BEFORE THE
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

In the Matter of
Applications for FDA Approval to Market a New Drug; Patent Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug is Invalid or Will Not be Infringed

Docket No. 02N-0417

Comments of the United States Federal Trade Commission

December 23, 2002

I. INTRODUCTION

On July 30, 2002, the Federal Trade Commission released a comprehensive study that described several industry practices that delay FDA approval of generic drug products.[1] The FTC Study included legislative recommendations to address the possibility of future abuses of the generic drug approval process governed by the Hatch-Waxman Amendments. Chief among these recommendations was a proposed limitation of only one automatic 30-month stay per drug product per abbreviated new drug application (ANDA) to resolve infringement disputes over patents listed in the Orange Book prior to the filing date of the generic applicant's ANDA. On October 24, 2002, the FDA released this proposed rulemaking to eliminate the multiple 30-month stays that the FTC Study had identified as most harmful to consumers.

In this proceeding, the Food and Drug Administration (FDA) has requested comment[2] on those proposals to amend its regulations governing the availability of, and triggers for, the 30-month stay provision of the Hatch-Waxman Amendments as suggested by the FTC Study. Specifically, the FDA proposes: (1) to amend its existing rules to state that there will be one and only one opportunity for a 30-month stay of FDA approval of each abbreviated new drug application (ANDA); (2) to clarify the types of patents that must and must not be listed in the Orange Book; and (3) to revise the declaration statement that new drug application (NDA) applicants must submit as part of an NDA, an amendment to an NDA, or a supplement to

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[1] *See Generic Drug Entry Prior to Patent Expiration: An FTC Study* (Jul. 2002), *available at* <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>.

[2] Department of Health and Human Services, Food and Drug Administration, *Applications for FDA Approval to Market a New Drug; Patent Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug is Invalid or Will Not be Infringed*, 67 Fed. Reg. 65,448 (Oct. 24, 2002).

A brand-name drug manufacturer seeking to market a new drug product must first obtain FDA approval by filing a New Drug Application ("NDA"). At the time the NDA is filed, the NDA filer must also provide the FDA with certain categories of information regarding patents that cover the drug that is the subject of its NDA.[3] Upon receipt of the patent information, the FDA is required to list it in an agency publication entitled "Approved Drug Products with Therapeutic Equivalence," commonly known as the "Orange Book."[4]

To obtain approval of a generic version of a brand-name drug, Hatch-Waxman requires a generic applicant to file an Abbreviated New Drug Application ("ANDA"). Under the ANDA process, an applicant must demonstrate that the active ingredient of the generic drug is "the same" as that of the relevant brand-name product,[5] and also show that the generic drug product is "bioequivalent" to the relevant brand-name product.[6] The ANDA must contain, among other things, a certification regarding each patent listed in the Orange Book in conjunction with the relevant NDA.[7] One way to satisfy this requirement is to provide a "Paragraph IV certification," asserting that the patent in question is invalid or not infringed.[8]

Filing a Paragraph IV certification potentially affects two regulatory provisions – the 30-month stay provision and the 180-day marketing exclusivity provision. An ANDA filer that makes a Paragraph IV certification must provide notice to both the patent holder and the NDA filer, including a detailed statement of the factual and legal basis for the ANDA filer's assertion that the patent is invalid or not infringed.[9] Once the ANDA filer has provided such notice, a patent holder wishing to take advantage of the statutory stay provision must bring an infringement suit within 45 days.[10] If the patent holder does not bring suit within 45 days, the FDA may approve the ANDA as soon as other regulatory conditions are fulfilled.[11] If the patent holder does bring suit, however, the filing of that suit triggers an automatic 30-month stay of FDA approval of

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[3] 21 U.S.C. § 355(b)(1).

[4] *Id.* at § 355(j)(7)(A).

[5] *Id.* at § 355(j)(2)(A)(ii).

[6] *Id.* at § 355(j)(2)(A)(iv).

