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Division of Dockets Management  
Food and Drug Administration  
5630 Fishers Lane, Room 1061 (HFA-305)  
Rockville, Maryland 20852

**CITIZEN PETITION**

ACTION REQUESTED

This Citizen Petition is submitted under Section 505 of the Food, Drug and Cosmetic Act ("FDCA") and Section 10.30 of the Food and Drug Administration's ("FDA") implementing regulations. This petition requests, on behalf of Ranbaxy Laboratories Limited ("Ranbaxy"), that FDA (1) refrain from the approval of any ANDA for simvastatin 80 mg tablets until Ranbaxy's 180-day exclusivity has expired and (2) confirm that Ranbaxy's rights to 180-day exclusivity with regard to ANDA No. 76-285 for simvastatin 80 mg have not been affected by FDA's delisting of U.S. Patent No. RE 36,481 (the "481 patent") and U.S. Patent No. RE 36,520 (the "520 patent"), the patents on which Ranbaxy's paragraph IV certifications were based. In order to preserve its entitlement to exclusivity, Ranbaxy requests that FDA correct its erroneous removal of these patent listings by reinserting the information in the Orange Book and maintain the listing until Ranbaxy's term of exclusivity has elapsed.<sup>1</sup>

STATEMENT OF GROUNDS

I. Background

In November 2001, Ranbaxy submitted ANDA No. 76-285 for multiple strengths of simvastatin tablets, which refers to Zocor® as the reference listed drug. Merck & Co. ("Merck") holds the NDA for Zocor®. With its ANDA, Ranbaxy submitted paragraph IV certifications for the '481 and '520 patents, both of which were listed in the Orange Book as patents that claim Zocor®. Ranbaxy believes that it is the first ANDA applicant to submit a substantially complete

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1. IVAX Pharmaceuticals, Inc. ("IVAX") filed a Citizen Petition on January 5, 2005 (docket 2005P-0008) in which it requests that FDA reinstate the '481 and '520 patents to the Orange Book, require subsequent ANDAs for simvastatin to contain certifications to these patents, and not approve ANDAs for simvastatin tablets, 5 mg, 10 mg, 20 mg, and 40 mg until IVAX's 180-day exclusivity expires. Ranbaxy has no objection to consolidating its petition and IVAX's petition in the same docket.

2005P-0046

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paragraph IV certification for simvastatin tablets 80 mg with regard to the '481 and '520 patents. Ranbaxy's ANDA has been tentatively approved.

Nearly three years later, on September 27, 2004, Ranbaxy discovered a statement on the FDA website for the Electronic Orange Book that FDA has delisted the '481 and '520 patents. This delisting came as a surprise to Ranbaxy. These patents claim related compounds of simvastatin that are believed by Ranbaxy to be present in Zocor® and that exist as a byproduct of Merck's manufacture of simvastatin. Each are listed as valid patents by the U.S. Patent and Trademark Office and Ranbaxy has no reason to believe that these patents had been erroneously listed in the Orange Book.

Whether or not these related compounds are actually present in Zocor®, Ranbaxy devoted considerable resources to designing its simvastatin so as not to infringe the '481 and '520 patents. Presumably because of its efforts, Ranbaxy has not been sued by Merck with respect to these certifications. Ranbaxy's paragraph IV certification has, however, exposed it to potential patent suits for almost three years. Unless FDA acts to recognize Ranbaxy's 180-day exclusivity, delisting these patents could deprive Ranbaxy of the exclusivity to which it is entitled.<sup>2</sup>

## II. Ranbaxy is Entitled to 180-Day Exclusivity.

Merck identified the '481 and '520 patents as patents that claim Zocor® when it submitted them for listing over three years ago. Because of the promptness and intensity with which it pursued its efforts to design its simvastatin to avoid infringement of these patents, Ranbaxy believes that it is the first ANDA applicant to submit a paragraph IV certification for simvastatin 80 mg tablets with regard to the '481 and '520 patents. Under the clear and unqualified mandate of the statute, Ranbaxy is therefore entitled to 180-day exclusivity.<sup>3</sup>

## III. FDA has Long Recognized That it Would Be Inappropriate to Nullify the Right to 180-Day Exclusivity by Delisting a Patent.

In its implementation of the Hatch-Waxman Amendments, FDA established a regulatory scheme requiring ANDA applicants to submit patent certifications based on the agency's official list, which is required by statute and maintained in the Orange Book.<sup>4</sup> As part of the scheme, FDA's regulation contemplates that FDA will amend the list in certain circumstances.<sup>5</sup> This regulation provides a mechanism to bring listing controversies to FDA and, through FDA to the NDA holder. The patent holder then has the opportunity to respond. FDA will not change the listing unless the patent holder withdraws or amends the patent information.

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2. It is Ranbaxy's understanding that, based on the removal of the patents from the list, FDA would require all ANDA applicants, including Ranbaxy, to withdraw their paragraph IV certifications for the delisted patents. FDA presumably would then take the position that Ranbaxy is not entitled to 180-day exclusivity on these patents. Pending disposition of this issue, Ranbaxy has not withdrawn its paragraph IV certifications for the '481 and '520 patents.

3. Section 505(j)(5)(B)(iv)(2004). See also, e.g., Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1069 (D.C. Cir. 1998).

4. 21 C.F.R. § 314.53 (2004).

5. 21 C.F.R. § 314.53(f) (2004).

Neither this regulation nor any other identifies the circumstances in which FDA will amend the list, or when FDA will amend the list. Once the FDA amends the list, ANDA applicants are required to withdraw paragraph IV certifications.<sup>6</sup>

In implementing this scheme, the agency recognized that removing patents from the list created the potential for nullification of the statutory right to 180-day exclusivity. Should the agency remove a patent from the list based on the withdrawal of a patent submission by an NDA holder, the statutory right to 180-day exclusivity could be nullified by the requirement that ANDA applicants withdraw their paragraph IV certifications referring to that patent. The agency noted that an ANDA applicant's entitlement to 180-day exclusivity could be extinguished if a patent were delisted after the accrual of the right to 180-day exclusivity based on a judicial holding that the listed patent is invalid. The delisting of the patent determined to be invalid would have required all ANDA applicants to withdraw their paragraph IV certifications, and would have thus nullified the first applicant's right to 180-day exclusivity. In the preamble to its 1994 regulations, the agency concluded that the entitlement to 180-day exclusivity should not be undermined in this way:

[T]he agency agrees that the protection offered by 180-day exclusivity should not be undermined by changes from paragraph IV certification or by the filing of original certifications other than paragraph IV certifications. If a patent were removed from the list immediately upon a court decision that the patent is invalid or unenforceable, an applicant with a subsequently filed application might seek to certify that there is no relevant patent and seek an immediately effective approval.<sup>7</sup>

The agency recognized that the right to 180-day exclusivity must be preserved in this circumstance, not only because of the clear command of the statute, but also because the 180-day exclusivity serves one of the fundamental purposes of the statute – to encourage generic competition by encouraging patent challenges through a reward to the first applicant to challenge a patent.<sup>8</sup> Those same principles are equally applicable when the certification and notice cause the patent holder to conclude that its patents should not, or cannot, be enforced in patent litigation.

IV. FDA Sought to Prevent Nullification of 180-Day Exclusivity in Its Implementing Regulation and Should Maintain that Position Following Changes in the Accrual of the Right to 180-Day Exclusivity.

The agency's solution to the potential dilemma posed by patent delistings was to deem a patent to be "relevant," and thus listable, during the pendency of any applicant's right to 180-day

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6. 21 C.F.R. § 314.94(a)(12)(viii)(B) (2004).

7. Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,348 (Oct. 3, 1994) (emphasis added).

8. See Purepac Pharm. Co. v. Torpharm, Inc., 354 F.3d 877, 879 (D.C. Cir. 2004). ("In order to encourage paragraph IV challenges, thereby increasing the availability of low-cost generic drugs, the FDCA provides that the first company to win FDA approval of an ANDA containing a paragraph IV certification has the right to sell its drug without competition for 180 days.")

exclusivity, without regard to subsequent determinations that the patent is invalid or unenforceable. The agency adopted this approach in its 1994 implementing regulation, explaining as follows:

To ensure that [withdrawal of a paragraph IV certification upon delisting] does not occur, the agency has required that a patent remain on the list after being declared invalid or unenforceable until the end of any applicable 180-day exclusivity period. This means that a patent is deemed to be relevant under [21 C.F.R.] § 314.94(a)(12)(ii) until the end of the term of the patent or applicable 180-day exclusivity period, whichever occurs first. Thus, where there is a patent that has been challenged by a paragraph IV applicant, a subsequent applicant will not be able to file a certification that there is no relevant patent or seek an immediately effective approval until either the patent or the 180-day exclusivity period expires.<sup>9</sup>

Thus, to ensure that 180-day exclusivity rights would not be extinguished by the removal of a patent from the list, the agency included the following provision in its implementing regulations:

If a patent is removed from the list, any applicant with a pending application (including a tentatively approved application with a delayed effective date) who has made a certification with respect to such patent shall amend its certification. The applicant shall certify under paragraph (a)(12)(ii) of this section that no patents described in paragraph (a)(12)(i) of this section claim the drug or, if other relevant patents claim the drug, shall amend the certification to refer only to those relevant patents. In the amendment, the applicant shall state the reason for the change in certification (that the patent is or has been removed from the list). A patent that is the subject of a lawsuit under [21 C.F.R.] § 314.107(c) shall not be removed from the list until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended.<sup>10</sup>

The references in the regulation to a patent that is the subject of a lawsuit, and to a delay in effective dates of approval based on the lawsuit, were required to limit the effect of the regulation to patents for which 180-day exclusivity rights had accrued. At the time of the 1994 rulemaking, FDA concluded that 180-day exclusivity rights did not accrue until the first ANDA applicant submitting a paragraph IV certification was sued by the NDA holder or patent holder,

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9. Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. at 50,348 (emphasis added).

10. 21 C.F.R. § 314.94(a)(12)(viii)(B) (2004) (emphasis added). This regulation necessarily recognizes FDA's legal authority to delay delisting in appropriate circumstances.

and had successfully defended against the challenge.<sup>11</sup> The “litigation” requirement, however, was subsequently overturned in court decisions,<sup>12</sup> and the agency acquiesced in the courts’ holding, thus eliminating the requirements of a lawsuit and successful defense as pre-requisites for 180-day exclusivity.<sup>13</sup>

Although the agency changed its interpretation of the statute to recognize accrual of 180-day exclusivity rights upon the submission of the paragraph IV certification rather than upon the initiation of an infringement suit, the agency did not amend 21 C.F.R. § 314.94(a)(12)(viii)(B) to reflect the new position.<sup>14</sup> Thus, despite being overturned in court and ostensibly abandoned by the agency, the agency’s initial position that the accrual of exclusivity depends on litigation continues to be reflected in its regulation, which is worded to protect exclusivity rights against patent delistings where a first applicant has been subjected to an infringement suit.

At the time that it acquiesced in the courts’ holdings, FDA stated in a guidance that it would remove the litigation and successful defense provision from the regulations and, in the meantime, “regulate directly from the statute” and “make decisions on 180-day generic drug exclusivity on a case-by-case basis.”<sup>15</sup> Although its statement was directed at 21 C.F.R. § 314.107(c), the regulation that had been directly challenged, the same logic would require that it treat 21 C.F.R. § 314.94(a)(12)(viii)(B) in the same way. Failing to do so would, in effect, resurrect the litigation requirement and nullify 180-day exclusivity rights that the agency has acknowledged accrue upon submission of the first paragraph IV certification.

V. The Statute Cannot Support an Interpretation That Would Resurrect the “Litigation” Requirement to Preserve Exclusivity.

An application of the statute that would nullify 180-day exclusivity in the absence of a patent infringement suit is contrary to congressional intent and to basic principles of statutory construction. The statute itself contains no provision authorizing the removal of a patent from

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11. Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. at 50,352-53. The proposed regulation required the initiation of a lawsuit against the ANDA applicant, but not the successful defense of the lawsuit. Abbreviated New Drug Regulations, 54 Fed. Reg. 28,872, 28,929 (proposed July 10, 1989) (to be codified at 21 C.F.R. Parts 10, 310, 314, and 320).

12. See Purepac v. Friedman, 162 F.3d 1201 (D.C. Cir. 1998); Granutec v. Shalala, No. 97-1873 and No. 97-1874, 1998 U.S. App. LEXIS 6685 (4th Cir. Apr. 3, 1998); Mova, 140 F.3d at 1060.

13. See 180-Day Generic Drug Exclusivity for Abbreviated New Drug Applications, 64 Fed. Reg. 42,873, 42,876 (proposed Aug. 6, 1999) (to be codified at 21 C.F.R. Part 314). See also Guidance for Industry: 180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act (June 1998) (“Guidance”); Guidance for Industry on 180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act; Availability, 63 Fed. Reg. 37,890 (notice announced July 14, 1998).

14. FDA did amend 21 C.F.R. § 314.107(c) to remove the express requirements of a lawsuit and successful defense, which had been directly challenged in the lawsuits. Effective Date of Approval of an Abbreviated New Drug Application, 63 Fed. Reg. 59,710 (Nov. 5, 1998).

15. Guidance at 4.

the list based on the withdrawal of a patent submission. It is not reasonable to infer authority to remove patent listings in a manner that would nullify an applicant's right to 180-day exclusivity, a right that is grounded in the statute. The statutory grant of 180-day exclusivity to the first ANDA applicant submitting a paragraph IV certification is clear and unqualified. It provides no exception for a patent that is later withdrawn by the NDA holder.

Indeed, this was clearly the agency's interpretation of the statute when it promulgated its implementing regulations, and stated that "180-day exclusivity should not be undermined by changes from paragraph IV certification or by the filing of original certifications other than paragraph IV certifications . . ."<sup>16</sup> This interpretation is compelled by the clear intent behind that 180-day exclusivity statutory provision. The award of 180-day exclusivity is designed to encourage ANDA applicants to challenge patents through the submission of such certifications. Once the ANDA applicant has fulfilled the statutory objective of challenging the patent and exposing itself to an infringement suit, the structure of the statute demonstrates a clear intent to reward the applicant by delaying approval of ANDAs submitted by subsequent challengers. The statutory does not permit an NDA holder to nullify this reward by withdrawing its patent submission.

An application of the agency's 1994 delisting regulation that would protect a first applicant's 180-day exclusivity only where the applicant has been sued is not consistent with the agency's current interpretation of the statute. As the courts have ruled, FDA may not limit 180-day exclusivity rights based on the initiation of an infringement suit.

#### VI. 180-Day Exclusivity Serves Important Policy Goals and Should Not be Undermined.

The Hatch Waxman incentives have increased generic drug entry,<sup>17</sup> and thereby brought consumers significant savings.<sup>18</sup> 180-day exclusivity is a central part of Hatch Waxman, providing an important incentive for generic drug manufacturers to file applications to enter the market with a generic version of a drug product prior to expiration of the brand name drug product's patents.<sup>19</sup> As the Federal Trade Commission ("FTC") has noted, through the "180-day

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16. Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. at 50,348.

17. Federal Trade Commission, Generic Drug Entry Prior to Patent Expiration: An FTC Study (July 2002) ("2002 FTC Study") at i, available at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf> (last accessed Feb. 1, 2005) (Attachment A).

18. Michelle Meadows, Greater Access to Generic Drugs: New FDA Initiatives to Improve Drug Reviews and Reduce Legal Loopholes, FDA Consumer Magazine (Sept.-Oct. 2003), available at [http://www.fda.gov/fdac/features/2003/503\\_drug.html](http://www.fda.gov/fdac/features/2003/503_drug.html) (last accessed Feb. 1, 2005) (Attachment B).

19. According to the FTC, during the 1980s only 2 percent of generic applications sought entry prior to patent expiration, but approximately 20% of the applications filed between 1998 and 2000 sought entry prior to expiration. 2002 FTC Study at ii. See Purepac, 354 F.3d at 879 (D.C. Cir. 2004) (recognizing that the purpose of the 180-day exclusivity is to encourage paragraph IV challenges, thereby increasing the availability of low cost generic drugs).

provision, Hatch-Waxman provides an incentive for companies to challenge patent validity and to ‘design around’ patents to find alternative, non-infringing forms of patented drugs.”<sup>20</sup>

When a brand name company receives notice of a paragraph IV certification, it is forced to examine its patent. If it is in fact defensible, the brand name company may file a patent infringement suit. As an alternative, however, the brand name company may decide that litigation is not justified.<sup>21</sup> A brand name company might decide, for example, that it does not want to engage in litigation or that its patent position is weak. Regardless of the reason for deciding not to file suit, the result is the same: there will be entry by generic competitors sooner than would otherwise be the case. Thus, 180-day exclusivity makes an important contribution to fostering competition.<sup>22</sup>

When a generic company has made the substantial effort to design around the patent and to be the first to file, it should not lose its entitlement to 180-day exclusivity because the innovator decides, for whatever reason, to delist the patent. That result would be unfair to the company that had made the effort to be the first paragraph IV filer, which would lose its exclusivity through no fault of its own, but due to the accident that a brand name company had chosen to withdraw the patent at that time. It would be especially unfair to withdraw 180-day exclusivity in a situation in which the paragraph IV notification caused the innovator to review its listing, to decide that the listing was inappropriate, and to withdraw the patent. FDA has previously acknowledged this possibility and stated that its policy is to avoid such a result:

FDA believes that if the first applicant avoids a lawsuit and the related 30-month stay of final approval (see section 505(j)(5)(B)(iii) of the act), for example, by designing around a patent in such a way that its drug product is clearly noninfringing, then that applicant should not be denied eligibility for exclusivity. In addition, an ANDA applicant should not be encouraged to file a frivolous certification that invites litigation so as to qualify for exclusivity. Permitting an applicant who avoids a lawsuit to be eligible for exclusivity is consistent with the statutory language and goal of facilitating prompt entry of generic drug products into the market.<sup>23</sup>

In these circumstances, the delisting of the patent would actually penalize the first applicant for its successful challenge. Further, it would cause generic companies to factor into

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20. 2002 FTC Study at vi.

21. The FTC calculated that generic companies prevailed in nearly 75% of the patent suits. 2002 FTC Study at viii.

22. The data indicate that “when not sued, first generic applicants, upon receiving FDA approval, begin commercial marketing in a timely manner that triggers the running of the 180 days and allows FDA approval of any subsequent generic applicant once the 180-day period has run.” *Id.*

23. 180-Day Generic Drug Exclusivity for Abbreviated New Drug Applications, 64 Fed. Reg. at 42,876.

their development decisions the possibility that they would lose 180-day exclusivity late in development, and thus, be a disincentive.

In addition, permitting delisting when the delisting would affect entitlement to 180-day exclusivity would place the decision as to whether 180-day exclusivity is awarded in the hands of the brand name company. That would invite anticompetitive activity in the form of agreements between branded and generic companies, an issue that has already drawn the government's attention in other circumstances. Giving a branded company the opportunity to decide whether 180-day exclusivity will be withdrawn would provide that company an additional bargaining chip in any such negotiations.

Moreover, if FDA allows exclusivity to be eliminated by the quality of the first applicant's challenge, first applicants will have the paradoxical incentive of providing paragraph IV letters with as little information as possible so as to initiate patent litigation and ensure qualification for 180-day exclusivity.<sup>24</sup>

Hatch Waxman requires that patents that claim the drug and could support a claim of infringement be listed. Merck certified that these patents claim the drug and nothing on the face of either patent signaled that the listing was improper.<sup>25</sup> FDA should not cooperate in delisting a patent that was certified as properly listed, and certainly should not do so when the consequence is to deprive Ranbaxy of its legitimately earned 180-day exclusivity.

