(b)(9), 211.110. It, therefore, considers that patents that claim intermediates do not claim the approved drug product and fail to satisfy the requirements for listing. See 68 Fed. Reg. at 36,680; 21 C.F.R. § 210.3(b)(9), 211.110.

## Benefits and Possible Consequences

### Benefits of Listing

Having a patent listed in the Orange Book provides significant benefits to the NDA holder. Companies seeking to market a generic version of a drug must certify as to each patent claiming the drug or a use of the drug for which the applicant seeks approval that (1) the NDA holder has not submitted patent information to the FDA for listing in the Orange Book; (2) the patent has expired; (3) the date the patent will expire; or (4) "[the] patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." 21 U.S.C. § 355(b)(2)(A) (for 505(b)(2) NDAs); *id.* § 355(j)(2)(A)(vii)(I)-(IV) (for ANDAs). These certifications must be made even if the company disputes the accuracy or relevance of the listed patent information. 21 C.F.R. § 314.50(i)(5) (for 505(b)(2) NDAs); *id.* § 314.94(a)(12)(vii) (for ANDAs). This includes if the company has initiated a patent listing dispute before the FDA, as discussed below. *Id.* § 314.53(f)(1)(ii).

Filing an ANDA or a 505(b)(2) NDA with a paragraph IV certification is an act of patent infringement, allowing a patent owner to sue the generic drug applicant before the generic drug product is marketed. 35 U.S.C. § 271(e)(2). In addition, if the patent owner files the suit within 45 days of receiving notice of a generic drug applicant's paragraph IV certification, a stay is triggered whereby the FDA will not approve the generic drug application for 30 months. 21 U.S.C. § 355(c)(3)(C) (for 505(b)(2) NDAs); *id.* § 355(j)(5)(B)(iii) (for ANDAs). The period of the regulatory stay can be lengthened or shortened in certain circumstances. *Id.* § 355(c)(3)(C) (for 505(b)(2) NDAs); *id.* § 355(j)(5)(B)(iii) (for ANDAs). The ability to sue a generic drug applicant before the generic drug is marketed and the resulting regulatory stay protects the NDA holder from harm that could otherwise result from FDA approval of an infringing drug product.

Jurisdiction under the Hatch-Waxman Act, however, does not depend on a paragraph IV certification. For example in *AstraZeneca Pharmaceuticals LP v. Apotex Corp.*, the Federal Circuit held that under the Hatch-Waxman Act, "the requirements for jurisdiction in the district courts are met once a patent owner alleges that another's filing of an ANDA infringes its patent under [35 U.S.C.] § 271(e)(2), and this threshold jurisdictional determination does not depend on the ultimate merits of the claims." 669 F.3d 1370, 1376-77 (Fed. Cir. 2012); see also *Vanda Pharm., Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1124 (Fed. Cir. 2018) (explaining that "once a patent owner alleges that another's filing of an ANDA infringes its patent under § 271(e)(2)," "[n]othing more was required"). Beyond the jurisdictional question, however, the Federal Circuit has not explicitly addressed whether a claim for infringement under 35 U.S.C. § 271(e)(2) can lie where a patent is not listed or is late-listed in the Orange Book. An NDA holder should therefore strive to timely submit patent information.

The Federal Circuit also has not addressed “whether district courts may exercise jurisdiction over a claim asserting future infringement of a non-Orange Book patent under the Declaratory Judgment Act when such a claim is based solely on the filing of an ANDA by a generic manufacturer.” *Takeda Pharm. Co. v. Mylan Inc.*, 62 F. Supp. 3d 1115, 1122 (N.D. Cal. 2014). Some district courts have exercised jurisdiction, while others have not. For example, in *Cephalon, Inc. v. Sandoz, Inc.*, the court found declaratory judgment jurisdiction existed regardless of whether § 271(e)(2) was applicable to the facts of record. Civ. No. 11-821-SLR, 2012 BL 49074, at \*1-2 (D. Del. Mar. 1, 2012). However, in *In re Rosuvastatin Calcium Patent Litigation*, the court granted defendants’ motion to dismiss the declaratory judgment count, stating, among other things, that a § 271(a) action would be “inconsistent with Congressional intent” because “Congress evidently believed that a patentee in AstraZeneca’s position did not have a cause of action under § 271(a).” MDL No. 08-1949, 2008 BL 267178, at \*14-15 (D. Del. Nov. 24, 2008).