[7] *Id.* at § 355(j)(2)(A)(vii).

[8] *Id.* at ' 355(j)(2)(A)(vii)(IV).

[9] *Id.* at § 355(j)(2)(B). Although the patent holder and the NDA filer are often the same person, this is not always the case. Hatch-Waxman requires that all patents that claim the drug described in an NDA be listed in the Orange Book. Occasionally, this requires an NDA filer to list a patent that it does not own.

[10] *Id.* at § 355(j)(5)(B)(iii).

[11] *Id.* For example, the statute requires the ANDA applicant to establish bioequivalence. *Id.* at § 355(j)(2)(A)(iv).

[12] *Id.* at § 355(j)(5)(B)(iii).

[13] *Id.* at § 355(j)(5)(B)(iv).

[14] *See, e.g.*, *Biovail Corp. and Elan Corp. PLC*, Dkt. No. C-4057 (Aug. 20, 2002) (consent order); *Biovail Corp*., Dkt. No. C-4060 (Oct. 2, 2002) (consent order);

[17] *Abbott Laboratories*

listing of a patent on its brand-name drug BuSpar[20] presented the Commission with an opportunity to clarify whether there would be potential antitrust immunity under the *Noerr* doctrine for improper Orange Book listings. The *Noerr* doctrine[21] provides antitrust immunity for individuals "petitioning" government. Specifically, plaintiffs alleged that, through fraudulent filings with the FDA, Bristol-Myers caused that agency to list the patent in question in the Orange Book, thereby blocking generic competition with its BuSpar product, in violation of Section 2 of the Sherman Act.[22] Bristol-Myers defended its actions by, among other things, claiming that its activities were immune from antitrust scrutiny under *Noerr* doctrine. The Commission filed an *amicus* brief arguing that Orange Book filings are not "petitioning activity" immune from antitrust scrutiny.[23] On February 14, 2002, the district court issued an opinion denying Bristol-Myers's immunity claim.[24]

In another action, the Commission issued a consent order against Biovail Corporation,[25] settling charges that Biovail illegally acquired an exclusive patent license and wrongfully listed that patent in the Orange Book for the purpose of blocking generic competition to its brand-name drug Tiazac. This was the Commission's first enforcement action to remedy the effects of an allegedly improper, anticompetitive Orange Book listing.

The Commission also has taken action against alleged anticompetitive agreements between generic manufacturers. In August, 2002, the Commission issued a consent order against two generic drug manufacturers to resolve charges that they entered into an agreement that unreasonably reduced competition in the market for a generic anti-hypertension drug.[26]

B. The Commission's Industry-Wide Generic Drug Competition Study

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[20] *In re Buspirone Patent Litigation/In re Buspirone Antitrust Litigation*, 185 F. Supp. 2d 363 (S.D.N.Y. 2002) ("*In re Buspirone*"). Some of the same plaintiffs previously had brought suit under the FDC Act, requesting that the court issue an order compelling Bristol-Myers to de-list the objectionable patent. Although plaintiffs prevailed at the district court level, the Federal Circuit reversed that decision, holding that the FDC Act did not provide a private right of action to compel de-listing of a patent from the Orange Book. *See Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323, 1331-32 (Fed. Cir. 2001).

[21] The *Noerr* doctrine was first articulated in *Eastern R.R. Presidents Conf. v. Noerr Motor Freight, Inc.*, 365 U.S. 127 (1961), and *United Mine Workers of America v. Pennington*, 381 U.S. 657 (1965).

[22] 15 U.S.C. § 2.

[23] Memorandum of Law of *Amicus Curiae* Federal Trade Commission in Opposition to Defendant's Motion to Dismiss, *available at* <http://www.ftc.gov/os/2002/01/busparbrief.pdf>.

[24] *In re Buspirone, supra* note 20.

[25] *Biovail Corp., supra* note 14.

[26] *Biovail Corp. and Elan Corp. PLC, supra* note 14.