## VII. Conclusion

Ranbaxy has invested considerable time and resources developing a formulation for its simvastatin 80 mg tablets. In doing so, it has had to design around the patents that FDA now proposes to delist so that its product is noninfringing. By filing a paragraph IV certification, Ranbaxy also exposed itself to costly patent litigation. Merck may change its patent information if it has now determined that it will not be asserting any claim of patent infringement for the '481 and '520 patents. But FDA should not deprive Ranbaxy of the 180-day exclusivity to which it is entitled by delisting the patents in a manner that extinguishes the exclusivity before it has run. Had Merck sued Ranbaxy, FDA would not be allowed to do so. The fact that Merck did not sue

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24. Allowing branded companies to delist in derogation of 180-day exclusivity may lead to the unintended consequence of causing first-to-file generic applicants with strong noninfringement or invalidity arguments to send paragraph IV notifications with minimal information purely to force the NDA holder to initiate litigation. Rather than presenting the noninfringement or invalidity arguments in the notification to avoid litigation, the generic company would invite litigation to avoid delisting and then provide the complete noninfringement or invalidity arguments that otherwise would be provided in the paragraph IV notification. While initiating litigation would benefit the generic company because it would ensure that the patents cannot later be delisted and the 180 day exclusivity eliminated, the litigation otherwise would be a waste of resources.

25. These are not patents whose ineligibility for listing is clearly stated in FDA's regulation. 21 C.F.R. § 314.53(b) (2004). To Ranbaxy's knowledge, the two patents at issue claim part of the Zocor® formulation.

Ranbaxy should not influence Ranbaxy's entitlement to 180-day exclusivity.<sup>26</sup> As FDA has said before, when a first applicant avoids a lawsuit "by designing around a patent in such a way that its drug product is noninfringing, then that applicant should not be denied eligibility for exclusivity."<sup>27</sup>

In this instance the agency has already removed the patents from the Orange Book. That act, however, does not impair the agency's ability to reassess its position and restore the listings for the period necessary to recognize Ranbaxy's exclusivity.<sup>28</sup> Agencies have broad discretion to fashion remedies to restore a party's rights.<sup>29</sup>

FDA must fashion a policy that is consistent with Congress' directives that the first applicant to challenge a patent by submitting a paragraph IV certification be rewarded by a delay in the approval of subsequently submitted ANDAs containing a paragraph IV certification and that appropriate patents are listed. This requires a patent listing policy that will avoid nullification of 180-day exclusivity that might result from delisting a patent prior to the end of an exclusivity period.<sup>30</sup>

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26. The same remedy should apply regardless of whether a listing was caused by an inadvertent error rather than a conscious decision by the holder. In either case the listing provides a barrier to entry of generic drugs. Moreover, it is exceedingly unlikely that inadvertent errors will occur given the declarations currently required by the agency under revised 21 C.F.R. § 314.53. *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. 36,676, (June 18, 2003).

27. 180-Day Generic Drug Exclusivity for Abbreviated New Drug Applications, 64 Fed. Reg. at 42,876.

28. See, e.g., Motor Vehicle Mfrs Ass'n v. State Farm, 463 U.S. 29, 42 (1983) (an agency may change course by providing reasoned analysis); Good Samaritan Hosp. v. Shalala, 508 U.S. 402, 417 (1993) (an administrative agency is not disqualified from changing its mind).

29. See Panhandle Eastern Pipe Line Co. v. FERC, 95 F.3d 62, 67 (D.C. Cir. 1996); Purepac Pharm. Co. v. Torpharm, 354 F.3d at 889.

30. To our knowledge, FDA has not issued a definitive interpretation of its regulations that would preclude the action sought in this petition. Compare Air Transport Ass'n v. FAA, 291 F.3d 49, 57-8 (D.C. Cir. 2002) (where previous interpretation does not constitute a definitive inconsistent interpretation of a regulation, no new rulemaking is required) with Alaska Prof'l Hunters Ass'n v. FAA, 177 F.3d 1030, 1034 (D.C. Cir. 1999) (reversal of 30 year interpretation of a regulation required notice and comment). In fact, FDA has previously refused requests to delist patents that were improperly listed. For example, FDA refused to delist a mirtazapine-related patent, even though the patent did not claim an approved use of the listed drug. Letter from Gary J. Buehler, Director, Office of Generic Drugs, Center for Drug Evaluation and Research, FDA to Gilbert's (Feb. 24, 2003) (Attachment C). See also Letter from Gary Buehler, Director, Office of Generic Drugs, Center for Drug Evaluation and Research, FDA to Daniel J. Tomasch, Esq. (May 28, 2003) (regarding brimonidine) (Attachment D).

ENVIRONMENTAL IMPACT

The relief requested by this petition would result in the recognition of a 180-day period of exclusivity for an ANDA. Because the grant of the petition would not have an effect on the environment, no environmental assessment is required. 21 C.F.R. § 25.31(a) (2004).

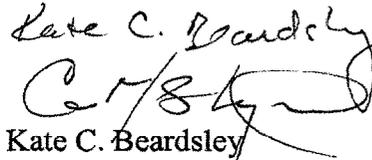
ECONOMIC IMPACT

Information on the economic impact of the action requested by this petition will be submitted if requested by the Commissioner.

CERTIFICATION

The undersigned certify that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to us, which are unfavorable to the petition.

Respectfully submitted,



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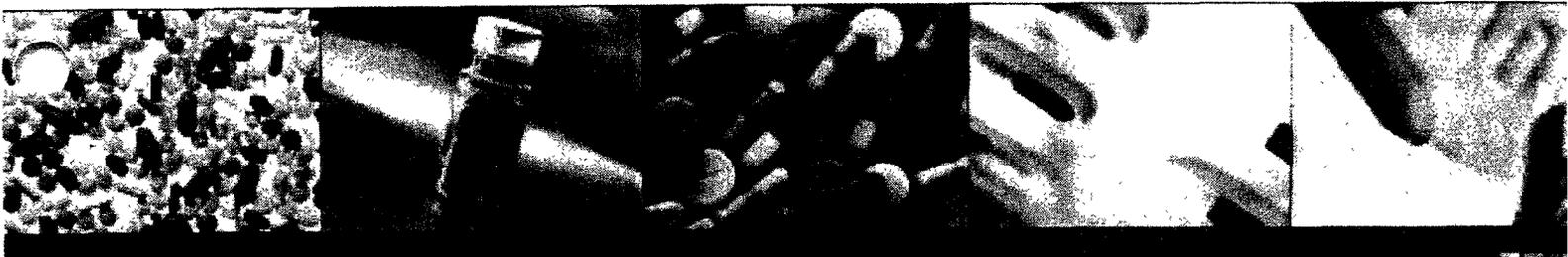
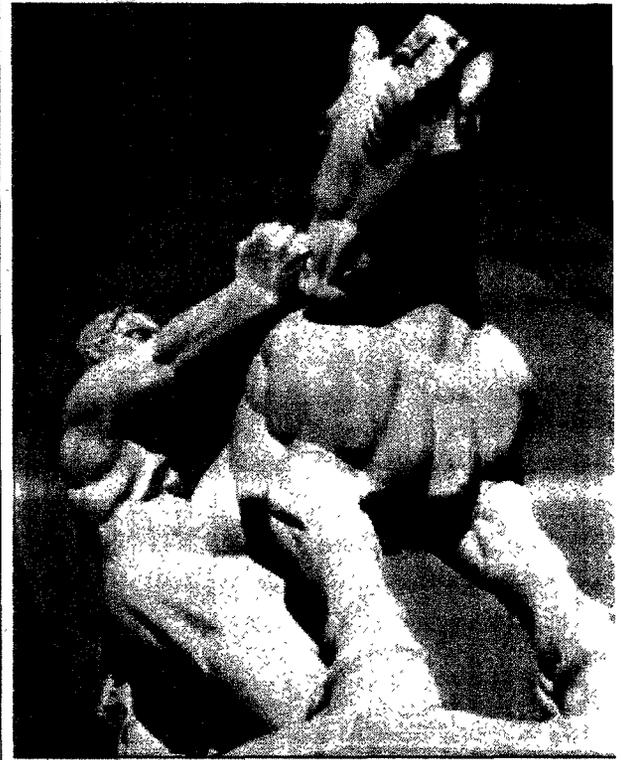
**ATTACHMENT A**



# Generic Drug Entry Prior to Patent Expiration:

## An FTC Study

Federal Trade Commission  
July 2002



# Federal Trade Commission

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# **GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY**

## **Executive Summary and Legislative Recommendations**

Pharmaceutical drug products have become increasingly important to providing consumers with a myriad of treatments and cures that increase life expectancy and enhance lives. It is critical to maintain appropriate incentives for the development of new drug products, because the necessary research and development is risky and costly. Innovation in the pharmaceutical industry, spurred in part by competitive market forces, continues to bring enormous benefits to Americans.

At the same time, expenditures on pharmaceutical products continue to grow and often outpace expenditures for other consumer products. Pharmaceutical expenditures concern not only consumers, but government payers, private health plans, and employers as well. Generic drugs offer opportunities for significant cost savings over brand-name drug products.

The Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act have shaped substantially the current legal environment governing Food and Drug Administration (FDA) approval of generic drug products. Hatch-Waxman established a regulatory framework that sought to balance incentives for continued innovation by research-based pharmaceutical companies and opportunities for market entry by generic drug manufacturers. The Amendments compensate brand-name companies, in certain circumstances, for a lengthy drug approval process, which can shorten the effective life of patent protection

for drug products. The Amendments also streamline the procedures for bringing generic drug products to the market.

Beyond any doubt, Hatch-Waxman has increased generic drug entry. Generic drugs now comprise more than 47 percent of the prescriptions filled for pharmaceutical products – up from 19 percent in 1984, when Hatch-Waxman was enacted.

In spite of this record of success, two of the provisions governing generic drug approval prior to patent expiration (the 180-day exclusivity and the 30-month stay provisions) are susceptible to strategies that, in some cases, may have prevented the availability of more generic drugs. These provisions continue to have the potential for abuse.

The Commission has taken antitrust law enforcement actions against certain brand-name and generic drug companies whose allegedly anticompetitive agreements took advantage of one or the other of these provisions. Through vigorous enforcement of the antitrust laws, the FTC has taken an active role in ensuring that consumers benefit from competition in the pharmaceutical industry.

This study examines whether the conduct that the FTC challenged represented isolated instances or is more typical, and whether the 180-day exclusivity and the 30-month stay provisions of the Hatch-Waxman Amendments are susceptible to strategies to

delay or deter consumer access to generic alternatives to brand-name drug products. The study focuses solely on the procedures used to facilitate generic drug market entry *prior to* expiration of the patent(s) that protect the brand-name drug product. The study does not address other procedures for generic entry, and it does not address the patent restoration features of Hatch-Waxman.

To accomplish the study, the Commission subpoenaed documents and information from brand-name and generic drug manufacturers, and examined instances since 1992 in which generic applicants filed an application with FDA seeking to enter the market with a generic version of a drug product prior to expiration of the brand-name drug products' patents.<sup>1</sup> An increasing number of generic applicants have sought entry prior to patent expiration. During the 1980s, only 2 percent of generic applications sought entry this way, but from 1998 to 2000, approximately 20 percent of the generic applications sought entry prior to patent expiration.

The brand-name drug products included in the study represent some of the largest drug products as measured by annual sales. They include "blockbuster" drugs<sup>2</sup> such as Capoten, Cardizem CD, Cipro, Claritin, Lupron, Neurontin, Paxil, Pepcid, Pravachol, Prilosec, Procardia XL, Prozac, Vasotec, Xanax, Zantac, Zocor, Zolofit, and

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<sup>1</sup> These applications are technically referred to as Abbreviated New Drug Applications (ANDAs) containing a paragraph IV certification.

<sup>2</sup> As used herein, "blockbuster" is defined as a drug product that appears in the top 20 drug products (as ranked publicly by annual gross sales) during one of the years covered by this study.

Zyprexa.

Based on the data obtained through the study, we make two primary recommendations concerning the 30-month stay provision and the 180-day exclusivity to mitigate the possibility of abuse that deters more generic drugs from becoming available.<sup>3</sup>

**Recommendation 1: 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.**

**The Current 30-Month Stay Provision:** A 30-month stay of FDA approval of a generic applicant<sup>4</sup> is invoked if a brand-name company receives notice of a generic applicant's paragraph IV certification and files suit for patent infringement within 45 days of that notice. Filing of the lawsuit stays FDA's approval of the ANDA until the earliest of: (1) the date the patents expire; (2) a determination of non-infringement or patent invalidity by a court in the patent litigation; or (3) the expiration of 30 months from the receipt of notice of the paragraph IV certification.

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<sup>3</sup> The study did not provide data on whether, or how, the suggested recommendations might affect brand-name companies' and generic applicant's incentives to enter the market with new brand-name or generic drug products.

<sup>4</sup> For ease of discussion purposes, the term "generic applicant" means those applicants who have filed an ANDA containing a paragraph IV certification. See Appendix A for a glossary of frequently used terms.

## **Key Facts From the Study:**

### ***To What Extent Does 30 Months Approximate the Time Typically Required for FDA Review of a Generic's ANDA or for Resolution of the Contemplated Patent Infringement Litigation?***

Thirty months historically has approximated the time required for FDA review and approval of the paragraph IV ANDAs of generic applicants that were not sued, and for district and appellate court resolutions of ANDA-related patent infringement litigation. On average, the time required for FDA review and approval was 25 months and 15 days from the application filing date in those cases where generic applicants filing a paragraph IV certification were not sued (and thus could begin commercial marketing once they had FDA approval). On average, the time between the filing of a patent infringement lawsuit and a district court decision in the case was 25 months and 13 days. On average, the time between the filing of a patent infringement lawsuit and a court of appeals decision in the case was 37 months and 20 days.

In the future, patent infringement litigation brought by brand-name companies against generic applicants that have filed ANDAs with paragraph IV certifications may take longer to resolve. The data suggest that cases involving multiple patents take longer than those involving fewer patents. As of June 1, 2002, for 6 out of the 7 cases that have been pending for more than 30 months before a decision from a district court, the brand-name company has alleged infringement of 3 or more patents.

Prior to 1998, for only 1 out of the 9 “blockbuster” drug products in which the brand-name company sued the first generic applicant did the brand-name company allege infringement of 3 patents. Since 1998, for 5 of the 8 “blockbuster” drug products where the brand-name company filed suit against the first generic applicant, the brand-name company alleged infringement of 3 or more patents. Thus, future 30-month stays may expire more frequently *before* the parties obtain a decision of a court in the patent infringement litigation.

### ***Has the Study Identified Any Circumstances That Can Prevent FDA Approval of Generic ANDAs Beyond 30 Months?***

Yes. If a brand-name company lists an additional patent in the Orange Book *after* the generic applicant has filed its ANDA, more than one 30-month stay may be generated. The generic applicant is required to re-certify to this later-listed patent, and if, upon notice of the generic's re-certification, the brand-name company sues within 45 days, then FDA approval of the generic's previously filed ANDA is stayed for *an additional* 30-months from the notice date or until a court decision in the newly instituted patent litigation.

From 1992 through 2000, brand-name companies have listed patents in the Orange Book after an ANDA has been filed for the drug product in 8 instances; 6 of these 8 instances occurred since 1998. For the 8 drug products, the additional delay of FDA approval caused by the additional 30-month stay (beyond the first 30-month stay) ranged from 4 to 40 months. In all 4 of the

cases so far with a court decision on the validity or infringement of a later-issued patent, the patent has been found either invalid or not infringed by the ANDA.

Arguments exist that the later-issued patents, which have provided the basis for additional 30-month stays, do not meet FDA's requirements for listing patents in the Orange Book. (These arguments are discussed in detail in Appendix H to the Report.) Under current court rulings and FDA procedures, however, it is very difficult for generic applicants to test these arguments. Recent court opinions have held that Hatch-Waxman does not provide a private right of action through which generic applicants may challenge a patent listing in the Orange Book. The FDA has stated that it lacks the resources and the expertise to review patents to determine whether they are properly listed.

#### **Reasons for the Recommendation:**

One 30-month period historically has approximated the time necessary for FDA review and approval of the generic's ANDA. Thus, it does not appear that the 30-month stay provision, as applied once to each ANDA for patents listed in the Orange Book prior to the ANDA's filing date, has a significant potential to delay generic entry beyond the time already necessary for FDA approval of the generic's ANDA. The data also do not indicate that court decisions in ANDA-related patent litigation typically are reached much earlier than 30 months from notice of the generic's ANDA.

The expiration of the 30-month stay may have more significance in the future, if ANDA-related patent litigation begins to last

longer than was the case from 1992-2000. Generic applicants may rely on expiration of the 30-month stay more frequently as the first point at which they may decide whether to enter the market, rather than to wait for a court decision on ANDA-related patent litigation that may take longer than 30 months.

The history thus far of multiple 30-month stays caused by the filing of later-issued patents appears problematic, however. The 4 courts that have ruled so far on the patents causing more than one 30-month stay each have found the relevant patent to be invalid or not infringed. The other 4 drug products with multiple 30-month stays involved patents whose listing in the Orange Book could have been the subject of non-frivolous challenges by the generic applicant, had either FDA review of listability or a private right of action to challenge listability under Hatch-Waxman been available.

Multiple 30-month stays prevented FDA approval of the generic applicants' ANDAs for 4 to 40 months *beyond* the initial 30-month period. FDA approval may have occurred more quickly in the absence of the multiple 30-month stays, because the data indicate that FDA approval has occurred, on average, within 25 months and 15 days for generic applicants with paragraph IV certifications that were not sued.

Even without an additional 30-month stay, later-listed patents still receive the usual protections of patent infringement litigation. The brand-name company may sue for patent infringement with respect to any of its patents that it believes may be

infringed by a generic applicant's ANDA, and may seek a preliminary injunction, just as other patent holders do against alleged infringers.<sup>5</sup>

One minor change to the patent statute, which would clarify when brand-name companies can sue generic applicants for patent infringement, would ensure that brand-name companies have recourse to the courts to protect their rights under later-issued patents. Congress may wish to overrule a recent district court decision, *Allergan, Inc. v. Alcon Labs, Inc.*, 200 F. Supp. 2d 1219 (C.D. Cal. 2002), which questions the rights of brand-name companies to sue for patent infringement regarding patents obtained or listed after an ANDA with a paragraph IV has been filed. Under the plain language of 35 U.S.C. § 271(e)(2), however, *all* ANDAs constitute acts of infringement sufficient to establish the existence of a case or controversy with respect to *all* patents that claim any drug or any method of using the drug that may be infringed by generic marketing under an ANDA – regardless of whether the patent has been listed in the Orange Book or has been the subject of a paragraph IV ANDA (as opposed to a different kind of ANDA).

To permit only one 30-month stay per drug product per ANDA<sup>6</sup> should eliminate most of the potential for improper

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<sup>5</sup> Thus, the usual patent protections would remain for brand-name companies whose patents may be listed in the Orange Book after the filing of a generic applicant's ANDA solely because it took a long time for the Patent Office to issue the patent.

<sup>6</sup> This would be applied only to resolve infringement disputes over patents listed in the Orange Book prior to the filing date of the generic applicant's ANDA.

Orange Book listings to generate unwarranted 30-month stays. However, it should be noted that, currently, the FDA does not review the propriety of patents listed in the Orange Book, and courts have ruled that generic applicants have no private right of action to challenge those listings. As a result, there is no mechanism to delist an improperly listed patent from the Orange Book. The lack of such a mechanism may have real world consequences in that the Commission is aware of at least a few instances in which a 30-month stay was generated solely by a patent that raised legitimate listability questions.

There have been various suggestions to address this situation, each with its own pros and cons. One proposal has been to establish an administrative procedure through which generic applicants could obtain substantive FDA review of listability. The FDA, however, has taken the position that it lacks the expertise and resources necessary to perform such a review, and its solely ministerial review of Orange Book listings has been upheld by the courts. At a minimum, it appears useful for the FDA to clarify its listing requirements (*see* Appendix H).