### **Possible Consequences of Not Listing or Late Listing**

The FDA regulations indicate that “to be timely filed, patent information for patents issued after the date of approval of the NDA must be submitted to FDA within 30 days of the date of issuance of the patent.” 21 C.F.R. § 314.53(c)(2) (ii); see also *id.* § 314.53(d)(3). “If the required patent information is not submitted within 30 days of the issuance of the patent, FDA will list the patent, but patent certifications . . . will be governed by the provisions regarding untimely filed patent information.” *Id.* § 314.53(d)(3) (citing *id.* § § 314.50(i)(4), (6), 314.94(a)(12)(vi),(viii)).

Whether a late-listed patent enjoys the benefits of listing that are described above depends on the timing of the generic drug application. If the patent is not timely filed but is listed before the generic drug application is filed, then the generic drug applicant must nonetheless certify as to the patent. *Id.* § 314.50(i)(4)(ii) (for 505(b)(2) NDAs); *id.* § 314.94(a)(12)(vi)(B) (for ANDAs). This triggers the 30-month regulatory stay when the patent owner files suit for infringement under 35 U.S.C. § 271(e)(2), as discussed above.

If, on the other hand, a patent is not timely filed, and it is listed after the generic drug application is filed, then the generic drug applicant need not certify as to the patent. *Id.* § 314.50(i)(4)(i) (for 505(b)(2) NDAs); *id.* § 314.94(a)(12)(vi)(A) (for ANDAs). Generic drug applicants may voluntarily certify as to an untimely filed patent, and if an ANDA is amended by submitting a paragraph IV certification “[s]uch an act is a qualifying act of infringement under [35 U.S.C.] § 271(e)(2)(A).” *Vanda Pharm.*, 887 F.3d at 1127 (citations omitted); see also 21 C.F.R. § 314.50(i)(6) (for 505(b)(2) NDAs); *id.* § 314.94(a)(12)(viii) (for ANDAs). However, a generic drug applicant also “may withdraw the patent certification for the untimely filed patent,” and “[o]nce an amendment is submitted to change the certification, [the application] will no longer be considered to contain the prior certification.” 21 C.F.R. § 314.50(i)(6) (for 505(b)(2) NDAs); *id.* § 314.94(a)(12)(viii) (for ANDAs).

### **Possible Consequences of Improper Listing**

An alleged improper listing potentially may be subject to administrative proceedings before the FDA or counterclaims in district court litigation. In addition, an alleged improper listing potentially may also give rise to penalties for perjury or even antitrust allegations.

First, a listing that is alleged to be improper may be subject to a request for “[c]orrection of patent information errors,” triggering an administrative procedure before the FDA. 21 C.F.R. § 314.53(f)(1). In the procedure, “any person [who] disputes the accuracy or relevance of patent information submitted to the Agency . . . and published by FDA in the list, or believes that an NDA holder has failed to submit required patent information. . . must first notify the Agency in a written or electronic communication titled ‘314.53(f) Patent Listing Dispute.’” *Id.*; see also 21 C.F.R. § 314.50(i)(5) (specifying that 505(b)(2) NDA applicants can initiate the procedure), § 314.94(a)(12)(vii) (specifying that ANDA applicants can initiate the procedure). “[The] communication must . . . [describe] the specific grounds for disagreement regarding the accuracy or relevance of patent information for FDA to send to the applicable NDA holder.” *Id.* § 314.53(f)(1). “For a dispute regarding the accuracy or relevance of patent information regarding an approved method of using the drug product, this statement of dispute must be only a narrative description (no more than 250 words) of the person’s interpretation of the scope of the patent.” *Id.* “FDA will send the text of the statement to the applicable NDA holder without review or redaction.” *Id.*

“For requests . . . directed to the accuracy or relevance of submitted patent information regarding a drug substance or drug product claim, . . . [t]he NDA holder must confirm the correctness of the patent information . . . or withdraw or amend the patent information . . . within 30 days of the date on which the Agency sends the statement of dispute.” *Id.* § 314.53(f)(1)(i)(A). “Unless the NDA holder withdraws or amends its patent information in response to the patent listing dispute, the Agency will not change the patent information in the Orange Book.” *Id.*