[27] 15 U.S.C. § 46(b).

[28] *See* 65 Fed. Reg. 61334 (Oct. 17, 2000); 66 Fed. Reg. 12512 (Feb. 27, 2001).

[29] 67 Fed. Reg. at 65454.

drug products (Platinol, Hytrin (tablets), Paxil, Taxol, BuSpar, Neurontin (tablets and capsules), and Tiazac) with 6 of the 8 instances occurring since 1998. The delay of FDA approval caused by these later-issued patents has ranged from 4 to 44 months. The net sales for each of these products ranged from greater than $100 million per year to greater than $1 billion per year. Thus, the economic impact of the delay caused by the unwarranted stay of FDA approval of a generic version of the brand-name product can be substantial.

A court found the later-issued patents for Platinol, Hytrin (tablets), Taxol, and BuSpar to be either invalid or not infringed by the ANDA. Pursuant to a consent agreement with the Commission, the NDA holder dismissed its patent infringement lawsuit involving the later-issued patent listed for Tiazac. The infringement litigation involving the later-issued patents for the remaining drug products (Paxil, Neurontin (tablets and capsules)) is pending.

The FTC Study further explained that the relationship between almost all of the later-issued patents and the corresponding 8 brand-name products raised issues of whether the patents had been appropriately listed in the Orange Book. In light of these findings, the Commission recommended that Congress permit only one automatic 30-month stay per drug product per ANDA to resolve infringement disputes over patents listed in the Orange Book prior to the filing date of the generic applicant's ANDA.

B. The FTC Recommendation Would Eliminate Stays Generated From "Later-Issued" Patents When an ANDA Has Already Been Filed

The FTC proposal does not guarantee the opportunity for one 30-month stay of every ANDA with a Paragraph IV certification. Rather, FDA approval would be stayed for 30 months based only on those patents that have been listed in the Orange Book before a generic applicant files an ANDA. The FTC recommendation eliminates the potential for harm caused by 30-month stays generated by later-issued patents. For example, if a generic applicant submits an ANDA that seeks FDA approval of a generic drug product at the expiration of a certain listed patent (*i.e.*, the generic applicant files an ANDA with a Paragraph III certification) and the brand-name company lists a later-issued patent in the Orange Book for that brand-name drug product, the FDA *would not be stayed* for 30 months from approving that previously filed ANDA. By contrast, under the FDA proposal, approval would be stayed under that scenario.

If the proposed FDA rule had been in place previously, it would have eliminated the second (or subsequent) 30-month stays of the ANDAs for 7 of the 8 brand-name drug products in which the FTC found that brand-name companies had listed later-issued patents in the Orange Book.[30] In the other instance, the proposed rule would not have affected the start of the 30-month stay of FDA approval for most of the ANDAs for the drug product Platinol. In that case, the brand-name company listed later-issued patents in the Orange Book on the eve of the expiration of the last patent that was blocking FDA approval of the pending ANDAs.

In sum, permitting only one 30-month stay will eliminate most of the potential for "gaming" the

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[30] For one of the 7 drug products (BuSpar), the brand-name company listed more than one later-issued patent in the Orange Book after several generic applicants had filed ANDAs that contained Paragraph III certifications relating to another patent. The FTC Study did not contain data describing when each generic applicant amended its pending ANDA to address each of the later-issued patents. It is likely, however, that most of the ANDAs for BuSpar would not have had the opportunity to be stayed for a second 30-month period had the proposed rule been in effect.

[31] 21 U.S.C. § 355(b)(1).

[32] 21 C.F.R.§ 314.53(b)

statute.[37] The court looked to the precedent, *Hoechst-Roussel Pharms., Inc. v. Lehman*,[38] which interpreted the term "claims" in the Patent Term Restoration portion of the Hatch-Waxman Amendments at 35 U.S.C. § 156(a) and concluded that a metabolite patent does not "claim" the approved drug product. In light of this interpretation, metabolite patents should not be listed in the Orange Book because they do not claim the drug as required by the listing statute's 2-prongs.