Another remedy that may warrant consideration would permit a generic applicant to raise listability issues as a counterclaim in the context of patent infringement litigation already initiated by the brand-name company in response to a paragraph IV notice from the generic applicant. This would permit resolution of the issue in the same district court proceeding in which other aspects of the relevant patents were at issue. It remains unclear how frequently such a provision

would be used.

**Recommendation 2: Pass legislation to require brand-name companies and first generic applicants to provide copies of certain agreements to the Federal Trade Commission.**

### **The Current 180-Day Marketing**

**Exclusivity Provision:** The first generic applicant to file an ANDA containing a paragraph IV certification is awarded 180 days of marketing exclusivity, during which the FDA may not approve a subsequent generic applicant's ANDA for the same drug product. The 180-day exclusivity period is calculated from either the date of the first commercial marketing of the generic drug product or the date of a court decision declaring the patent invalid or not infringed, whichever is sooner. Through this 180-day provision, Hatch-Waxman provides an incentive for companies to challenge patent validity and to "design around" patents to find alternative, non-infringing forms of patented drugs. The 180-day marketing exclusivity provision was intended to increase the economic incentives for a generic company to be the first to file an ANDA containing a paragraph IV certification and get to market.

### **Key Facts From the Study:**

#### ***How Frequently Has FDA Granted 180-Day Exclusivity?***

The regulatory landscape implementing 180-day exclusivity has shifted over the last several years. Before 1992 (a time period not included in this study), the FDA granted 180-day exclusivity to 3 generic applicants. From 1992 until

1998, the FDA did not grant 180-day exclusivity to any generic applicant. Since 1998, when the FDA changed its regulations in response to a court ruling, and more ANDAs containing paragraph IV certifications have been filed, the FDA has granted 180-day exclusivity to the first generic applicant for 31 drug products. Thus, the 180-day exclusivity has been granted for 31 out of the 104 drug products for which a first generic applicant filed an ANDA containing a paragraph IV certification from 1992 through 2000.

#### ***Has the 180-Days Exclusivity Been Triggered Most Often by a Court Decision or by the First Generic's Commercial Marketing?***

For 19 of the 31 drug products, commercial marketing triggered the running of the first generic applicant's 180-day exclusivity.<sup>7</sup> For the other 12 drug products, a court decision favorable to the generic applicant triggered the 180-day exclusivity.

#### ***How Have Generic Applicants Fared in Patent Infringement Litigation?***

Generic applicants have prevailed in 73 percent of the cases in which a court has resolved the patent dispute.<sup>8</sup> The rate at

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<sup>7</sup> The data further indicate that, when not sued, first generic applicants begin commercial marketing, after receiving FDA approval, in a timely manner that triggers the running of the 180 days and thus would allow FDA approval of subsequent eligible generic applicants once the 180 days has run.

<sup>8</sup> These statistics include other cases in addition to those involving the 12 drug products where a court decision triggered the 180-day exclusivity. For example, during a time when FDA did not consider a *district court* decision sufficient to trigger the 180-day exclusivity, some generic applicants began commercial marketing following

which the U.S. Court of Appeals for the Federal Circuit reversed district court decisions of patent invalidity and non-infringement for drug products in this study was 8 percent.

***When Did Generic Applicants Enter the Market?***

In most instances, generic applicants have waited to enter the market until at least a district court has held that the patent covering the brand-name company's drug product was invalid or not infringed by the generic applicant's ANDA.

***Are There Circumstances in which the 180-Day Exclusivity Has Been "Parked" For Some Period of Time, So That the First Generic Applicant Does Not Trigger It, and FDA Approval of Any Subsequent Eligible Generic Applicant Would Be Precluded?***

Yes. During the time period of the study, there were 20 final settlements of ANDA-related patent litigation. Fourteen of the 20,<sup>9</sup> at the time they were executed, had the potential to delay the start of the first generic applicant's 180-day exclusivity.<sup>10</sup> If the 180-day exclusivity for the first generic applicant does not run, then the FDA may not approve any subsequent eligible generic

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expiration of the 30-month stay and a favorable decision of a district court. In each of these instances, the generic applicant ultimately prevailed in the appellate court, but commercial marketing, not the district court decision, triggered the 180-day exclusivity.

<sup>9</sup> Ten brand-name companies and 10 generic companies used these types of agreements with respect to 14 drug products.

<sup>10</sup> In some cases, this delay did not occur due to subsequent events.

applicants. Once the 180-day exclusivity runs, the FDA may approve any additional generic ANDAs that have been filed and meet regulatory requirements.

Under 2 of these 14 settlement agreements, the first generic applicant did begin commercial marketing, but each generic was marketing the brand-name company's product as a generic – neither was marketing under its own ANDA. As discussed in more detail below, it is unclear whether this type of "commercial marketing" is sufficient to trigger the running of the 180-day exclusivity.

In addition to the 20 final settlement agreements, there were 4 interim settlement agreements pursuant to which the patent litigation continued, but the parties agreed upon certain conditions in the meantime. The Commission has challenged interim settlements for 3 drug products.<sup>11</sup> In those agreements, the Commission alleged that the brand-name drug company paid the first generic applicant not to enter the market, thereby retaining its (unused) 180-day marketing exclusivity and precluding FDA from approving any eligible subsequent generic applicants.

***Have Such Agreements Continued Following FTC Enforcement Action in this Area?***

Between April 1999 (shortly after FTC investigations in this area became

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<sup>11</sup> See *Abbott Laboratories*, No. C-3945 (May 22, 2000) (consent order), available at <<http://www.ftc.gov/os/2000/03/abbott.do.htm>> (this consent order related to 2 drug products: Hytrin tablets and Hytrin capsules). *Hoechst Marion Roussel, Inc.*, No. 9293 (May 8, 2001) (consent order), available at <<http://www.ftc.gov/os/2001/05/hoechstdo.pdf>>.

public) and the end of the period covered by this study, brand-name companies and first generic applicants have not entered agreements similar to the interim agreements challenged by the FTC.

**Reasons for the Recommendation:**

The data in the study suggest that the generic applicants have brought appropriate patent challenges: generic applicants prevailed in nearly 75% of the patent litigation ultimately resolved by a court decision.<sup>12</sup> Moreover, most generic applicants have waited to enter the market until at least a district court has held that the patent covering the brand-name company's drug product was invalid or not infringed by the ANDA. This may reflect the fact that a generic applicant's potential liability for lost profits on the brand-name drug usually will vastly exceed its own potential profits after market entry.

The data also indicate that, when not sued, first generic applicants, upon receiving FDA approval, begin commercial marketing in a timely manner that triggers the running of the 180 days and allows FDA approval of any subsequent eligible generic applicant once the 180 days has run. Thus, the data suggest that, in and of itself, the 180-day exclusivity provision generally has not created a bottleneck to prevent FDA approval of subsequent eligible generic applicants.

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<sup>12</sup> The data do not establish, however, whether even more appropriate patent challenges might have been brought if the period of generic market exclusivity was longer than 180 days.

*Require Brand-Name Companies and First Generic Applicants to Provide Copies of Certain Agreements to the Federal Trade Commission*

Issues that merit antitrust scrutiny, however, may arise when brand-name companies and first generic applicants reach agreements that have the potential to "park" the first generic applicant's 180-day exclusivity for some period of time. Fourteen of the 20 final settlement agreements obtained through the study had this potential as of the time they were executed. Such agreements may be procompetitive or competitively neutral. But they also may raise antitrust issues, as was alleged to be the case in the interim settlement agreements the FTC challenged.

Given this history, we believe that notification of such agreements to the Federal Trade Commission and the U.S. Department of Justice is warranted. We support the Drug Competition Act of 2001 (S. 754) introduced by Senator Leahy, as reported by the Committee on the Judiciary, which would require that if a brand-name company and a generic applicant enter into an agreement that relates in any way to the 180-day exclusivity or which concerns the manufacture, marketing, or sale of either the brand name drug or its generic equivalent, then both companies must file a copy of the agreement (or a complete written summary of any oral agreement), along with copies of any other related agreements, with the Commission and the Department of Justice.

**Minor Recommendations to the 180-Day Exclusivity Provision:**

It is unclear whether a few types of

factual circumstances trigger the running of the 180-day exclusivity. Three minor changes would clarify that these circumstances should trigger the 180-day exclusivity and thus reduce any potential for the 180-day marketing exclusivity provision to function as a bottleneck to subsequent generic entry.

*Minor Recommendation 1: Clarify that “commercial marketing” includes the first generic applicant’s marketing of the brand-name product.*

The data revealed 2 instances when the brand-name company and the first generic applicant settled the patent infringement lawsuit with a supply agreement, and 3 other instances in which an optional supply agreement was one part of a patent settlement. In all instances, the agreements contemplated that the brand-name company would supply the generic applicant with the brand-name drug product, so that the generic applicant could market it as a generic version. Currently, it is somewhat unclear whether marketing of the brand-name product by the first generic applicant constitutes “commercial marketing” sufficient to trigger the 180-day exclusivity.<sup>13</sup>

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<sup>13</sup> In response to a citizen petition involving the 30 mg strength of Procardia XL, the FDA determined that the first generic applicant was ineligible for 180-day exclusivity, because the generic applicant and the brand-name company had settled their patent litigation and effectively changed the generic applicant’s certification from a paragraph IV to a paragraph III. In addition, and under alternative reasoning, the FDA determined that even if the first generic applicant was eligible for the 180-day exclusivity, that exclusivity already had been triggered by the generic applicant’s marketing under a supply agreement with the brand-name company. See FDA Letter to Deborah A. Jaskot, Docket No. OPP-1446/CP1 (Feb. 6, 2001). This letter leaves somewhat unclear whether a supply agreement alone would be sufficient to satisfy the commercial marketing trigger for the 180-day exclusivity. See, also,

To avoid situations in which the running of the 180 days is not triggered because of this uncertainty, it would be desirable to clarify that “commercial marketing” includes *any* marketing by the first generic applicant, even under a supply agreement with the brand-name company. In some circumstances, such commercial marketing may be the only event that can trigger the running of the 180-day exclusivity. For example, if there is a second generic applicant, but it is not sued by the brand-name company, then there will not be a court decision to trigger the 180 days, and only the first generic applicant’s commercial marketing under the supply agreement could start the running of the 180 days and thus, after 180 days, free the FDA to approve any eligible subsequent generic applicants.

*Minor Recommendation 2: Codify that the decision of any court on the same patent being litigated by the first generic applicant constitutes a “court decision” sufficient to start the running of the 180-day exclusivity.*

There is some question as to which court’s decision is sufficient to activate the “court decision” trigger of the 180-day exclusivity. Two courts of appeal have held,<sup>14</sup> and the FDA has issued guidance,<sup>15</sup> that *any* court’s decision on whether the

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*Mylan Pharmaceuticals, Inc. v. Tommy G. Thompson*, 2001 U.S. Dist. LEXIS 24234 (N.D. WV Apr. 18, 2001).

<sup>14</sup> See *Teva Pharmaceuticals, USA, Inc. v. FDA*, 182 F.3d 1003 (D. C. Cir 1999), *Granutec, Inc. v. Shalala*, 139 F.3d 889 (4<sup>th</sup> Cir. 1998).

<sup>15</sup> See FDA Guidance for Industry: 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act (Jun. 1998). See also *Teva Pharmaceuticals, USA, Inc. v. FDA*, 182 F.3d 1003, 1005 (D.C. Cir. 1999).

patent at issue is invalid or not infringed is sufficient to trigger the running of the first generic applicant's 180-day exclusivity.

On balance, we believe this is the correct result, but there are pros and cons. On the one hand, the rule would make it less likely that agreements between brand-name and generic companies that had the effect of "parking" the 180-day exclusivity for some period of time could forestall FDA approval of a subsequent eligible generic applicant. This is because, if the brand-name company sues the second (or later) generic applicant, and that generic applicant won its patent litigation, then the 180-day exclusivity of the first generic applicant would begin to run from the date of the later generic applicant's favorable court decision. Such circumstances may arise; the data showed that brand-name companies sued later generic applicants in nearly 85% of the cases. The rule would be consistent with the mandate in the legislative history of Hatch-Waxman to "make available more low-cost drugs,"<sup>16</sup> because the rule would assist in eliminating potential bottlenecks to FDA approval of subsequent eligible generic applicants.

Such a rule also could speed generic entry when the second generic applicant's lawsuit is resolved prior to that of the first applicant. This appears to be appropriate given the low reversal rate of district court opinions of patent invalidity and non-infringement. For example, under this rule, if both the first and second generic applicants are sued, but the court hearing the

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<sup>16</sup> H.R.Rep. No. 98-857, pt. 1, 98<sup>th</sup> Cong., 2d Sess., at 14 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647.

second generic applicant's case is the first to arrive at a decision, then that court's decision would trigger the running of the first generic applicant's 180-day exclusivity, regardless of whether the first generic applicant had received FDA approval. The data revealed 1 such case.

On the other hand, as illustrated in the preceding paragraph, the operation of this rule could deprive the first generic applicant of its ability to market under the 180-days exclusivity, even though the first generic applicant had been diligently pursuing resolution of its patent litigation. This result could dampen the incentive to become the first generic applicant.<sup>17</sup> Moreover, if the later court issues a non-infringement decision, the reasoning underlying the holding may not apply to the first generic applicant's ANDA, depending upon the facts of the case.

*Minor Recommendation 3: Clarify that a court decision dismissing a declaratory judgment action for lack of subject matter jurisdiction constitutes a "court decision" sufficient to trigger the 180-day exclusivity.*

One court of appeals has held that a dismissal of a declaratory judgment action for lack of a case or controversy is a "court decision" of non-infringement sufficient to trigger the 180-day exclusivity.<sup>18</sup> We believe that the court's reasoning is persuasive and should be adopted.

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<sup>17</sup> By contrast, the absence of such a rule also could dampen the incentive for later generic applicants to develop eligible ANDAs containing paragraph IV certifications.

<sup>18</sup> *Teva Pharmaceuticals, USA, Inc. v. FDA*, 182 F.3d 1003 (D. C. Cir 1999).

The U.S. Court of Appeals for the District of Columbia confronted a situation in which the brand-name company did not sue any of the generic applicants for patent infringement, presumably because the brand-name company's patents were not infringed by the ANDA. To trigger the first generic applicant's 180-day exclusivity (because it had not yet been approved by the FDA), the second generic applicant sought a declaratory judgment that its ANDA did not infringe the brand-name product's patents. The district court hearing the case dismissed the lawsuit for lack of subject matter jurisdiction, because the brand-name company indicated that it would not sue the second generic applicant for patent infringement, thus eliminating its reasonable apprehension of a patent infringement suit and the existence of a case or controversy. This dismissal also estopped the brand-name company from suing the generic applicant in the future.

The Court of Appeals determined that the dismissal for lack of case or controversy was, in fact, a court decision, because the brand-name company indicated that the second generic applicant's ANDA did not infringe the relevant patent. As a result, the dismissal activated the court decision trigger. Such a rule eliminates the potential for a bottleneck created by a first generic applicant that does not exercise its commercial marketing rights.

## Table of Contents

<b>EXECUTIVE SUMMARY</b> .....	i
--------------------------------	---

### **CHAPTER 1 Introduction and Background**

Introduction .....	1
Overview of the Hatch-Waxman Act and the FDA's Implementing Regulations .....	3
Price Effect of Generic Entry .....	9
Scope of the Study .....	9
Organization of the Report .....	11

### **CHAPTER 2 Outcomes of Patent Infringement Lawsuits Under the Hatch-Waxman Amendments**

Introduction .....	13
How Frequently Have Brand-Name Companies Sued the First Generic Applicant? .....	14
What Were the Results of Patent Infringement Litigation with the First Generic Applicant? .....	15
How Frequently Have Brand-Name Companies Sued the Second Generic Applicant? .....	18
What Are the Results of Litigation with the Second Generic Applicant if the Brand-Name Company Settles with the First Generic Applicant? .....	19
For Those Patent Litigations that Resulted in a Court Decision, How Often Did Generic Applicants Prevail for All of the Drug Products in the Study? .....	19
How Frequently Did the Federal Circuit Reverse a District Court Decision of Non-Infringement or Patent Invalidity? .....	21

In Which District Courts Did Brand-Name Companies Initiate Patent Infringement Litigation? .....	21
--	----

When Did Generic Applicants Enter the Market? .....	22
---	----

**CHAPTER 3            Settlements Related to Paragraph IV Certifications**

Introduction .....	25
--------------------	----

Scope of Information Requested and Received .....	26
---	----

Settlements Involving Patent Licenses or Supply Arrangements .....	27
--	----

Final Settlements Involving Brand Payments .....	31
--	----

Interim Agreements .....	34
--------------------------	----

Agreements Between Brand-Name Companies and the Second Generic Applicant .....	35
--	----

Agreements Between First and Second Generic Applicants .....	36
--	----

**CHAPTER 4            Orange Book Patent Listing Practices and Use of Multiple 30-Month Stays**

Introduction .....	39
--------------------	----

Legal and Regulatory Background of the 30-Month Stay Provision .....	41
--	----

Duration of Patent Infringement Litigation .....	47
--	----

Multiple 30-Month Stays on Later-Issued Patents For Drug Products in the Study .....	48
--	----

Analysis of Later-Issued Patents in the Orange Book .....	52
---	----

**CHAPTER 5            180-Day Marketing Exclusivity Under the Hatch-Waxman Amendments**

Introduction .....	57
--------------------	----

The Shifting Regulatory Landscape Implementing  
the 180-Day Exclusivity Period ..... 58

Triggers for the 180-Day Exclusivity Period ..... 60

**CHAPTER 6        FDA Citizen Petitions and Generic Drug Applications**

Introduction ..... 65

FDA Regulations Governing Citizen Petitions ..... 65

The Use of Citizen Petitions About Drug Products for Which  
an ANDA Containing a Paragraph IV Certification Was Filed ..... 66

Conclusions ..... 68

**APPENDIX A        Glossary of Terms ..... A-1**

**APPENDIX B        Relevant Provisions of the Hatch-Waxman Amendments ..... A-2**

**APPENDIX C        New Drug Applications Examined in Study ..... A-15**

**APPENDIX D        Brand-Name Companies Served Special Orders ..... A-17**

**APPENDIX E        Specifications in the Special Orders Sent to  
Brand-Name Companies ..... A-20**

**APPENDIX F        FTC Staff's Citizen Petition on the Listability of  
Certain Patents in the Orange Book ..... A-24**

**APPENDIX G        Orange Book Listing and Analysis ..... A-29**

**APPENDIX H        Orange Book Patent Analysis ..... A-39**

# Chapter 1 Introduction and Background

## Introduction

In April 2001, the Commission began an industry-wide study focused on certain aspects of generic drug competition under the Hatch-Waxman Amendments.<sup>1</sup> The Amendments provide certain methods by which generic drug manufacturers can obtain approval to market a generic version of a brand-name product. The study's purpose was to provide a more complete picture of how generic drug competition has developed under one method the Amendments established: generic entry *prior to* expiration of the brand-name company's patents on the relevant drug product.<sup>2</sup> This report sets forth the results of the study.<sup>3</sup>

The study was prompted, in part, by the Commission's enforcement actions against alleged anticompetitive agreements that relied on certain Hatch-Waxman provisions.<sup>4</sup> The study was designed to

determine whether such agreements are isolated instances or more typical, and whether particular provisions of the Hatch-Waxman Amendments are susceptible to strategies to delay or deter consumer access to low-cost generic alternatives to brand-name drug products.

The study also was requested by Representative Henry Waxman, one of the co-sponsors of Hatch-Waxman, who asked the FTC to "investigate and produce a study on the use of agreements between and among pharmaceutical companies and potential generic competitors and any other strategies that may delay generic drug competition throughout the U.S." Other members of Congress have proposed legislation to amend various portions of Hatch-Waxman, including the sections that

<sup>1</sup> Drug Price Competition and Patent Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended 21 U.S.C. § 355 (1994)).