“For requests . . . directed to the accuracy or relevance of submitted patent information regarding an approved method of using the drug product, . . . [t]he NDA holder must confirm the correctness of its description of the approved method of use claimed by the patent that has been included as the ‘Use Code’ in the Orange Book, or withdraw or amend the patent information . . . , provide a narrative description (no more than 250 words) of the NDA holder’s interpretation of the scope of the patent that explains why the existing or amended ‘Use Code’ describes only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product . . . within 30 days of the date on which the Agency sends the statement of dispute.” *Id.* § 314.53(f)(1)(i)(B). “FDA will send the text of the statement to the person who submitted the patent listing dispute without review or redaction.” *Id.* “If the NDA holder confirms the correctness of the patent information, . . . the Agency will not change the patent information in the Orange Book.” *Id.* § 314.53(f)(1)(i)(B)(1). “If the NDA holder responds to the patent listing dispute with amended patent information . . . , FDA will update the Orange Book to reflect the amended patent information.” *Id.* § 314.53(f)(1)(i)(B)(2).

A generic drug applicant who has triggered the administrative procedure for an Orange Book-listed patent must nonetheless certify as to that patent. *Id.* § 314.53(f)(1)(ii). And “[t]he patent listing dispute procedure would not have an impact on the availability of a 30-month stay if other statutory and regulatory criteria are met.” 81 Fed. Reg. at 69,606 (citing sections 505(c)(3)(C) and (j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act; 21 C.F.R. § 314.107).

Second, if a patent owner or NDA holder brings a patent infringement suit against a generic drug applicant, “the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder . . . on the ground that the patent does not claim either—(aa) the drug for which the application was approved; or (bb) an approved method of using the drug.” 21 U.S.C. § 355(c)(3)(D)(ii)(I) (for 505(b)(2) NDAs); *id.* § 355(j)(5)(C)(ii)(I) (for ANDAs). These statutory provisions “[do] not authorize the assertion of a claim . . . in any civil action or proceeding other than [the described] counterclaim.” *Id.* § 355(c)(3)(D)(ii)(II) (for 505(b)(2) NDAs); *id.* § 355(j)(5)(C)(ii)(II) (for ANDAs). In addition, the applicant would not be entitled to damages for the counterclaim. *Id.* § 355(c)(3)(D) iii) (for 505(b)(2) NDAs); *id.* § 355(j)(5)(C)(iii) (for ANDAs). Instead, an applicant who succeeds on its counterclaim may be eligible for an injunction to correct its patent information. See *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 688 F.3d 766, 768-69 (Fed. Cir. 2012) (holding that “the District Court was correct in issuing an injunction requiring correction of Novo’s use code” but “abused its discretion in dictating the precise terms of the use code to be submitted”).

Third, allegations of antitrust violations have been made on the basis that Orange Book patent information was improperly listed. See, e.g., *In re Remeron Antitrust Litig.*, 335 F. Supp. 2d 522, 529-30 (D.N.J. 2004); *In re Buspirone Patent Litig.*, 185 F. Supp. 2d 363, 374, 376 (S.D.N.Y. 2002). Courts have found no violation, however, where the patent was reasonably listed in the Orange Book. See *Organon, Inc. v. Mylan Pharm., Inc.*, 293 F. Supp. 2d 453, 460 (D.N.J. 2003); see also *In re Lantus*, 284 F. Supp. 3d 91 at 104; *In re Lipitor Antitrust Litig.*, MDL No. 2332, 2013 BL 236932, at \*21 (D.N.J. Sept. 5, 2013).

Fourth, in signing the declaration for submission of patent information, the NDA holder verifies “under penalty of perjury” that the information included is true and correct. 21 C.F.R. § 314.53(c)(2)(i)(Q). The FDA includes this statement in the declaration specifically as a warning statement “to alert the submitter that a willfully and knowingly false statement is a criminal offense.” 68 Fed. Reg. at 36,686-87. Indeed, before the federal government, perjury includes any “materially false, fictitious, or fraudulent statement or representation” made “knowingly and willfully.” 18 U.S.C. § 1001(a). Perjury carries with it the penalty of up to five years in prison. *Id.*

## Conclusion

Listing patent information in the FDA’s Orange Book requires a generic drug applicant seeking to come on the market before patent expiration to certify against the listed patents, which often results in a suit for infringement by the patent owner against the generic applicant. In addition, the suit triggers a regulatory stay that further protects the NDA holder from harm that could otherwise result from FDA approval of an infringing drug product. In deciding which patent information to submit to the FDA for listing, pharmaceutical companies should consider the statutory and regulatory requirements for listing. They should also consider the possible consequences of improper listing, including administrative proceedings before the FDA and counterclaims in district court litigation.

## Tags

Orange Book

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