Likewise, "intermediate" patents listed in the Orange Book present a category that also do not literally claim the approved drug product. An intermediate patent claims a chemical compound that is used during the production of an active ingredient, but is not present in the final, marketed form of the drug product. The claimed compound is an "intermediate" on the pathway to the approved drug. The FDA notes that under its regulations, intermediates are "in-process materials" rather than drug substances or even drug components. Thus, patents that claim intermediates do not claim the approved drug product and fail the first prong for listing.[39]

B. Patents Reciting a Known Product, but a Novel Process Drafted in the Product-By-Process Format, Do Not Claim the Drug Product And Should Not Be Listed in the Orange Book

The FDA proposes to clarify that patents containing product-by-process claims are to be listed in the Orange Book because in such claims the "patented invention is the product (as opposed to the process used to make the product)."[40] Product-by-process patents must be listed in the Orange Book if they meet the 2-prong test of the listing statute. We suggest that the FDA refine its approach to safeguard against the listing of claims reciting a *known* product and a *novel* process that are drafted in the product-by-process format. Such claims do not claim a product and, therefore, do not meet the 2-prong test of the listing statute.

Product-by-process claims typically are used when a novel product cannot be adequately identified or described by its physical c rally arh3914 2ar2used whelistp6ec0.138 a

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[37] *Mylan Pharmaceuticals, Inc. v. Thompson*, 139 F. Supp. 2d 1, 19-21 (D.D.C. 2001), *rev'd on other grounds*, 268 F.3d 1323 (Fed. Cir. 2001).

[38] 109 F.3d 756 (Fed. Cir. 1997).

[39] 67 Fed. Reg. at 65452.

[40] *Id.*

[41] *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) ("Product-by-process claims are not specifically discussed in the patent statute. The practice and governing law have developed in response to the need to enable an applicant to claim an otherwise patentable product that resists definition by other than the process by which it is made").

[42] *In re Bridgeford*, 357 F.2d 679, 682 (C.C.P.A. 1966). The use of product-by-process claims, however, appears to be rare in the patenting of pharmaceutical products and drug substances

governed by Hatch-Waxman because it is possible to identify and claim such products by their physical characteristics rather than by the process of making the product.

listing statute requires these claims to be listed in the Orange Book (provided they also satisfy the other criteria of the listing statute). When a claim relies solely on a novel process for patentability, even if such a claim is drafted in product-by-process format, it is not a product claim, and therefore, does not satisfy the first prong. Neither the listing statute nor FDA's proposal allows the listing of patents based on claims in which the patentee only relied on the *process* as the novel invention.

The Commission in its Study identified several patents listed in the Orange Book based on claims

[48] *See* FTC Study at A-42- A-44.

[49] 67 Fed. Reg. at 65452.

[50] Patents claiming a chemical compound that differ by water-of-hydration or that form a crystalline structure different from the active ingredient are referred to as "polymorphs." Under the proposed change, an NDA holder who had obtained FDA approval of the *an*hydrate form of a drug substance (having no water) would be required to list a patent, if it obtained one, claiming the *mono*hydrate form of the same drug substance (having one water molecule in its crystalline structure for each molecule of the drug substance) or any patent it obtains that claims another hydrated form of the

language of the listing statute and the underlying purpose of Hatch-Waxman support retaining the FDA's existing regulations that do not allow listing patents in the Orange Book that claim a different form of a drug substance than that approved through the NDA.

As discussed above, the first prong of the listing statute requires that a patent be listed in the Orange Book that "claims the drug or a method of using the drug that is the subject of the new drug application or amendment." The FDA proposes to add to the language in its regulation implementing the first prong (which is nearly identical to the listing statute) the phrase "or that claim a drug substance that is the same as the active ingredient that is subject of the approved or pending application within the meaning of section 505(j)(2)(A)(ii) of the act."[51]

Section 505(j)(2)(A)(ii) requires generic the app-107n62rrlFDA propose2 alwiw8a that

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drug substance.