<sup>2</sup> The study did not examine how generic competition has developed under the other methods the Amendments established. Nor did the study examine whether Hatch-Waxman provisions have achieved another purpose of the Amendments: to compensate brand-name companies for lost patent life due to the time needed for FDA's safety and efficacy review process.

<sup>3</sup> Appendix A contains a glossary of frequently used terms and their meanings under Hatch-Waxman.

<sup>4</sup> See, e.g., *Abbott Laboratories*, No. C-3945 (May 22, 2000) (consent order), available at <<http://www.ftc.gov/os/2000/03/abbott.do.htm>>. *Hoechst Marion Roussel, Inc.*, No. 9293 (May 8, 2001) (consent order), available at <<http://www.ftc.gov/os/2001/05/hoechstdo.pdf>>. The same issues are raised by another case in which the Commission settled similar allegations, see *American*

*Home Products*, Docket No. 9297 (Feb. 19, 2002) (decision and order) available at <<http://www.ftc.gov/os/2002/02/ahpdo.pdf>>. See also *Schering-Plough Corp., et al.*, Docket No. 9297, Initial Decision (Jul. 2, 2002), available at <<http://www.ftc.gov/os/2002/07/scheringinitialdecisionpl.pdf>>. The Commission also has accepted for public comment a consent order settling charges that Biovail illegally acquired an exclusive patent license and wrongfully listed that patent pursuant to another provision of the FDA's regulations implementing Hatch-Waxman. *Biovail Corp.*, File No. 011-0094, Agreement Containing Consent Order, (Apr. 19, 2002), available at <<http://www.ftc.gov/os/2002/04/biovaildecision.htm>>. Moreover, the Commission has accepted for public comment a consent order settling charges that Elan and Biovail entered into a supply and distribution agreement for a generic drug product that may have unreasonably restrained their incentives to compete against each other. See *FTC, Biovail Corp. and Elan Corp.*, File No. 011 0132, Agreement Containing Consent Order (Jun. 27, 2002), available at <<http://www.ftc.gov/os/2002/06/biovailelanagreement.pdf>>

are the subject of the Commission's study.<sup>5</sup>

Finally, the study was motivated, in part, by the prospect of a substantial sales volume of brand-name drug products coming off patent in the next several years.<sup>6</sup> This represents an enormous opportunity for the generic drug industry and, conceivably, a commensurate threat to the brand-name pharmaceutical industry. Brand-name pharmaceutical drug manufacturers seeking to protect the sales of brand-name drugs may have an incentive and ability to enter into agreements with would-be generic competitors, or engage in other types of activities, that would slow or thwart the entry of competing generic drug products.

The Commission has developed significant expertise regarding competition in the pharmaceutical industry. The Commission has, for example, brought antitrust enforcement actions affecting both brand-name and generic drug manufacturers.<sup>7</sup> Commission staff have conducted empirical analyses of competition in the pharmaceutical industry, including in-depth studies by the staff of the Bureau of Economics.<sup>8</sup> The Commission has provided

<sup>5</sup> See, e.g., S. 812, 107<sup>th</sup> Cong. (2001) (introduced by Sens. Schumer and McCain); S. 2677, 107<sup>th</sup> Cong. (2002) (introduced by Sen. Rockefeller); S. 754, 107<sup>th</sup> Cong. (2001) (introduced by Sen. Leahy).

<sup>6</sup> National Institute for Health Care Management, "Prescription Drugs and Intellectual Property Protection" (Aug. 2000) at 3.

<sup>7</sup> See, e.g., *FTC v. Mylan Laboratories, Inc. et al.*, 62 F. Supp. 2d 25 (D.D.C. 1999); *Roche Holding Ltd.*, 125 F.T.C. 919 (1998) (consent order); *Ciba-Geigy Ltd.*, 123 F.T.C. 842 (1997) (consent order).

<sup>8</sup> Bureau of Economics Staff Report, Federal Trade Commission, *The Pharmaceutical Industry: A Discussion of Competitive and Antitrust Issues in an Environment of Change* (Mar. 1999) available at <<http://www.ftc.gov/reports/pharmaceutical/drugrep.pdf>>; David Reiffen and Michael R. Ward, *Generic Drug Industry Dynamics*, Bureau of Economics Working Paper No. 248 (Feb. 2002) ("Reiffen and Ward"), available at

testimony before Congress,<sup>9</sup> and Commission staff have filed comments with the Food and Drug Administration ("FDA") regarding competitive aspects of Hatch-Waxman implementation.<sup>10</sup> In addition, individual Commissioners have addressed the subject of pharmaceutical competition before a variety of audiences, both to solicit input from affected parties and to promote dialogue regarding practical solutions.<sup>11</sup>

<<http://www.ftc.gov/be/econwork.htm>>

<sup>9</sup> Testimony of Federal Trade Commission before the Committee on Commerce, Science and Transportation, United States Senate (April 23, 2002) available at <<http://www.ftc.gov/os/2002/04/pharmtestimony.htm>>; Testimony of the Federal Trade Commission before the Committee on the Judiciary, United States Senate, *Competition in the Pharmaceutical Marketplace: Antitrust Implications of Patent Settlements* (May 24, 2001) available at <<http://www.ftc.gov/os/2001/05/pharmtstny.htm>>.

<sup>10</sup> *FDA: Citizen Petition*, Comment of the Staff of the Bureau of Competition and of Policy Planning of the Federal Trade Commission Before the Food and Drug Administration (Mar. 2, 2000) available at <<http://www.ftc.gov/be/v000005.pdf>> (recommending modifications to the FDA's Proposed Rule on citizen petitions intended to discourage anticompetitive abuses of the FDA's regulatory processes); *FDA: 180-Day Marketing Exclusivity for Generic Drugs*, Comment of the Staff of the Bureau of Competition and of Policy Planning of the Federal Trade Commission Before the Food and Drug Administration (Nov. 4, 1999) (AMarketing Exclusivity Comment@) available at <<http://www.ftc.gov/be/v990016.htm>> (recommending that the FDA's Proposed Rule on 180-day marketing exclusivity be modified to limit exclusivity to the first ANDA filer and to require filing of patent litigation settlement agreements).

<sup>11</sup> See, e.g., Sheila F. Anthony, *Riddles and Lessons from the Prescription Drug Wars: Antitrust Implications of Certain Types of Agreements Involving Intellectual Property* (June 1, 2000) available at <<http://www.ftc.gov/speeches/anthony/sfip000601.htm>>; Thomas B. Leary, *Antitrust Issues in Settlement of Pharmaceutical Patent Disputes* (Nov. 3, 2000) available at <<http://www.ftc.gov/speeches/leary/learypharma.htm>>; Thomas B. Leary, *Antitrust Issues in the Settlement of Pharmaceutical Patent Disputes, Part II* (May 17, 2001) available at <<http://www.ftc.gov/speeches/leary/learypharmaceuticalsettlement.htm>>; Timothy J. Muris, *Competition and*

In October 2000, the Commission began the formal process of obtaining authorization to conduct this study. As required by the Paperwork Reduction Act and implementing regulations of the Office of Management and Budget,<sup>12</sup> the Commission published a Federal Register notice<sup>13</sup> that included, among other things, the special orders under Section 6(b) of the Federal Trade Commission Act<sup>14</sup> that the Commission planned to serve on brand-name pharmaceutical companies and generic drug manufacturers.

In response to the public comments received following this Federal Register notice, the Commission clarified the proposed information requests as suggested by several parties and published in March 2001 a second notice requesting public comments.<sup>15</sup> On April 6, 2001, the Commission obtained OMB approval to conduct the study, and on April 25, 2001, the Commission began service of the special orders on 28 brand-name companies and over 50 generic drug companies.<sup>16</sup> By December 31, 2001, the Commission had

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*Intellectual Property Policy: The Way Ahead*, at 5-6 (Nov. 15, 2001) available at <http://www.ftc.gov/speeches/muris/intellectual.htm>.

<sup>12</sup> The Commission was required to obtain OMB clearance before it could begin the study because the number of special orders to be sent triggered the requirements of the Paperwork Reduction Act of 1995, 44 U.S.C. Ch. 35, as amended.

<sup>13</sup> See 65 Fed. Reg. 61334 (Oct. 17, 2000).

<sup>14</sup> 15 U.S.C. § 46(b).

<sup>15</sup> See 66 Fed. Reg. 12512 (Feb. 27, 2001).

<sup>16</sup> Several brand-name drug companies have equity interests in generic subsidiaries and, thus, were requested to answer questions relating to both brand-name products and generic products.

received substantial compliance with the special orders.

## **Overview of the Hatch-Waxman Act and the FDA's Implementing Regulations**

Before describing the scope of the study, it is important to understand the historical context in which Hatch-Waxman arose. Moreover, the generic approval process Hatch-Waxman implemented demands an understanding of the interaction of the patent system and the regulatory structure governing the approval of brand-name drugs.

### *Pre-Hatch-Waxman Regulatory Environment*

In 1962, amendments to the Federal Food, Drug, and Cosmetic Act added a proof-of-efficacy requirement to new drug approvals; before that time, the FDA approved drugs for safety only. As a result of the amendments, brand-name companies are required to prove that new drugs are safe and effective prior to FDA approval. To prove safety and efficacy, brand-name companies are required to conduct tests on humans ("clinical trials") and to submit those results to the FDA with their new drug application (NDA).

Those seeking to market a generic version of an existing post-1962 brand-name drug also had to perform their own safety and efficacy studies, much like the brand-name companies had to demonstrate the safety and efficacy of the brand-name drug.<sup>17</sup> The FDA did not have a streamlined

<sup>17</sup> The FDA considered "such retesting to be unnecessary and wasteful because the drug [had] already been determined to be safe and effective. Moreover, such

procedure by which to approve generic versions of brand-name drug products whose patents had expired.<sup>18</sup> By 1984, the FDA estimated that there were approximately 150 brand-name drugs whose patents had expired for which there was no generic equivalent.<sup>19</sup>

Another factor complicating generic drug approval concerned the timing of when generic companies could perform their clinical tests. Before Hatch-Waxman was enacted, a generic company could not begin the required FDA approval process until *after* patents on the relevant brand-name product had expired; to begin earlier would typically have infringed the brand-name company's patents.<sup>20</sup> Thus, at that time, patent law coupled with the FDA generic approval process, in effect, extended the term of the brand-name company's patent protection and delayed market entry by generic versions of brand-name pharmaceutical drug products.

Brand-name pharmaceutical companies also confronted problems. The discovery and development of new drug products are expensive and time-consuming.<sup>21</sup> To spur this investment, as

retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective." See H.R. Rep. No. 98-857, Part I at 16 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2649.

<sup>18</sup> The FDA did establish, however, a procedure to determine the effectiveness of all drugs approved prior to 1962, and it established a policy of permitting the approval of a generic equivalent to a safe and effective pre-1962 brand-name drug. This generic approval procedure, however, did not apply to drugs approved after 1962. *Id.*

<sup>19</sup> *Id.* at 17.

<sup>20</sup> *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 1984).

<sup>21</sup> See Pharmaceutical Research and Manufacturers of America, "Delivering on the Promise of Pharmaceutical Innovation: The Need to Maintain Strong

well as to recoup investments made, brand-name companies obtain patent protection to exclude others from making, using, or selling an invention for a number of years. Often, however, the brand-name companies obtained patents prior to FDA approval of the drug product. Thus, the effective terms of many patents were shortened due to the time required for the FDA to ensure the safety and efficacy of the brand-name company's drug product.

### *The Hatch-Waxman Amendments*

Congress passed the Hatch-Waxman Amendments to address both issues.<sup>22</sup> To enable earlier generic entry, the Amendments provided that certain conduct related to obtaining FDA approval that would otherwise constitute patent infringement would be exempt from infringement liability under the patent laws. In addition, generic applicants were permitted to rely on the brand-name company's trade secret data demonstrating the safety and efficacy of the brand-name drug product. To restore patent protection to brand-name companies to compensate them for the time used to obtain FDA approval, the Amendments contained provisions to extend patent terms in certain circumstances.

Thus, Hatch-Waxman balanced an expedited FDA approval process to speed generic entry with patent term restoration to

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and Predictable Intellectual Property Rights, White Paper," submitted to Federal Trade Commission and the Department of Justice - Antitrust Division (Apr. 22, 2002) at 7-10, available at <http://www.ftc.gov/os/comments/intelpropertycomments/phrma020422.pdf>.

<sup>22</sup> Appendix B contains the Hatch-Waxman Amendments, as codified at 21 U.S.C. 355 et seq.

ensure continuing innovation. As one federal appellate judge explained, the Amendments “emerged from Congress’s efforts to balance two conflicting policy objectives: to induce brand-name pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market.”<sup>23</sup>

Pursuant to the Federal Food, Drug, and Cosmetic Act, a brand-name company seeking to market a new drug product must first obtain FDA approval by filing a New Drug Application (NDA). The NDA ultimately must include a variety of information that is extremely expensive and time-consuming to develop, including clinical trial data.

When the NDA is filed, the NDA filer also must provide the FDA with certain categories of information regarding the patents that cover the drug that is the subject of its NDA.<sup>24</sup> Upon approval of the NDA, the FDA lists the patents in an agency publication entitled “Approved Drug Products with Therapeutic Equivalence,” commonly known as the “Orange Book.”<sup>25</sup> In addition to patents on the active ingredient in a drug product, patents on specific formulations (*i.e.*, a tablet form) or methods of use (*i.e.*, used to treat heartburn in mammals) of the drug product are also listed in the Orange Book.

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<sup>23</sup> *Abbott Labs. v. Young*, 920 F.2d 984, 991 (D.C. Cir. 1990) (Edwards, J., dissenting on other grounds) (citations omitted).

<sup>24</sup> 21 U.S.C. § 355(b)(1).

<sup>25</sup> *Id.* at § 355(j)(7)(A).

Rather than requiring a generic manufacturer to repeat the costly and time-consuming NDA process, the Amendments permit the company to file an Abbreviated New Drug Application (“ANDA”). The object of the ANDA process is to demonstrate that the generic drug product has the same active ingredient, route of administration, dosage form and strength, and proposed labeling as the brand-name drug. The ANDA also must contain sufficient information to demonstrate that the generic drug is “bioequivalent” to the relevant brand-name product.<sup>26</sup> As a result of providing this information, the generic applicant is allowed to rely on the FDA’s previous findings of safety and effectiveness for the referenced brand-name drug, and thus the applicant does not have to provide its own clinical studies to demonstrate the generic drug product’s safety and effectiveness. This reliance on the innovator’s safety and efficacy data allows generic applicants to save very substantial amounts of money in development costs.

An ANDA also must contain a certification regarding each patent listed in the Orange Book that relates to the relevant NDA for which the generic applicant is seeking to make a generic version. The statute provides ANDA applicants with four certification options: they may certify (I) that the required patent information has not been filed; (II) that the patent has expired; (III) that the patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (IV) that the patent is invalid or will not be infringed by the generic drug for which the ANDA

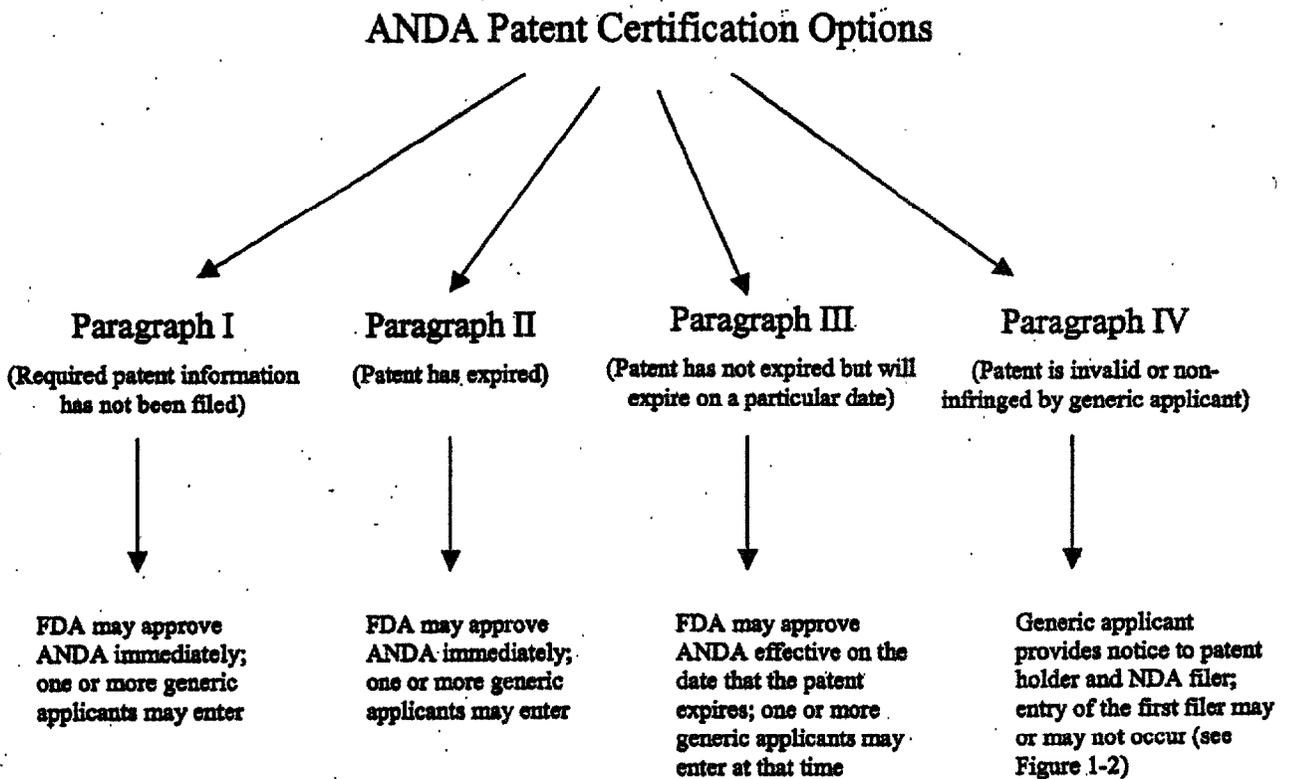
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<sup>26</sup> *Id.* at § 355(j)(2)(A)(iv). Bioequivalence means that the rate and extent of absorption of the generic drug is not significantly different from the rate and extent of absorption of the listed drug when administered at the same dosage.

applicant seeks approval. For ease of discussion throughout this study, these certifications will be referred to as paragraph I, II, III and IV certifications,

respectively. Figure 1-1 depicts graphically the FDA approval process depending upon which certifications the generic applicant makes.

**Figure 1-1 ANDA Patent Certifications**



If the applicant makes a certification under paragraphs I or II, the FDA may approve the ANDA immediately, provided other requirements are met.<sup>27</sup> If the applicant makes a paragraph III certification, the FDA may approve the ANDA effective on the date that the patent expires.<sup>28</sup>

*Paragraph IV Certifications*

When an applicant makes a paragraph IV certification, two additional provisions of Hatch-Waxman are implicated. These two provisions are at the heart of the FTC's study.

The first is the automatic "30-month stay" protection afforded brand-name companies. An ANDA filer that makes a paragraph IV certification must provide a notice to both the patent holder and the

<sup>27</sup> *Id.* at § 355(j)(5)(B)(ii).

<sup>28</sup> *Id.*

NDA filer<sup>29</sup> with a detailed statement of the factual and legal basis for the ANDA filer's assertion that the patent is invalid or not infringed. Once the ANDA filer has provided such notice, a patent holder (usually the brand-name company) must bring an infringement suit within 45 days to take advantage of the statutory stay provision.<sup>30</sup> If the patent holder does not bring suit within 45 days, the FDA approval process may proceed, and the FDA may approve an ANDA as soon as regulatory requirements are fulfilled.<sup>31</sup> A 30-month stay of FDA approval of an ANDA applicant is invoked when a brand-name company receives notice of a generic applicant's paragraph IV certification and files suit for patent infringement within 45 days of that notice.<sup>32</sup> Filing of the lawsuit stays the FDA's approval of the ANDA until the earliest of: (1) the date the patent(s) expire; (2) a final determination of non-infringement or patent invalidity by a court in the patent litigation; or (3) the expiration of 30 months from the receipt of notice of the paragraph IV certification.

The second provision is the "180-day

period of exclusivity." The first generic applicant to file an ANDA containing a paragraph IV certification is eligible for 180 days of marketing exclusivity, during which the FDA may not approve subsequent ANDAs for the same drug product.<sup>33</sup> The 180-day exclusivity period thus increases the economic incentives for a generic company to be the first to file an ANDA containing a paragraph IV certification. Through this 180-day provision, the Amendments also provide an incentive for generic companies to litigate patents that may be invalid and to "design around" patents to find alternative, non-infringing forms of patented drugs.<sup>34</sup> The 180-day exclusivity period is calculated from either the date of the first commercial marketing of the generic drug product or the date of a court decision declaring the patent invalid or not infringed, whichever is sooner.<sup>35</sup> After the 180 days, other generic products can enter the market, provided they obtain the FDA regulatory approval. Subsequent eligible generic applicants must wait until the first generic applicant's 180 days have run before the FDA can approve the subsequent ANDA.

Figure 1-2 describes graphically how the 30-month stay and 180-day exclusivity provisions affect FDA approval of a generic applicant's ANDA.

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<sup>29</sup> *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. The Hatch-Waxman Amendments require that all patents that claim the drug described in an NDA must be listed in the Orange Book. Occasionally, this requires an NDA filer to list a patent that it does not own.

<sup>30</sup> *Id.* at § 355(j)(5)(B)(iii).

<sup>31</sup> *Id.* For example, the statute requires the ANDA applicant to establish bioequivalence.

<sup>32</sup> 21 U.S.C. at § 355(j)(5)(B)(iii).

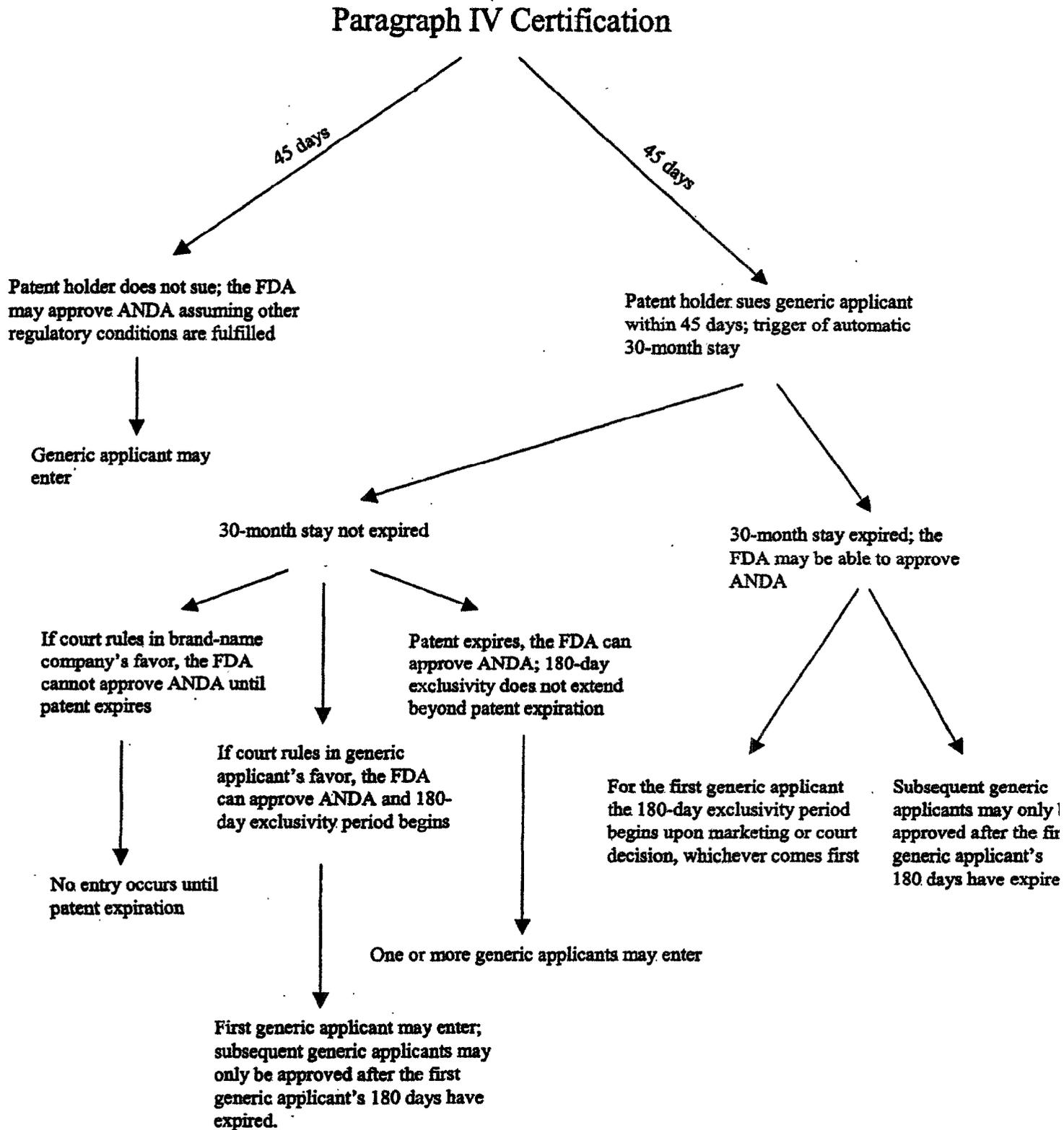
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<sup>33</sup> *Id.* at § 355(j)(5)(B)(iv).

<sup>34</sup> See *Granutec, Inc. v. Shalala*, 139 F.3d 889, 891 (4th Cir. 1998).

<sup>35</sup> 21 U.S.C. § 355(j)(5)(B)(iv).

# Figure 1-2 Paragraph IV Certifications



## Price Effect of Generic Entry

Because generic drugs are typically far less expensive than their corresponding brand-name versions, competition from generic drugs can deliver large savings to consumers. A Congressional Budget Office (CBO) study attempted to quantify the magnitude of this effect by analyzing retail pharmacy data from 1993 and 1994. The study found that, for drugs that are available in both generic and brand-name versions, the average price of a generic prescription was approximately half of the average price of a brand-name prescription.<sup>36</sup> The CBO estimated that, in 1994, the availability of generic drugs saved purchasers between \$8 billion and \$10 billion.<sup>37</sup>

The broader empirical economics literature also points to a number of competitive effects associated with the introduction of generic drugs. Early research using small data samples with information on brand name and generic prescription drug prices and sales found that (1) brand name drug prices rose slightly, but that average drug prices declined some 20 percent within approximately two years of generic entry,<sup>38</sup> and (2) generic entry produces slight reductions in brand name drug prices and declines in generic prices as

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<sup>36</sup> Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* (July 1998) ("CBO Study") at 28, available at <http://www.cbo.gov/showdoc.cfm?index=655&sequence=0>.

<sup>37</sup> *Id.* at 31.

<sup>38</sup> Henry Grabowski & John M. Vernon, "Brand Loyalty, Entry and Price Competition In Pharmaceuticals After the 1984 Drug Act," 35 *J. of Law & Econ.* 331-50 (Oct. 1992).

the number of generic rivals increases.<sup>39</sup>

A more recent study of 32 drugs that lost patent protection around the time of the passage of the Hatch-Waxman Amendments found that generic entry results in somewhat higher prices for brand-name prescription drugs (in light of factors such as inelastic demand among users of brand-name products), but large decreases in the prices of corresponding generic drugs.<sup>40</sup> Another recent study of 32 drugs that lost patent protection after passage of the Hatch-Waxman found that generic drug prices fell until at least the fifth generic firm enters, and that falling prices from increased competition can continue with the entry of additional generic competitors.<sup>41</sup> It is also noteworthy that elements of this literature indicate that generic entrants gain significant market share at the expense of their rival brand name drug companies after their entry. Overall, this literature points to significant short-run competitive impacts of generic entry that can lead to substantial benefits for consumers of prescription drugs.

## Scope of the Study

This study focuses solely on the competitive circumstances surrounding

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<sup>39</sup> Richard E. Caves, et al., "Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry" (Brookings Papers on Economic Activity, Microeconomics, Martin Neil Baily & Clifford Winston, eds., Brookings Institution, Washington, DC 1991).

<sup>40</sup> Richard G. Frank & David S. Salkever, "Generic Entry and the Pricing of Pharmaceuticals," 6 *J. of Econ. & Mgmt Strategy*, 75-90 (Spring 1997) (Generic entry will induce those buyers who are highly sensitive to price to switch to low-price generics; price-insensitive buyers continue to purchase branded products. This segmentation of the market means that the branded drug often will face a less elastic demand curve, which can induce the profit-maximizing branded producer to raise its price.).

<sup>41</sup> Reiffen and Ward, *supra* n. 8.

generic competition for those brand-name drug products (1) subject to an ANDA notice containing a paragraph IV certification (2) that brand-name companies received after January 1, 1992 and prior to January 1, 2001. By focusing on these brand-name drug products, the study could examine how the 180-day marketing exclusivity and the 30-month stay provisions have influenced the development of generic drug competition.

The study does not address how generic competition has developed under paragraph I, II, or III certifications. The study also does not address the patent restoration features of Hatch-Waxman.

#### *ANDAs Under Hatch-Waxman*

According to the FDA, from the time Hatch-Waxman became effective in 1984 through December 31, 2000, 8,019 ANDAs were filed with the FDA.<sup>42</sup> Of these applications, 7,536 (94 percent) raised no patent issues (*i.e.*, the ANDAs did not contain a paragraph IV certification). A substantial portion of the total number of ANDAs, however, relate to the same brand-name product or NDA. Thus, the total number of ANDAs does not represent 8,019 unique brand-name drug products, and it is unclear as to how many unique brand-name drug products the total 8,019 ANDAs related.

Four hundred eighty-three (483) (or six percent of the total number of ANDAs filed) contained Paragraph IV certifications. The 483 ANDAs relate to 130 unique brand-name drug products as measured by unique NDAs. The share of ANDAs with paragraph

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<sup>42</sup> FDA staff provided this information to the FTC staff.

IV certifications compared to all ANDAs filed (those with paragraph I-IV certifications) -- has increased significantly since Hatch-Waxman was enacted. According to the data provided by the FDA, during the 1980s (1984-89), only 2 percent of ANDAs contained paragraph IV certifications. This share increased to approximately 12 percent for the 1990s, and it has increased substantially in the last few years: from 1998-2000, approximately 20 percent of ANDAs contained paragraph IV certifications.

The brand-name drug products this study covered include any drug product for which the brand-name company received notification of an ANDA containing a paragraph IV certification after January 1, 1992 and prior to January 1, 2001.<sup>43</sup> This selection criteria resulted in 104 drug products, as represented by New Drug Applications (NDAs) filed with the FDA, within the scope of the study. As noted previously, from 1984 to January 2001, 130 unique NDAs were subject to at least one ANDA with a paragraph IV certification. The most recent 104 brand-name drug products (of the 130 total) are included within the scope of the study.

Appendix C contains a list of the NDAs within the scope of the study. The drug products included in the study represent some of the largest drug products as measured by annual sales, including so-called "blockbuster" drugs such as Capoten, Cardizem CD, Cipro, Claritin, Lupron Depot, Neurontin, Paxil, Pepcid, Pravachol,

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<sup>43</sup> If any later-filed generic applicant filed its ANDA with the requisite certification after January 1, 1992, even if the first generic applicant for a particular drug product filed its application prior to January 1, 1992, the drug product was included within the scope of the study.

Prilosec, Procardia XL, Prozac, Vasotec, Xanax, Zantac, Zocor, Zoloft, and Zyprexa.

The FDA provided the Commission with the identity of the generic companies that have filed ANDAs containing paragraph IV certifications since enactment of Hatch-Waxman in 1984. Using this information, FTC staff identified which brand-name companies had received notice of the filing of an ANDA containing a paragraph IV certification. The list of brand-name companies and generic companies are attached as Appendix D. Special orders were served on all identified brand-name companies who received notice of, and on the first three generic drug companies who had filed, the ANDA.<sup>44</sup>

The FTC's special orders required the brand-name companies to produce agreements with generic applicants that relate to the ANDA filing, results of ANDA patent infringement litigation with generic applicants, listing of patents in the FDA's Orange Book, sales information, and the use of citizen petitions. Generic applicants were required to produce agreements relating to the innovator's drug products for which they had filed an ANDA containing a paragraph IV certification, and to respond to questions about the results of patent infringement litigation with the brand-name company, sharing of litigation expenses with other generic applicants, allegations of improper Orange Book listings, and sales information.

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<sup>44</sup> In many instances, only one generic applicant had filed an ANDA containing a paragraph IV certification for a particular drug product. In these cases, special orders were served only on the first generic applicant.

## Organization of the Report

Chapter 2 of the Report reviews the frequency and outcome of patent infringement lawsuits in connection with paragraph IV certifications. Chapter 3 discusses the agreements that litigants have used to settle patent infringement litigation under Hatch-Waxman. Chapters 4 and 5 examine in more detail how certain Hatch-Waxman provisions, the 30-month stay and the 180-day exclusivity provisions respectively, affect generic entry. Chapter 6 discusses the use of citizen petitions by brand-name companies for drug products included in the study.

Appendix A contains a glossary of terms used most frequently. Appendix B contains the text of Hatch-Waxman. Appendix C lists the NDAs within the scope of the study. Appendix D lists the brand-name companies and generic companies that received special orders. Copies of the questions in the special orders are contained in Appendix E. Appendix F contains a copy of the FTC Staff's Citizen Petition on the listability of certain patents in the Orange Book. Appendix G describes the drug products where the brand-name company has filed a patent in the Orange Book after being notified of the ANDA, which, in turn, generated an additional 30-month stay upon suit. Appendix H analyzes certain categories of patents that raise Orange Book listability issues.



## Chapter 2 Outcomes of Patent Infringement Lawsuits Under the Hatch-Waxman Amendments

### Introduction

The application of both the 180-day exclusivity and 30-month stay provisions depends, at least in part, upon whether the brand-name company initiates patent infringement litigation against a generic applicant.<sup>1</sup> As noted earlier, the 180-day exclusivity provision grants, under certain circumstances, 180 days of exclusive marketing to the first generic applicant that files an ANDA containing a paragraph IV certification. A 30-month stay of FDA approval of a potential generic competitor is invoked if a brand-name company receives notice of a generic applicant's paragraph IV certification and files suit for patent infringement within 45 days of that notice.

Filing of the lawsuit stays the FDA's approval of the ANDA until the earliest of: (1) the date the patents expire; (2) a final determination of non-infringement or patent invalidity by a court in the patent litigation; or (3) the expiration of 30 months from the receipt of notice of the paragraph IV certification. This chapter reviews the frequency and outcome of these patent infringement lawsuits.

For nearly 75 percent of drug products this study covered, brand-name companies initiated patent infringement litigation against the *first* generic applicant. In the other 25 percent, there was no suit,

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<sup>1</sup> For ease of discussion purposes, the term "generic applicant" means those applicants who have filed an ANDA containing a paragraph IV certification. See Appendix A for a glossary of frequently used terms.

and the FDA has approved most of the generic products, thus allowing generic entry to occur. FDA approval of ANDAs submitted by first generic applicants who were not sued by the brand-name company took, on average, 24 months and 2 weeks from the ANDA filing date.

In 70 percent of the cases in which the brand-name company sued the *first* generic applicant, there has been either a court decision, or the parties have agreed to a final settlement. Of these lawsuits, involving 53 drug products, 20 settled without a court decision on the merits of the patent infringement lawsuit. These settlement agreements are discussed in detail in Chapter 3. In the other 30 percent of the cases, a district court had not yet ruled as of June 1, 2002.

Of all the patent infringement cases (including first and subsequent generic applicants) in which there has been a decision of a court as of June 1, 2002, generic applicants prevailed in 73 percent of the cases, and brand-name companies prevailed in 27 percent. Of the decisions favoring the generic applicant, there were slightly more non-infringement decisions (14) than patent invalidity decisions (11). The rate at which the U.S. Court of Appeals for the Federal Circuit overturned district court decisions of patent invalidity for drug products in this study was 8 percent.

In most instances when the 30-month

stay has expired without a decision of a district court and the FDA approved the generic applicant's ANDA, the generic applicant did not enter the market until it secured a district court decision of patent invalidity or non-infringement.

### How Frequently Have Brand-Name Companies Sued the First Generic Applicant?

The study sought to determine the frequency with which brand-name companies have initiated patent infringement lawsuits against generic applicants within the required 45-day period, thus triggering the 30-month stay provision. The data revealed 75 drug products, out of a total of 104 NDAs (72 percent), in which the brand-name company sued the *first* generic applicant. For all but 5 of the 104, the first generic applicant for one dosage strength of the drug product (e.g., 10, 20, and 40 mg tablets) was the first applicant for all strengths of the drug product. In light of this fact, unless otherwise noted, all of the drug products with multiple strengths (with the same 5 exceptions) involved one NDA, and therefore were counted as one brand-name drug product with one first generic applicant. The 5 exceptions are presented in footnotes 4, 7, and 8 to ensure completeness. Table 2-1 summarizes this result.

**Table 2-1 Patent Litigation Frequency**

Litigation Between Brand-name Company and Generic Applicant	Number of NDAs
Brand-Name Company Sued the First Generic Applicant	75
Brand-Name Company Did Not Sue the First Generic Applicant	29 <sup>2</sup>
<b>Total</b>	<b>104</b>

For the 75 drug products where patent litigation was brought, the median net sales in the year the first generic applicant filed its ANDA were \$190 million per year. By contrast, the majority of the 29 NDAs for which no suit was filed had net sales of less than \$100 million in the year the generic applicant filed its application.<sup>3</sup>

For 15 of the 29 drug products where the brand-name company did not sue the first generic applicant, the generic applicant began commercial marketing soon after FDA approval and prior to patent expiration. In 6 cases, the FDA has not approved the generic applicant's ANDA as of June 1, 2002, and the patents have not yet expired. In 6 cases the FDA has approved the ANDA, but commercial marketing has not yet begun. And in the remaining 2 cases, the

<sup>2</sup> For 1 of the 29 drug products, 2 different generic applicants were the first to file for each of the 3 different strengths of this drug product. In each strength, the brand-name company did not sue the generic applicant. As noted above, this brand-name drug product is only counted once in the total of 29.

<sup>3</sup> For 2 of the 29 drug products in which no suit was filed, the brand-name company's patents would have expired during the first several months of the 30-month stay. Because patent expiration terminates the 30-month stay, it may not have made sense in those cases to initiate patent infringement litigation, which takes, on average, 25 months to resolve.