[51] 67 Fed. Reg at 65452.

[52] 21 U.S.C. § 355(j)(2)(A)(ii). For ease of discussion, this section will be referred to as the "ANDA submission section."

[53] 67 Fed. Reg. at 65452

[54] *Association of American Physicians and Surgeons, Inc. v. FDA*, 2002 U.S. Dist. LEXIS 19689, 709 (D.D.C. 2002) *citing Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc*. 467 U.S. 837, 842-43 (1984).

substance. The first prong of the listing statute requires the NDA holder to list any patents claiming the approved form in the Orange Book. Conversely, the plain language of the statute does not allow the listing of patents that claim an unapproved form of the drug substance.

The requirements of the ANDA submission section do not change this analysis because they do not alter the plain language of the listing statute. The FDA allows generic drug products to contain a drug substance that differ from that approved through the NDA because the FDA looks to principles of pharmaceutical equivalence in defining the "same active ingredient" requirement of the ANDA submission section.[55] Critically, the term "same" does not appear in the listing statute.

No harmonization of the two section is necessary because the scope of drug substances to be considered the "same" in the ANDA submission section is broader than the requirements governing the patents to be listed in the Orange Book. Indeed, the very structure of the Hatch-Waxman system works precisely because Congress took advantage of the fact that drugs can be pharmaceutically and therapeutically equivalent without being identical (infringing) in a patent law sense. It is this lack of patent law identity that allow generic drugs to be marketed under Hatch-Waxman before the relevant patents have expired.

The analysis required to determine whether a patent must be listed in the Orange Book is a patent law analysis (whether the patent "claims" NDA's drug),[56] whereas the analysis required to determine whether a generic product contains the same active ingredient as that of a listed drug is a pharmaceutical analysis.[57] As explained below, the two analyses will give different results.

For example, to obtain a later polymorph patent from the PTO, the patentee typically demonstrates how the polymorph is patentably distinct from the FDA-approved drug substance. If the later polymorph were "the same" in a patent sense, then the patent claiming it would not issue in the first instance. Thus, by virtue of obtaining the later patent, the NDA holder often explicitly takes the position that the polymorph patent does not satisfy the listing statute (*i.e.*, that it does not claim the drug substance that is the subject of the NDA). Nevertheless, the FDA-approved drug substance and the later polymorph may well be pharmaceutically equivalent and, therefore, the "same" in the sense of the ANDA submission section of Hatch-Waxman.

The drug substance patents listed for the drug product Paxil illustrates the distinction between a patent law analysis and a pharmaceutical analysis. The original drug substance patent (Patent No. 4,007,196) covering all forms of paroxetine hydrochloride has expired. The NDA holder obtained another drug substance patent (Patent No. 4,721,723) that claims paroxetine hydrochloride *hemihydrate*, the form of

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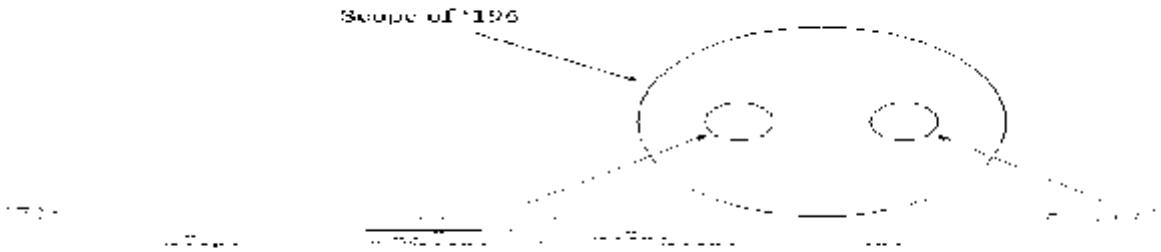
[55] *Serono Labs, Inc., v. Shalala*, 158 F.3d 1313, 1320-21 (D.C. Cir. 1998).