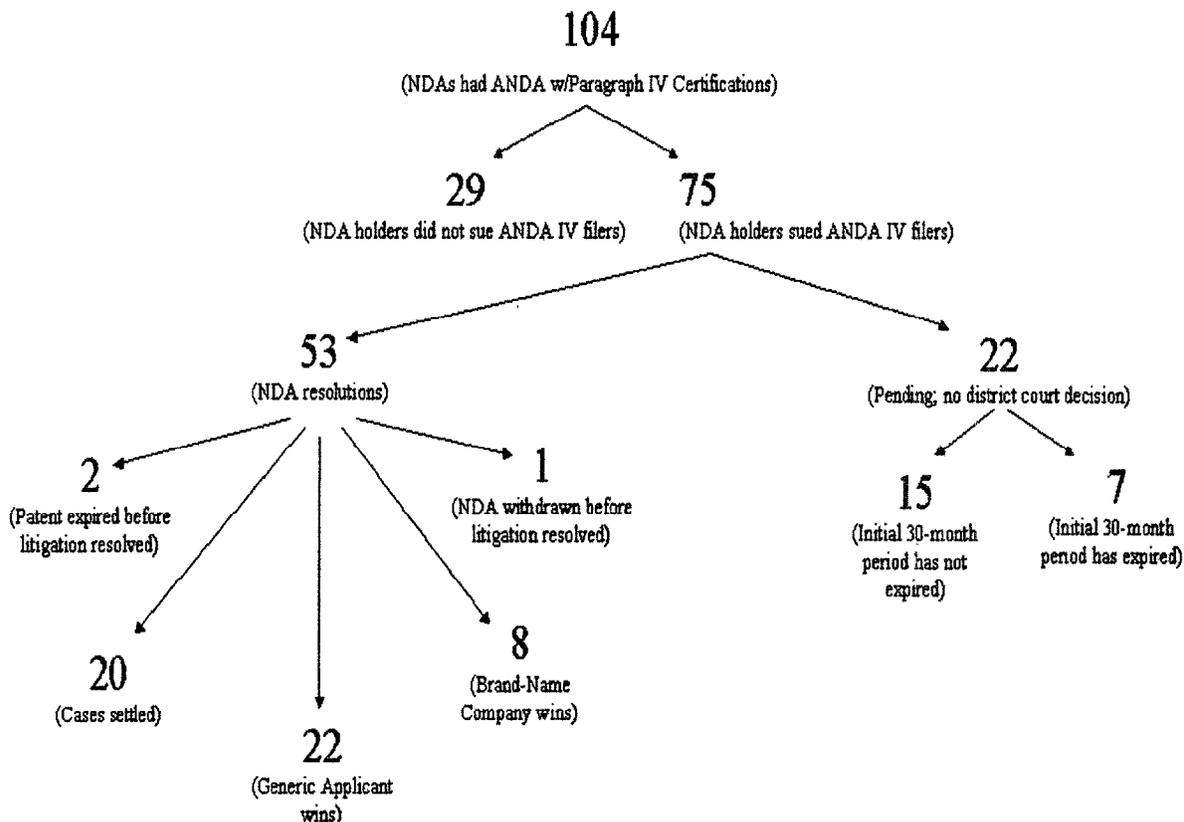
patents expired before FDA approved the generic applicant's ANDA.

## What Were the Results of Patent Infringement Litigation with the First Generic Applicant?

The brand-name company sued the first generic applicant for patent infringement involving 75 NDAs. Figure 2-1 shows a graphical depiction of the resolution (*i.e.*, a decision of a court, a final

settlement, or miscellaneous resolutions) of each case as of June 1, 2002. For 4 drug products, different generic applicants were the first to file on different dosage strengths of the drug product, thus contributing to multiple suits on the same drug product (and the same patent) with different generic applicants. For clarity, the results of more than one suit involving the same drug product are not included in the totals reported, but are described in footnotes 4, 7, and 8. Only results from the first applicant for a drug product are included in the totals discussed below.

Figure 2-1 Summary of Brand Company and 1<sup>st</sup> ANDA IV Filer Activity



## *Pending Patent Infringement Litigation*

As of June 1, 2002, for 22 of the 75 drug products,<sup>4</sup> the district court hearing the lawsuit has not yet ruled on the merits of the patent infringement allegations.<sup>5</sup> For 7 of these 22 drug products, the 30-month stay has expired. For 3 of these 7 drug products, the brand-name company also sued for infringement of a patent that was listed in the Orange Book *after* the first generic applicant had filed its ANDA.<sup>6</sup> In these cases, it has been possible for a brand-name company to obtain more than one 30-month stay. The first 30-month stay has expired in these 3 cases, but the second (or even later) one has not. In none of these cases has the generic applicant entered the market.

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<sup>4</sup> In addition to these 22 cases, there are 2 more pending cases on a dosage strength of a drug product for which the patent litigation on another strength has been resolved. The resolution of these cases is discussed in the following section.

<sup>5</sup> In one pending case, the FDA determined that the brand-name company failed to submit the required information for a particular patent in a timely manner. Therefore, the generic applicant was not required to submit a patent certification to address that patent, the 30-month stay was dissolved, and the FDA subsequently approved the ANDA. Commercial patent litigation was still pending as of June 1, 2002, however, and the generic applicant has not yet entered the market.

<sup>6</sup> As discussed further in Chapter 4, if a brand-name company lists in the Orange Book later-issued patents (*i.e.*, patents obtained from the U.S. Patent and Trademark Office after obtaining NDA approval) after receiving notification from a generic applicant, the generic applicant must re-certify that its ANDA does not infringe the later-issued patent. If the brand-name company initiates a patent infringement suit within 45 days of notice of the generic applicant's re-certification, then FDA approval of the ANDA is stayed automatically for an *additional* 30 months from the notice date or upon final determination of non-infringement or patent invalidity by a court in the patent litigation.

## *Resolution of Patent Infringement Suits*

There has been a court decision for 53 drug products (75 in total less 22 pending). The resolution of each is classified in Table 2-2 and also is described in Figure 2-1. Settlements were used in 38 percent of the instances (20 drug products out of 53 settled).<sup>7</sup> A court decision resolved the patent infringement claims for 30 drug products. Generic applicants prevailed 73 percent of the time (22 out of 30),<sup>8</sup> and brand-name companies prevailed 27 percent of the time (8 out of 30). In 3 miscellaneous instances, either the patents expired before the 30-month stay expired, or the brand-name company withdrew the NDA due to safety reasons.

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<sup>7</sup> For one of these 20 drug products, a different generic applicant was first for each of the product's 3 strengths; the brand-name company settled with 2 of these applicants, and the litigation involving the other strength is pending. This drug product is counted only once as "settled." *See supra* n. 4. For another of these 20 drug products, a different generic applicant was first for each of the product's 2 strengths; the brand-name company entered a settlement with one generic applicant, and the first applicant for the other strength prevailed on non-infringement at the Federal Circuit. This drug product is counted only as "settled."

<sup>8</sup> For one of these 22 drug products, a different generic applicant was first for each of the product's 2 strengths; the first generic applicant prevailed on non-infringement at the Federal Circuit on one strength, while the other case is pending. This drug product is counted only once as "generic prevails." *See supra* n. 4. For another of these 22 products, a different generic applicant was first for each of the product's 3 strengths; the first generic applicant for each strength prevailed in each patent suit, which were on the same patent. This drug product is counted only once as "generic prevails."

**Table 2-2 Results of Lawsuits with the First Generic Applicant**

<b>Resolution of Patent Litigation with First Generic Applicant</b>	<b>Number of NDAs</b>
Settlement Between Brand-Name Company and Generic Applicant	20
Generic Applicant Prevails in Patent Infringement Suit	22
Brand-Name Company Prevails in Patent Infringement Suit	8
Miscellaneous	3
<b>Total Number of Cases Resolved</b>	<b>53</b>

*Patent Settlements with the First Generic Applicant*

As shown in Table 2-2, the brand-name company and the first generic applicant settled patent infringement litigation involving 20 drug products. Most of the settlements can be classified into 3 types. Nine of these settlements contained a provision by which the brand-name company, as one part of the settlement, paid the generic applicant (settlements involving “brand payments”). Seven of the 20 settlements involved the brand-name company licensing the generic applicant to use the patents for the brand-name drug product prior to patent expiration. Two of the settlements allowed the generic applicant to market the brand-name drug product as a generic product, under the brand-name company’s NDA, not the generic applicant’s own ANDA. The remaining 2 settlements do not fit into any of these 3 categories. The provisions of each of these settlement agreements are discussed more fully in Chapter 3.

*Generic Applicant Prevails*

Table 2-3 shows that the generic applicant prevailed in litigation over 22 drug products.<sup>9</sup> In 18 instances, a court held that the brand-name company’s patents were either invalid or not infringed. Of these 18 court decisions, 13 were appellate and 5 were district court (4 of which the brand-name companies have appealed as of June 1, 2002, but the decisions are pending). In 9 of these instances, the court held that the generic applicant’s ANDA did not infringe the brand-name company’s product; in the remaining 9 instances, a court held that the underlying patent was invalid for reasons such as being anticipated by prior art or double patenting.

For 2 of the 18 drug products, the parties implemented interim settlements that included brand payments to the generic applicant. For both of these drug products, the generic applicant began marketing after the interim settlement was terminated and the Federal Circuit had affirmed the district court’s ruling of patent invalidity.<sup>10</sup>

For 3 of the 4 remaining drug

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<sup>9</sup> This total does not include the resolution of follow-on lawsuits on 2 drug products that are counted as “settled.” In the first instance, after the parties settled, the brand-name company submitted a late-issued patent for listing in the Orange Book, and a second round of litigation ensued in which the generic applicant prevailed. In the second instance, the parties settled the initial lawsuit, but the generic applicant later re-filed an ANDA for a reformulated version of the product. The brand-name company dismissed this second case with prejudice after determining that the reformulated version did not infringe its patents.

<sup>10</sup> One of these drug products (Hytrin tablets) was discussed in *Abbott Laboratories*, No. C-3945 (May 22, 2000) (consent order), available at <<http://www.ftc.gov/os/2000/03/abbott.do.htm>>.

products (of the 22), the brand-name company dismissed the litigation after receiving samples of the generic applicant's proposed product. In 2 of these cases, the FDA approved the generic drug soon thereafter, and generic entry occurred after the case was dismissed.<sup>11</sup> In the other case, the FDA had not approved the generic drug product as of June 1, 2002. For the last of the 4 drug products, the brand-name company dismissed the litigation without prejudice. Entry was delayed in light of an interim settlement on a later-listed patent for which the brand-name company failed to sue the first generic applicant within the requisite 45 days.<sup>12</sup>

The patents covering the 22 brand-name drug products in which the generic applicant prevailed involved formulation or method of use patents. In 3 instances (out of 6 where a drug substance patent was at issue), a drug substance patent was found invalid or not infringed.

### *Brand-Name Company Prevails*

For 8 drug products, the brand-name company prevailed in the patent infringement litigation. For 7 drug products, a court held that the generic applicant's ANDA infringed the brand-name company's patents. Two of these decisions were appellate decisions; the other 5 were district

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<sup>11</sup> For the details of one of these case, see Hoechst Marion Roussel, Inc., No. 9293 (May 8, 2001) (consent order), available at <http://www.ftc.gov/os/2001/05/hoechstdo.pdf>.

<sup>12</sup> This drug products (Hytrin capsules) was discussed in *Abbott Laboratories*, No. C-3945 (May 22, 2000) (consent order), available at <http://www.ftc.gov/os/2000/03/abbott.do.htm>.

court decisions, of which only one has been appealed by the generic applicant. As of June 1, 2002, this appeal is pending. By contrast, brand-name companies appealed nearly 90 percent of the cases in which they obtained an adverse district court opinion. In the last of the 8 cases, the generic applicant abandoned its ANDA after it was sued, and the court did not issue a final judgment.

The patent claims in 3 of these patent lawsuits involved drug substance claims, and the other 5 involved method of use and/or formulation claims.

## **How Frequently Have Brand-Name Companies Sued the Second Generic Applicant?**

If the brand-name company sued the first generic applicant, it also sued the second generic applicant, if there was one, in nearly 85 percent of the cases. There were 43 such instances. Of the suits that have been resolved as of June 1, 2002, in no instance did different district courts reach different results in resolving infringement issues over the same brand-name drug product.

The brand-name company generally sued all generic applicants if the drug product had annual sales larger than \$500 million in the year the first generic applicant filed its ANDA. Twenty such drug products are included in the study.

## What Are the Results of Litigation with the Second Generic Applicant if the Brand-Name Company Settles with the First Generic Applicant?

Table 2-3 shows the results of litigation with the second generic applicant in those instances in which the first generic applicant settled its patent infringement litigation. Out of a total of 20 drug products with first generic settlements (*see* Figure 2-1), 9 drug products involved litigation with the second generic applicant.<sup>13</sup> In 1 case, litigation is still pending. Table 2-3 shows the resolution of the 8 decided cases.

**Table 2-3 Resolution of Patent Litigation with Second Generic Applicant if the First Generic Applicant Settled its Litigation**

Resolution of Subsequent Litigation	Number of NDAs
Settlement with Second Generic Applicant	4
Second Generic Applicant Wins Patent Infringement Suit	3
Brand-Name Company Wins Patent Infringement Suit	1
<b>Total</b>	<b>8</b>

In these 8 cases, the parties settled in 4, while in 3 the generic applicant prevailed (2 non-infringement decisions and 1 invalidity decision). In 1 case, the brand-

<sup>13</sup> Eleven drug products either did not have a second generic applicant, or the brand-name company did not sue the second applicant.

name company won a decision of infringement.

## For Those Patent Litigations that Resulted in a Court Decision, How Often Did Generic Applicants Prevail for All of the Drug Products in the Study?

For many drug products, the brand-name company sued several generic applicants over the same patents. Thus, in determining how frequently generic applicants or brand-name companies prevailed in patent litigation on a drug product basis, it would be misleading simply to count the number of decisions in either party's favor, because several of the decisions may be related to the same patent. Table 2-4 shows the results of the resolution of the patent suits without counting any similar outcomes involving the same drug product. For example, if both the first and second generic applicant obtained court decisions of non-infringement, the drug product is included only once as a generic win. If the case against the first generic applicant settled or is pending, but the case against the second applicant was resolved, the resolution of the second case is included. In no instance were the outcomes of the suits against the first and second generic applicant different.

There were court decisions on 40 different drug products. Table 2-4 presents the resolution of the patent litigation derived from five sources: (1) litigation with the first generic applicant (Table 2-2), (2) litigation with the second generic applicant if the first

generic applicant settled (Table 2-3), (3) litigation with the second generic applicant was resolved, but either the first generic applicant was not sued or the case is pending (3 drug products), (4) litigation with a third generic applicant when the first two generic applicants had settled, and (5) follow-on litigation with the first generic applicants on two drug products described in footnote 9.

Generic applicants prevailed for 29 out of 40 drug products (or 73 percent). Decisions involving 14 drug products held that the generic applicant did not infringe the patent, decisions involving 11 drug products held the relevant patent(s) invalid, and in 4 cases, the brand-name company abandoned the litigation with the first generic applicant before a decision of a court.

The brand-name company prevailed against the generic applicant in litigation involving 11 drug products. In one of these 11 cases, the generic applicant abandoned the litigation and admitted infringement before the court issued a decision.

**Table 2-4 Patent Litigation Results per Drug Product**

Result of Litigation	Number of NDAs
Generic Applicant Wins	29
Brand-Name Company Wins	11
<b>Total</b>	<b>40</b>

### *Results of Litigation and Patent Invalidation Rates*

Out of 40 drug products in Table 2-4, 11 drug products had at least one patent listed in the Orange Book that was

determined to be invalid. Thus, the minimum invalidity rate of patents that the parties chose to litigate to conclusion is 28 percent (11 invalid findings / 40 total). This rate assumes that the patents underlying the non-infringement decisions and cases when the brand-name company abandoned the litigation are valid, even though the courts in these cases may not have addressed the validity question. Thus, the invalidity rate may be higher than 28 percent, although we do not have data to determine it.

The recent empirical literature on the outcome of patent litigation provides a point of comparison with these findings, and suggests that this invalidity rate, although it may be understated as noted above, is not out of line with that of patents generally. Moore compares the outcomes of patent cases decided by judges with the outcomes of patent cases in which the finder-of-fact is a jury.<sup>14</sup> In her data set of 1209 patent trial decisions from 1983 through 1999, she finds that patents are invalidated in 36 percent of cases with a judge as the adjudicator and in 29 percent of cases with a jury.<sup>15</sup>

<sup>14</sup> Kimberly A. Moore, *Judges, Juries & Patent Cases: An Empirical Peek Inside the Black Box*, 98 Mich. L. Rev. 365 (2000).

<sup>15</sup> *Id.* at 391. See, also, John R. Allison & Mark A. Lemley, *Empirical Evidence on the Validity of Litigated Patents*, 26 AIPLA L.Q. 185 (1998). Allison and Lemley study the outcomes of patent validity cases from 1989 to 1996. They focus on those cases in which there exist final written decisions at either the district court or the Federal Circuit levels. In their study, a district court decision is "final" if a later decision by the Federal Circuit does not supersede it. In their data set of 299 patents in 239 different cases, they find that 46 percent of the final decisions hold the relevant patent invalid. In contrast to this figure which covers all patent validity decisions, they find that pharmaceutical patents are found invalid in 27 percent of cases. Allison and Lemley do not consider decisions that focus only on infringement.

## **How Frequently Did the Federal Circuit Reverse a District Court Decision of Non-Infringement or Patent Invalidity?**

Of the 29 NDAs where the generic applicant prevailed, as noted in Table 2-4, in 14 instances, the brand-name company appealed a district court decision that the patent at issue was either invalid or not infringed in a patent suit against either the first or second generic applicant.<sup>16</sup> In 13 of these decisions, the U.S. Court of Appeals for the Federal Circuit affirmed district court decisions of patent invalidity or non-infringement – 8 affirmed decisions of non-infringement,<sup>17</sup> and 5 affirmed decisions of patent invalidity. In the remaining case, two patents were at issue. The district court had determined both patents to be valid, but the Federal Circuit reversed as to one of the patents, and affirmed the validity decision for the other. Thus, the rate at which the Federal Circuit reversed decisions of invalidity and non-infringement for drug

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<sup>16</sup> To ensure no double counting, if the suits against the first and second generic applicant were consolidated into 1 district court opinion, and that decision was appealed, the appellate decision is counted only once. This also does not include one case where the district court's decision on summary judgment was vacated and remanded. Moreover, of the 29 drug products in which the generic applicant prevailed, some of the appeals are pending, or the district court decision was not appealed.

<sup>17</sup> In one of these decisions, the district court held the patent invalid and not infringed. The Federal Circuit upheld the non-infringement holding, but reversed on the invalidity holding. This has not been counted in the rate at which the Federal Circuit reversed decisions of invalidity and non-infringement for drug products included in this study because the non-infringement decision was affirmed and generic entry occurred prior to patent expiration.

products included in this study was 8 percent.<sup>18</sup>

Table 2-4 shows that the brand-name company prevailed in litigation for 11 drug products. Of the 4 cases in which the generic applicant appealed the district court's decision of infringement, the Federal Circuit affirmed all 4 of these district court decisions of infringement.

## **In Which District Courts Did Brand-Name Companies Initiate Patent Infringement Litigation?**

In 62 percent of the cases involving litigation with the first and second generic applicants, brand-name companies initiated patent litigation in just five federal judicial districts. These were the District of New Jersey, the Southern District of New York, the Southern District of Indiana, the Northern District of Illinois, and the Southern District of Florida. Thus, these courts have more experience with ANDA patent infringement litigation than most other federal district courts.<sup>19</sup>

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<sup>18</sup> This rate does not include Federal Circuit overrules of summary judgement or collateral estoppel decisions.

<sup>19</sup> For those drug products in which both the first and second generic applicant were sued, approximately 50 percent of the suits were pursued in different district courts.

## **When Did Generic Applicants Enter the Market?**

If a generic applicant was sued for patent infringement, it generally did not enter the market until there was a district court holding that the brand-name company's patent was invalid or not-infringed. In no instance has a generic applicant (either the first or second) entered the market and then a court later has found that the patent was infringed, making the generic applicant subject to damages.

In 22 cases (out of 75, Table 2-1) involving litigation between the brand-name company and the first generic applicant, as of June 1, 2002, the first 30-month stay had expired before the district court decision. In 8 of those cases, the FDA approved the generic applicant's ANDA prior to a district court ruling on the merits of the patent infringement suit.<sup>20</sup> In the first 2 cases, the district court case was ongoing as of June 1, 2002, and the generic applicant had not entered, although it had FDA approval to do so. In the next 2 cases, the generic applicant entered after obtaining a district court decision, but prior to the Federal Circuit's decision.<sup>21</sup> In the fifth case, the generic applicant waited until the Federal Circuit affirmed the district court's ruling. In the sixth case, the generic applicant

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<sup>20</sup> In the other 14 cases (22 less 8), either the district court had not ruled as of June 1, 2002 and the FDA has not yet approved the ANDA, or the district court ruled and the FDA acted accordingly, depending upon the outcome of the litigation.

<sup>21</sup> In addition to these 2 instances, generic applicants for 3 other drug products entered after a district court case, but prior to the Federal Circuit's ruling. In these cases, however, the 30 month stay had not expired before the district court ruled.

reformulated its product and the brand-name company dismissed the litigation before a ruling on the merits. The generic applicant entered the market soon thereafter.

In the seventh case in which the FDA approved the generic applicant after the 30-month stay had expired but before a district court decision, there were two generic applicants for different dosage strengths (30 mg and 60 mg) of the same drug product (Drug Product A). The discussion of generic entry that follows only relates to the 60 mg product. The brand-name company sued each generic applicant over the same patent in different district courts. The first generic applicant on the 30 mg product obtained a district court decision of non-infringement and the Federal Circuit affirmed this decision. The 60 mg generic applicant entered once the Federal Circuit affirmed the district court's decision of non-infringement on the 30 mg product. This occurred, however, before the district court reached a decision on the litigation involving the 60 mg generic applicant's litigation.

In the eighth case involving a drug product that was covered by the same patent that covered Drug Product A (described above), the generic applicant also entered prior to a district court decision. Like the 60 mg generic applicant, the first applicant for this drug product also entered after the 30 mg decision of non-infringement of Drug Product A was affirmed by the Federal Circuit.

In separate instances involving the drug products Taxol and BuSpar, which are not included in the 22 described above, the generic applicants began commercial marketing without waiting for a district

court decision in their favor on the patent the brand-name companies had listed in the Orange Book after the generic applicants had filed their ANDAs.<sup>22</sup> In both cases the district court eventually held the patent to be invalid or not infringed.

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<sup>22</sup> See Chapter 4 for a full discussion of multiple 30-month stays. Both suits on the later-issued patents raised questions whether the patents should be listed in the Orange Book.



## Chapter 3 Settlements Related to Paragraph IV Certifications

### Introduction

Certain patent settlement agreements between brand-name companies and potential generic competitors have received antitrust scrutiny in recent years. Parties have debated whether these settlements increased or harmed consumer welfare.

Patent settlements can resolve disputes in whole, or in part, and in a timely manner. Public policy favors the use of settlements to reduce the use of limited judicial resources. Moreover, settlements may provide for generic entry that might otherwise be delayed by patent disputes, and can reduce uncertainty by clarifying intellectual property rights among the parties. Thus, patent settlements can be procompetitive. This potential is not always fulfilled, however. As noted earlier, the FTC has alleged that certain settlements between brand-name and generic companies were anticompetitive.

This chapter describes the contours of agreements that settled patent litigation between brand-name companies and generic applicants concerning patents listed in the Orange Book for the drug products this study covers.<sup>1</sup> The chapter discusses trends concerning the settlements produced in the study, and describes similarities and differences among such settlements. It also describes how these settlements compare to the ones that the Commission alleged to be

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<sup>1</sup> Brand-name and generic companies produced a range of other types of agreements relating to the drug products included in the study. These agreements are not discussed in this report.

anticompetitive in its enforcement actions. This chapter does not reach any conclusions about the competitive effects of the settlements produced.

Twenty final<sup>2</sup> and 4 interim<sup>3</sup> agreements that settled litigation between the brand-name company and the first generic applicant were produced in response to the FTC's special orders. In 9 of the final settlement agreements, the brand-name company agreed to pay the generic applicant (a "brand payment"). In 7 of the 20 final settlements, the brand-name company granted a license to the generic applicant to use the patents that cover the brand-name drug product prior to patent expiration so that the generic applicant could market under its ANDA. Two of the final settlements allowed the generic applicant to distribute the brand-name drug product as a generic product, marketed under the brand-name company's NDA, not the generic applicant's own ANDA. The remaining 2 final settlements do not fit into any of these 3 categories of settlement types.

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<sup>2</sup> One of these agreements is subject to litigation currently pending at the FTC. See *Schering-Plough Corp., et al.*, Docket No. 9297, Initial Decision (Jul. 2, 2002), available at <http://www.ftc.gov/os/2002/07/scheringinitialdecisionp1.pdf>.

<sup>3</sup> For 3 out of the 4, see *Abbott Laboratories*, No. C-3945 (May 22, 2000) (consent order), available at <http://www.ftc.gov/os/2000/03/abbott.do.htm> (this consent order related to 2 drug products: Hytrin tablets and Hytrin capsules). *Hoechst Marion Roussel, Inc.*, No. 9293 (May 8, 2001) (consent order), available at <http://www.ftc.gov/os/2001/05/hoechstdo.pdf>.

Fourteen of the final settlements with the first generic applicants, at the time they were executed, had the potential to delay the triggering of the first generic applicant's 180-day exclusivity for some period of time, and thus to delay FDA approval of any subsequent eligible applicants.<sup>4</sup> This potential to delay the triggering of the 180-day exclusivity existed because the settlement contained a waiting period before which the generic applicant could enter the market. All of the waiting periods expired at some time either before the patent(s) expired or at patent expiration. Ten brand-name companies and 10 generic companies used agreements with respect to 14 drug products. See Chapter 5 for a further discussion of 180-day exclusivity.

Most of the final settlements with brand payments involved drug products with higher sales than the drug products that the brand-name companies chose to license or supply to generic applicants. Final settlements with brand payments have been used by 7 brand-name companies (of which two companies had 2 such agreements) and 8 generic companies (one of which was a party to 2 agreements).

In addition to the final settlements with the first generic applicant, in 7 instances, brand-name companies entered final patent settlements with the second generic applicant. In 6 of the 7, the brand-name company also had settled with the first generic applicant.

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<sup>4</sup> Whether the FDA actually was prevented from approving subsequent eligible generic applicants depends on specific facts, including whether there were subsequent generic applicant(s) and the result(s) of any patent litigation with those applicants.

Finally, in 6 instances (out of the 53 resolved cases noted in Chapter 2), the first and second generic applicants entered into agreements with each other that related to generic market entry. Most involved either relinquishing the 180-day exclusivity or determining which generic company had rights to the 180-day exclusivity in light of agreements between the first generic applicant and the brand-name company.

## **Scope of Information Requested and Received**

The FTC's special orders required each brand-name company to submit all agreements between itself and any person relating to an ANDA containing a paragraph IV certification involving any drug product, when the brand-name company holds the rights to the NDA corresponding to the ANDA that is the subject of the agreement. Examples of such agreements include, but are not limited to: (a) patent litigation settlements; (b) agreements related to the filing (or non-filing) of an ANDA by any applicant (or potential applicant) involving any drug product; (c) licensing agreements between the company and persons that have filed an ANDA involving any drug product; and (d) agreements related to any acquisition, divestiture, joint venture, alliance, license, or merger by the company of any business involving the research, development, manufacture, or sale of any drug product that is the subject of an ANDA. The companies were also requested to produce all studies, surveys, analyses, and reports prepared by or for any officer(s) or director(s) of the company (or, in the case of unincorporated entities, individuals exercising similar functions) that evaluate or

analyze the reasons for making such agreements. Generic companies received similar requests.

Brand-name and generic companies produced a variety of other agreements relating to the drug products subject to the study. Examples of these agreements include brand-name and generic companies obtaining third-party arrangements for the supply of raw materials, manufacturing, repackaging, distribution, marketing, development, and license of formulation technologies relating to the drug products. These agreements are not analyzed in this chapter.

### *Overview of Patent Settlements*

As discussed in Chapter 2, litigants reached agreements that finally settled patent suits involving 20 out of 53 drug products for which a brand-name company sued the first generic applicant who had filed an ANDA containing a paragraph IV certification (*see* Figure 2-1).

For 9 drug products, the brand-name company and the generic applicant settled the patent infringement litigation through a license or supply agreement.<sup>5</sup> Six of these agreements occurred in 2000 and 2001. For 9 other drug products, one component of the settlement agreement was a payment from the brand-name company to the generic applicant. The existence of brand payment

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<sup>5</sup> Two different generic applicants were the first to file on different strengths of the same drug product. The brand-name company settled the litigation with both applicants (one settlement was a license agreement and the other was a supply agreement). Because the different strengths are covered by only one NDA, the drug product is counted only once as a "supply agreement" to ensure consistency in counting drug products with agreements.

provisions distinguished these agreements from those involving a license or supply arrangement, which did not contain a brand payment.<sup>6</sup> The remaining 2 of the 20 settlements did not fit into either of these categories. Table 3-1 categories these 20 final settlements.

## **Settlements Involving Patent Licenses or Supply Arrangements**

In light of the confidential nature of many of the provisions of these settlements, the following discussion has been written to ensure anonymity. Each lettered drug product corresponds to a distinct brand-name drug product.

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<sup>6</sup> Two district court decisions have examined the use of brand payment provisions in the settlement agreements involving Cardizem CD and Hytrin. Both courts have found the agreements to be *per se* restraints of trade under Section 1 of the Sherman Antitrust Act. *In re Cardizem CD Antitrust Litigation*, 105 F.Supp.2d 618, 684 (E.D. Mich. 2000) and 105 F.Supp.2d 618, 622 (E.D. Mich. 2000); *In re Terazosin Hydrochloride Antitrust Litigation*, 164 F.Supp.2d 1340, 1342 (S.D. Fl. 2000). Both of these district court decisions are currently on appeal.

**Table 3-1 Overview of Final Settlements with the First Generic Applicant**

Type of Agreement	Number of Drug Products	Net Sales	Number of Brand-Name Companies	Number of Generic Applicants
License Agreements	7	Less than \$100 million = 3 Between \$100 and \$250 million = 4; Between \$250 and \$500 million = 0; Greater than \$500 million = 1	6 (two had 2 agreements)	7 (one had 2 agreements)
Supply Agreements	2	Between \$250 and 500 million = 1; Greater than \$500 million = 1	2	2
Agreements with Brand Payments	9	Less than \$100 million = 3 Between \$100 and \$250 million = 2; Between \$250 and \$500 million = 2; Greater than \$500 million = 2	7 (two had 2 agreements)	8 (one had 2 agreements)
Other	2	Less than \$100 million = 1 Between \$100 and \$250 million = 1	2	2
<b>Total</b>	<b>20</b>	<b>N/A</b>	<b>11 (3 had 2 agreements each, 2 had 3 agreements each, and 1 had 4 agreements)</b>	<b>14 (3 had 2 agreements each, and 2 had 3 agreements)</b>

*Settlements Involving Patent Licenses*

As discussed in Table 3-2, for 8 drug products,<sup>7</sup> the generic applicant obtained a non-exclusive, royalty-bearing license (except for drug product F, which was an exclusive license, and drug product H,

which was royalty-free) to use the brand-name company's patents for the particular brand-name product prior to the patent expiration. In 4 instances (B, C, D, and G), generic entry proceeded immediately after executing the settlement and obtaining FDA approval. In the other 4 instances (A, E, F, and H), the parties agreed to a waiting period before the generic applicant could enter.

<sup>7</sup> Although 8 drug products involved licenses with the first generic applicant, the generic applicant for drug product G was first for only one strength of the product. At the time the brand-name company entered into this license, it had already entered a supply agreement, see discussion in the following section, with the first generic applicant for another strength of the drug product. See supra n. 5. For purposes of Table 3-2, this license agreement is discussed separately.

**Table 3-2 Settlement Agreements Involving Patent Licenses**

<b>Drug Product</b>	<b>Time Between Agreement Date and Patent Expiration</b>	<b>Effective Date of the License</b>	<b>Brand-Name Products' Annual Net Sales in the Year Prior to the Agreement</b>	<b>Royalties Paid by the Generic Company to the Brand-Name Company for the License Agreement</b>
A	15 years, 2 months	7 months after date of agreement.	Less than \$100 million	1.5% of sales for 5 years.
B	13 years, 10 months	Immediately	Between \$100 and \$250 million	\$1 million at signing. \$500,000 when the FDA approves the generic product; \$1.5 million if generic company sells its product prior to another entity having sold a generic version of the product; and an additional payments of \$500,000 if the generic company is the sole company selling a generic version of the product at certain future dates.
C	15 years, 8 months	Immediately	Less than \$100 million	A license fee of \$3 million plus a royalty of 3.0% of net sales for first 6 years of sales; \$1 million when the suit is dismissed; and \$1 million at the first and second anniversaries of the shipment of the generic product.
D	5 years, 2 months	Immediately	Between \$100 and \$250 million	\$2.5 million upon dismissal of litigation.
E	2 years, 6 months	15 months after date of agreement.	Between \$100 and \$250 million	The generic company's royalty payment is 20% of generic company's first \$15 million in net sales, 40% of net sales between \$15 and \$30 million; and 60% of net sales greater than \$30 million.
F	3 years, 6 months	17 months after date of agreement.	Between \$100 and \$250 million	A royalty payment of 7.5% of the generic company's net sales for months 21 through 15 prior to expiration of patents, 5% royalty of net sales for months 14 through 8, and 2.5% of net sales for months 7 through end of patent term.
G	10 years, 5 months	Immediately	Less than \$100 million	No royalty payment unless generic company changes its formulation, then it must pay a 5% royalty.
H	1 year, 11 months	14 months after date of agreement.	Between \$500 and \$750 million	Royalty-free license.

In 4 instances (A, E, F, and H), there was only one generic applicant for the drug product. The brand-name company did not sue the second generic applicant for 3 drug products (B, C, and D) as of June 1, 2002.

The brand-name company sued the second generic applicant for drug product G, and this litigation settled.

Table 3-2 describes the attributes of

these 8 patent license agreements and the royalty provisions in each. The licenses were for formulation or method of use patents. In each case, except for drug product D, the generic applicant affirmed the validity and enforceability of the patent(s) at issue. None of the license agreements prohibited the generic applicant from developing non-infringing generic versions of the brand-name drug product, nor did they involve licenses for other products other than the one subject to the ANDA litigation.

Among the license agreements described in Table 3-2, the four agreements with waiting periods (A, E, F, and H) related to brand-name drug products in which there was not yet a second generic applicant for the drug product as of January 1, 2001.

#### *Settlements Involving Supply Agreements*

As part of two settlements, the brand-name company entered into a supply agreement that allowed the generic applicant to market the brand-name company's product as a generic product. These agreements differ from the licenses described above because the generic applicant distributes the brand-name company's drug and does not sell product pursuant to its ANDA.

- In one of the supply agreements, generic marketing did not begin until a *subsequent* generic applicant was ready to ship its product to customers. Annual net sales for this drug product in the year prior to the agreement date were over \$500 million. The district court had not yet ruled in the brand-name company's patent infringement suit against subsequent generic

applicants when the supply agreement with the first generic applicant was executed. Under the agreement, if the patent litigation with these subsequent applicants resulted in the patent being declared invalid or not infringed, then the brand-name company's obligation to supply the first generic applicant would be triggered.<sup>8</sup> The patents at issue were formulation patents, and the time difference between the agreement date and patent expiration was 14 years and one month.

- In the other supply agreement, the generic applicant agreed to pay a substantial royalty to distribute exclusively a generic version of the brand-name product manufactured by the brand-name company.<sup>9</sup> Alternatively, the generic company could choose a patent license agreement (similar to those discussed above) in exchange for a small royalty on net sales. The agreement is dated 10 years, 9 months before the formulation/method of use patent was due to expire.

#### *Miscellaneous Agreements with the First Generic Applicant*

Two additional agreements did not appear to raise issues related specifically to Hatch-Waxman. For example, one of the agreements settled litigation over when the

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<sup>8</sup> The supply agreement sets forth the transfer price at which the generic company is obligated to purchase all of its requirements. The generic applicant is required to pay a 50% royalty of the net profits from all sales of the generic product.

<sup>9</sup> The supply agreement was for not only the strength of the drug product for which the generic company was the first ANDA IV filer, but also for two additional strengths of the same drug product for which it had not filed an ANDA with a paragraph IV certification.

brand-name company's patent should expire. These agreements are not discussed in this report.

## **Final Settlements Involving Brand Payments**

Nine out of 20 final settlements between brand-name companies and generic applicants involved brand payments from the brand-name company to the generic applicant. The first such agreement included in the study was executed in March 1993.

### *The Basic Model*

Eight of the 9 agreements with brand payments followed the same basic model. Each prohibited the generic applicant from purchasing, manufacturing, using, selling, distributing, and shipping to third parties any form of the generic's drug product until the expiration of the patents (or in 2 cases, until the end of waiting period specified in the agreement, which occurred prior to patent expiration).

Four of these settlements also prohibited the generic applicant from marketing *any* other form of the brand-name company's drug product, which was the subject of the ANDA, prior to patent expiration or the waiting period established in the agreement. These four settlements involved formulation or method of use patents.

Two of the settlements included licenses for drug products other than one

subject to the ANDA litigation.<sup>10</sup>

These 8 settlements each had the effect of precluding FDA approval of the generic applicant's ANDA until patent expiration or, in 2 cases, until the date specified in the agreement. Each also had the further effect of precluding the FDA, for the duration of the agreement, from approving a later-filed ANDA with a paragraph IV certification for the same brand-name drug product, unless a second (or later) generic applicant obtained a court decision of non-infringement or invalidity. None of these 8 agreements contained a provision that prohibited the generic applicant from relinquishing the 180-day exclusivity.

As described in Table 3-3, the range of brand payments was \$1.75 million to \$132.5 million, and the time between the date of agreement and patent expiration ranged between 4 months and 10 years.

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<sup>10</sup> For a discussion of one of these agreements, see *Schering-Plough Corp.*, *supra* n. 2.

**Table 3-3 Settlement Agreement with Brand Payments: Basic Model**

<b>Drug Product</b>	<b>Total Brand Payment from Brand-name Company to Generic Applicant</b>	<b>Time Between Agreement Date and Patent Expiration</b>	<b>Brand-Name Company's Annual Net Sales in Year of Agreement</b>
I	\$132.5 million (in part to settle additional patent litigation)	1 year, 9 months	Greater than \$1 billion
J	\$72.5 million paid in four installments of increasing amounts	4 years, 1 month	Between \$250 and \$500 million
K	\$66.4 million in a lump sum (includes payments to ANDA filer and its raw material manufacturer)	9 years, 5 months	Less than \$100 million (year after agreement)
L	\$60 million (includes fees for licenses to other products)	4 years, 3 months*	Between \$100 and \$250 million (year after agreement)
M	\$49.1 million, plus optional annual payments for 6 years of at least \$50 million in lieu of a supply agreement	6 years, 11 months	Between \$750 million and \$1 billion
N	\$22 million paid in 2 installments (plus \$2.5 million per month beyond the 4 <sup>th</sup> month if certain events occur)	4 months	Between \$250 and \$500 million
O	An 8.5 percent royalty fee of the brand-name company's sales of the product during the first and second year of the 2.5 year period (based on sales of the first year, the payment was approximately \$5 million), a 7.5 percent royalty fee for the remaining 6 months of the 2.5 year period.	2 years, 6 months*	Less than \$100 million
P	\$1.75 million divided in three equal installments.	10 years	Less than \$100 million

\* Time between agreement date and generic entry allowed under the agreement. In each case generic entry was permitted prior to patent expiration pursuant to a license.