[56] Indeed, in the discussion of why metabolites patents do not satisfy the requirements of the listing statute, the FDA cites with approval the notion that the term "claims" as used in the first prong of the listing statute is based on patent law concepts. *See* 67 Fed. Reg. at 65451. There is no reason why the listing statute would require a different analysis for determining whether metabolite patents and polymorph patents should be listed in the Orange Book.

[57] *But see Zenith Laboratories, Inc. v. Abbott Laboratories, Inc.*, 1997 LEXIS U.S.Dist. 23954 (D. NJ 1997).

the active ingredient approved through the NDA. The NDA holder then obtained a third drug substance patent (Patent No. 5,900,423) claiming paroxetine hydrochloride *anhydrate form A*. To prevent the '723 hemihydrate patent from being considered invaliding prior art to the '423, the patentee distinguished the anhydrate of the '423 patent from the hemihydrate form claimed in the '723 patent.[58] (The relationship of the scope of coverage of the three patents is illustrated in Figure 1.) Although the hemihydrate and anhydrate forms both fall within the broader category of all paroxetine compounds covered by the '196 patent, the '723 and '423 patents are necessarily patentably distinct from each other. They *cannot* be the "same" in a patent analysis. If they were the "same," then the '723 patent would invalidate the '423 patent. In spite of the fact that the anhydrate and hemihydrate forms are patentably distinct; however, they may react identically in a pharmaceutical sense and, therefore, be pharmaceutically equivalent.

Figure 1



[58] Patent law allows the patenting of a species compound (*i.e.*, the anhydrate of the '423 patent) even when a broad category, called a genus, of compounds (*i.e.*, all paroxetine compounds of the '196 patent) has been described in an earlier publication. *See In re Kaplan*, 789 F.2d 1574, 1578 (Fed. Cir. 1986).

different polymorphs than those approved for Hytrin, Paxil, and Neurontin that have provided the basis of 30-month stays on FDA approval of generic versions of these drug products.

Fifth, the proposed change to require the listing of patents that claim a different form of the drug

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[62] This prohibition is rooted in 35 U.S.C. § 101, which provides that an inventor "may obtain a patent" for a new invention. 35 U.S.C. § 101; *see also In re Hallman*, 655 F.2d 212, 216 (C.C.P.A. 1981). The courts have interpreted the word "a" in this provision to mean that only one patent may issue for a single scientific advance. *In re Vogel*, 422 F.2d 438, 441(C.C.P.A. 1970).

[63] *See In re Vogel*, 422 F.2d at 441.

[64] *See* U. S. Patent and Trademark Office, "Manual of Patent Examining Procedure," Section 804.02, *available at* <http://www.uspto/web/offices/pac/mpep/documents/0431.htm>.

[65] *See id*. at 4 (discussing why a terminal disclaimer is required to overcome judicially created double patenting rejections in applications filed on or after June 8, 1995).

[66] We note that although this problem may be limited if there is only one 30-month stay, it is important to ensure that only patents that meet the requirements of the listing statute are included in the Orange Book. *See supra* text accompanying note 33.

subpart F. It could read as follows:

> F. For each drug substance or drug product claim that was (1) identified as listable in subparts B and C and (2) is drafted in product-by-process format, please provide the following information:
>
> 1. Is the product of the recited process novel? [*If the answer to question F.1 is "no," stop. The patent cannot be listed. If yes, please identify the claim(s) by number.*]

To address the terminal disclaimer issue, the FDA may wish to add the following questions to subpart A of the proposed declaration:

> 5. Does this patent contain a terminal disclaimer over a patent that has been listed in the Orange Book? [*If the answer to question A.5 is yes, stop here. The patent may not be listed in the Orange Book. If the answer is no, proceed to subpart B.*]

Finally, in its proposed declaration, the FDA included a new emphasis on the specific claims of the