*Additional Conditions:* These 8 final agreements included additional conditions. For example, in most of the agreements, the generic applicant agreed not to cause, aid, assist others in the purchase, manufacture, use, sale of a generic version of the drug product prior to patent expiration or the date the patent is held invalid by a court of competent jurisdiction and the decision becomes final. Another frequent provision was that the generic applicant not aid or assist any third party in the preparation, filing, or processing of an application for a generic version of the drug product,

including the sharing of any information obtained through the litigation.

*Timing of Settlements:* The agreements were entered at various times in relation to whether a court had ruled on the underlying patent infringement lawsuit. A court had not yet ruled on the merits of the patent infringement suit for 4 drug products. For the other 4 drug products, a district court had ruled on the merits of the brand-name company's infringement claims as follows: (1) the district court held the patent invalid on summary judgment, but the Federal

Circuit reversed and remanded for trial on certain factual issues; (2) the district court held the patent invalid, but the parties settled and the lower court's decision was then vacated; (3) the district court denied the brand-name company's summary judgment motion of infringement, thus indicating triable issues of fact remained; and (4) the brand-name company obtained a temporary restraining order prohibiting the generic applicant's sale of the drug product.

*Optional Licenses:* The brand-name company for one drug product had the option of granting the generic company a non-exclusive, royalty-free license for the underlying patent rather than making the brand payments to the generic applicant. If the license had been granted, the generic applicant would have been able to seek approval of its ANDA and brand payments would have stopped. The brand-name company did not exercise this option.

*Optional Supply Agreements:* Three of the final settlements in Table 3-3 involved optional supply agreements under which the generic applicant would distribute the brand-name product as a generic. For 2 of these drug products, the supply agreements were implemented. For the other product, the supply agreement was not implemented. These 3 supply agreements are described below.

The supply agreement involving one drug product specified that the brand-name company would supply brand-name product to foreign affiliates of the generic applicant for marketing outside the United States during the 6-month period prior to patent expiration.

Under the supply agreement involving another drug product, the brand-name company appointed the generic applicant as the non-exclusive distributor for the sale of the product under a private label at a cost to the generic applicant equal to 75% of the brand-name company's wholesale druggist price. The generic applicant used this supply agreement to market the brand-name company's product as a generic product.

The brand-name company of the third drug product entered into an agreement, not implemented, to supply the generic applicant with the drug to sell as the generic version; the agreement prohibited the generic applicant from manufacturing the product drug itself. This agreement specified the generic's resale price at a limited discount (15% to 30%, based on certain contingencies) off the brand-name drug product's price. The brand-name company was to receive substantial royalties from the generic company's sales of the product (40% to 33.3%, based on when the royalty was paid).

Alternatively, this brand-name company could decide to make quarterly payments to the generic applicant instead of fulfilling the supply agreement. The payment schedule, which continued until expiration of the patent, provided for total annual payments of at least \$50 million. The agreement guaranteed the generic company the right to enter the market with a generic version of the product (under the NDA) either 6 months prior to patent expiration, or immediately upon the patent being declared invalid or unenforceable. Because the supply agreement was not implemented, the brand-name company

made the brand payments to the generic applicant.

### *Miscellaneous Final Agreement with Brand Payments*

A ninth final agreement involved brand payments, but did not fit into the basic model described above. In this case, the parties agreed to terminate the 30-month stay and allow the generic applicant's ANDA to be approved soon thereafter. Prior to executing the settlement agreement, the two companies had been involved in commercial patent infringement litigation over the brand-name drug product (and another related drug product) that the generic company had initiated. The parties settled that litigation, entering into an agreement with cross-royalty provisions. One of the cross-royalty provisions provided the generic company with a 1 percent royalty on net sales of the brand-name drug product. Thus, the brand payment was in the form of a royalty on the brand-name drug company's drug product.

### *Final Agreements with the First Generic Applicant that Could "Park" the Applicant's 180-Day Exclusivity*

Fourteen of the 20 settlements obtained through the study, at the time they were executed, had the potential to "park" the first generic applicant's 180-day exclusivity for some period of time, and thus to prevent FDA approval of any subsequent eligible applicants. Whether the FDA actually was prevented from approving subsequent eligible generic applicants

depends on specific facts, including whether there were subsequent generic applicant(s) and the result(s) of any patent litigation with those applicants.

These agreements include the 4 license agreements with waiting periods (drug products A, E, F, and H in Table 3-2), the 2 supply agreements, and settlements with brand payments (drug products I through P in Table 3-3) that had the effect of precluding FDA approval of the generic applicant's ANDA. Ten brand-name companies and 10 generic companies used agreements with respect to the 14 drug products. Chapter 5 discusses how these settlements could be used to delay FDA approval of any subsequent eligible generic applicants.

## **Interim Agreements**

In addition to the 20 final settlements, 4 interim settlements with the first generic applicant were produced. The interim settlements did not resolve the underlying patent litigation, but were contingent upon the outcome of the litigation. The FTC has taken law enforcement actions relating to 3 of these drug products.<sup>11</sup> The FTC's actions relating to 2 of those agreements, involving Hytrin tablets and capsules, are described in Box 3-1. No settlements similar to the interim settlements challenged by the Commission were executed after April, 1999 (shortly after the FTC's investigations in this area became public) and the end of the period covered by this study.

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<sup>11</sup> See *supra*, n. 3. The FTC's action regarding Hytrin involved two drug products (Hytrin capsules and Hytrin tablets).

### **Box 3-1 Summary of the Commission's Action in the Abbott/Geneva Matter**

In May 2000, the Commission issued a complaint and consent order against Abbott Laboratories and Geneva Pharmaceuticals, Inc. The complaint charged that Abbott paid Geneva approximately \$4.5 million per month to keep Geneva's generic version of Abbott's Hytrin, in both tablets and capsules, off the U.S. market, potentially costing consumers hundreds of millions of dollars a year. Hytrin is used to treat hypertension and benign prostatic hyperplasia (BPH or enlarged prostate) - chronic conditions that affect millions of Americans each year. BPH alone afflicts at least 50% of men over 60. In 1998, Abbott's sales of Hytrin amounted to \$542 million (over 8 million prescriptions) in the United States. Abbott projected that Geneva's entry with a generic version of Hytrin would eliminate over \$185 million in Hytrin sales in just six months.

According to the complaint, Geneva agreed not to enter the market with any generic version of Hytrin, even if it were non-infringing, until the earlier of: (1) the final resolution of the patent infringement litigation involving Geneva's generic version of Hytrin tablets, including review through the U.S. Supreme Court; or (2) entry of another generic Hytrin product. Geneva also agreed not to transfer, assign, or relinquish its 180-day exclusivity right. These provisions ensured that no other company's generic version of Hytrin could obtain FDA approval and enter the market during the term of the agreement, because Geneva's agreement not to launch its product meant the 180-day exclusivity period would not begin to run.

Under the Commission's consent order, Abbott and Geneva are barred from entering into agreements pursuant to which a first-filing generic company agrees with a manufacturer of a branded drug that the generic company will not (1) give up or transfer its exclusivity or (2) bring a non-infringing drug to market. In addition, agreements to which Abbott or Geneva is a party that involve payments to a generic company to stay off the market must be approved by the court when undertaken during the pendency of patent litigation (with prior notice to the Commission), and the companies are required to give the Commission 30 days' notice before entering into such agreements in other settings. Moreover, Geneva was required to waive its right to a 180-day exclusivity period for its generic version of Hytrin tablets, so other generic tablets

The fourth interim agreement involved a brand-name drug that had net sales of over \$1 billion per year in the year before the settlement was executed. The settlement was entered at approximately the same time the 30-month stay had expired. To ensure that the generic drug applicant did not begin commercial marketing until the district court ruled on the patent infringement claims, the brand-name company agreed that, if the patent was found invalid, the brand-name company would pay the generic applicant based on the generic applicant's lost profits from the date of the expiration of the 30-month through appeals. Since the date of this agreement, generic entry has occurred because of a court decision.

### **Agreements Between Brand-Name Companies and the Second Generic Applicant**

Brand-name companies settled patent litigation with the second generic applicant for 7 drug products, out of a total of 43 suits against the second generic applicant (*see* Chapter 2) – or at a rate of 16 percent. This settlement rate is substantially lower than the settlement rate between brand-name companies and the first generic applicant of 38 percent (20 of 53 total lawsuits against the first generic applicant settled). In 6 of the 7 instances, the brand-company had also entered into a patent settlement with the first generic applicant.

One of the 7 settlements involved brand payments. The agreement specified that the brand-name company would make brand payments up to \$15 million, and that entry by the second generic could not occur until 5 years and 6 months after the date of the agreement (or 2 years and 9 months before patent expiration).

Four of the 7 agreements involved patent licenses that allowed the second generic applicant to enter the market prior to patent expiration using the generic version of the brand-name drug product approved through its ANDA. In 2 of these instances, the second generic applicant was allowed to market its generic product immediately after executing the agreement, obtaining FDA approval, and paying the brand-name company a royalty.

In 1 of the 4 instances, the license agreement prohibited the generic applicant from introducing its product into the market until the brand-name company or another licensee marketed a generic version of the brand-name company's generic product. The brand-name company also entered a license agreement with the third generic applicant for the drug product, specifying that it could come on the market 4 years and 2 months prior to patent expiration.

In the remaining license agreement, the parties agreed to cross-license related products in settlement of not only the patent infringement litigation in response to the ANDA that had been filed, but also related infringement litigation involving another

drug product.<sup>12</sup>

## Agreements Between First and Second Generic Applicants

For 6 out of 68 drug products in which there was more than one generic applicant, the first and second generic applicants entered into agreements related to generic market entry. In 4 of these agreements, one of the main provisions specified which generic applicant had or retained rights to the 180 day exclusivity.<sup>13</sup> The other two agreements did not focus on the 180-day exclusivity provision.

*Agreements Focusing on 180-Day Exclusivity:* In 1 agreement, the first generic applicant relinquished its rights to 180-day exclusivity for a \$3.5 million license and royalty payment based on the second generic applicant's sales for a period of 7 years. In another agreement, the first and second generic applicants entered into a supply arrangement under which the first generic applicant relinquished its rights to 180-day exclusivity so that the second generic applicant's ANDA could be approved, and the first applicant could market the second applicant's product. This step was necessary because the first generic applicant's ANDA was not ready to be approved at the time of the agreement.

Two other agreements clarified

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<sup>12</sup> The other 2 of the 7 settlements with the second generic applicant did not appear to raise issues related specifically to Hatch-Waxman.

<sup>13</sup> For a fuller discussion of the 180-day exclusivity, see Chapter 5, n. 18 and accompanying text.

which generic applicant had rights to the 180-day exclusivity in light of a settlement agreement between the first generic applicant and the brand-name company. In one case, the first generic applicant changed its patent certification from a paragraph IV to a paragraph III, and the agreement settled a dispute between the first and second generic applicant regarding whether the first generic applicant retained its 180-day exclusivity in those circumstances. In the other case, the agreement related to a drug product that had been the subject of one of the court cases that invalidated certain of the FDA's rules governing the 180-day exclusivity.<sup>14</sup>

*Remaining Agreements:* The other 2 agreements involve more detailed relationships between the first and second generic applicants. In one instance, the brand-name company had licensed its patents to an over-the-counter product to the first generic applicant, with a right to sublicense the patents. The first generic applicant granted the sublicense to the second generic applicant. In the second agreement, the first and second generic applicants allegedly entered into a supply and distribution agreement that unreasonably restrained their incentives to compete against each other.<sup>15</sup>

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<sup>14</sup> *Granutec Inc. v. Shalala*, 139 F.3d 889(4<sup>th</sup> Cir. 1998).

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<sup>15</sup> See FTC, In the Matter of Biovail Corp. and Elan Corp., File No. 011 0132, Agreement Containing Consent Order, available at <http://www.ftc.gov/os/2002/06/biovailelanagreement.pdf>.



## Chapter 4 Orange Book Patent Listing Practices and Use of Multiple 30-Month Stays

### Introduction

The 30-month stay provision of the Hatch-Waxman Amendments protects brand-name companies beyond their existing intellectual property rights. A 30-month stay of FDA approval of a potential generic competitor is invoked if a brand-name company receives notice of a generic applicant's paragraph IV certification and files suit for patent infringement within 45 days of that notice. Filing of the lawsuit stays the FDA's approval of the ANDA until the earliest of: (1) the date the patents expire; (2) a final determination of non-infringement or patent invalidity by a court in the patent litigation; or (3) the expiration of 30 months from the receipt of notice of the paragraph IV certification. The 30-month stay affords both the brand-name company and the generic applicant the opportunity to resolve patent disputes prior to commercial marketing, and in tandem with FDA review of the ANDA for approval.

The 30-month stay has received increased attention, because it can have a significant impact on market entry by generic drugs. One 30-month period to resolve disputes over patents listed in the Orange Book prior to the ANDA's filing date appears unlikely to delay generic entry, however, because it historically has approximated the time necessary for FDA review and approval of the ANDA and the duration of a patent lawsuit. FDA approval of generic applicants that filed paragraph IV certifications and were not sued took, on

average, 25 months and 15 days from the filing date. On average, the time between the complaint and a district court decision in litigation between a brand-name company and first or second generic applicants was 25 months and 13 days. The average time between the complaint and an appellate decision was 37 months and 20 days.

Prior to 1998, litigation between a brand-name company and a first or second generic applicant generated, at most, one 30-month stay per drug product per ANDA, except for two drug products. For 8 out of the 9 "blockbuster" drug products (*i.e.*, drug products that are among the top 20 drug products, ranked publicly by annual gross sales, during one of the years included in the study) as to which the brand-name company filed suit against the first generic applicant prior to 1998, the brand-name company alleged infringement of 1 or 2 patents. In the remaining case, the brand-name company alleged infringement of 3 patents.

Since 1998, however, two new phenomena appear to be emerging. First, for drug products with substantial annual net sales, brand-name companies are suing generic applicants over more patents. Since 1998, for only 3 of the 8 "blockbuster" drug products as to which the brand-name company filed suit against the first generic applicant, the brand-name company alleged infringement of 1 or 2 patents. In the remaining 5 instances, the brand-name company alleged infringement of 3 or more

patents. With additional patents to be litigated, the average time to obtain a court decision has increased. As of June 1, 2002, for 6 of the 7 cases that have been pending for more than 30 months without a decision from a district court, the brand-name company has alleged infringement of 3 or more patents.

Second, by the timely listing of additional patents in the Orange Book *after* a generic applicant has filed its ANDA (later-issued patents), brand-name companies can obtain additional 30-month stays of FDA approval of the generic applicant's ANDA. Although the generic applicant had already certified to the patents previously listed in the Orange Book for a particular drug product, it must re-certify to the newly listed patent(s) and notify the brand-name company of its re-certification. If the brand-name company sues for patent infringement on the new certification within 45 days of notification, a new 30-month stay will begin to run. The FDA is prohibited from approving the ANDA until the new 30-month stay expires.

In 8 instances, brand-name companies have listed later-issued patents in the Orange Book after an ANDA has been filed for the drug product. For the 8 drug products, the additional delay of FDA approval (beyond the first 30 months) ranged from 4 to 40 months. In all of the 4 cases so far with a court decision on the validity or infringement of a later-issued patent, the patent has been found either invalid or not infringed by the ANDA.

Moreover, most of the later-issued patents in the Orange Book raise questions about whether the FDA's patent listing

requirements have been met. For example, many of the later-issued patents do not appear to claim the approved drug product or an approved use of the drug. Recent court opinions hold that Hatch-Waxman does not provide a right of action through which generic applicants may challenge a patent listing in the Orange Book. Thus, to terminate a second 30-month stay, a generic applicant's only recourse is to obtain a decision of a court on patent infringement or invalidity.

This chapter sets forth the legal and regulatory background of the 30-month stay provision, including a discussion of the patent listing requirements. It then reviews the patent-related information requested from brand-name company and generic companies. For each NDA that was within the scope of the study, brand-name companies were required to identify all patents that the company has listed in the Orange Book and the date of listing (regardless of whether currently listed in the Orange Book).<sup>1</sup> This information provides the basis for an examination of the patents that led to the granting of multiple 30-month stays. Generic companies were required to provide information on instances in which they alleged that a patent had been improperly or untimely listed in the Orange Book. This information was used to identify any trends in the patent listings.

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<sup>1</sup> Many brand-name companies noted that they could only provide information about when they had submitted the patent to the FDA for Orange Book listing rather than the date on which the patent was actually listed.

## Legal and Regulatory Background of the 30-Month Stay Provision

As part of the FDA process to obtain approval of a new drug product under Hatch-Waxman, brand-name companies must submit information on any patent claiming the approved drug and for which a claim of patent infringement could reasonably be asserted. The FDA then lists the approved drug and its related patents in the Orange Book. Box 4-1 describes how patents are obtained and how the pharmaceutical industry uses them. A generic applicant, as part of the ANDA process, must provide a certification to the FDA regarding its generic product and any patents listed in the Orange Book that claim the brand-name drug. When a generic applicant makes a paragraph IV certification, it claims that the patents listed in the Orange Book either are invalid or will not be infringed by the manufacture, use, or sale of the generic drug product for which the ANDA is submitted. Frequently, a generic applicant will make multiple certifications in

its ANDA, depending upon the number of patents listed in the Orange Book. For example, a generic applicant may make a paragraph III certification (indicating that it will not begin commercial marketing until that patent expires) for a brand-name drug product's drug substance patent, but also make paragraph IV certification(s) with respect to listed method of use and/or formulation patents.

The Hatch-Waxman Amendments further provide that each generic applicant making a paragraph IV certification must notify each patent owner and the brand-name company for the listed drug. If the patent owner and/or brand-name company do not initiate a patent infringement suit within 45 days after receiving notice of a paragraph IV certification, then the FDA's review and generic approval process may proceed according to the FDA's schedule. If, however, a patent infringement suit is filed within the 45-day window, the FDA's approval of the ANDA is automatically stayed until the earliest of: (1) the date the patents expire; (2) a final determination of non-infringement or patent invalidity by a

### Box 4-1 Patents and Patentability

A patent is the grant of a right to exclude others from "making, using, offering for sale, or selling" an invention. U.S. patent laws are enacted pursuant to Article I, Section 8 of the U.S. Constitution, which states that Congress shall have the power "[t]o promote the Progress of Science and useful Arts, by securing for limited times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."

There are three basic types of patents: utility, plant, and design patents. Utility patents generally have a term of 20 years from the date on which the application for the patent was filed. Utility patents are divided into three basic categories: chemical, electrical and mechanical. Pharmaceutical patents are a subset of chemical patents and are issued over four different categories: drug substance, method of use, formulation, and process. Drug substance patents cover the compound or active ingredient in the drug product, such as fluoxetine hydrochloride, which is the active ingredient in Prozac. Method of use patents cover the use of the product to treat certain health problems, such as depression or asthma. Formulation patents cover the physical composition or delivery mechanism of the drug product, such as an extended release tablet or capsule. Process patents generally cover the procedure used to make the active ingredient.

To be patentable, an invention must be new and useful, as well as non-obvious. The Patent Office determines novelty by searching prior patents and publications. The patent must also contain a written description to "enable any person skilled in the art to which it pertains . . . to make and use" the invention. Non-obviousness is determined in light of the prior art and involves asking whether a person skilled in the art would consider the invention to be "obvious."

court in the patent litigation; or (3) the expiration of thirty months from the receipt of notice of the Paragraph IV certification.

The initial 30-month stay is not dependent upon the number of patents for which a paragraph IV certification is made. Whether a generic applicant makes an initial paragraph IV certification with respect to one patent, or to multiple patents, only one 30-month stay will be invoked.

The 30-month stay provision provides the brand-name company an additional exclusionary right beyond those granted by the patent system. Even absent the 30-month stay, a brand-name company may file suit against an accused infringer, such as an ANDA applicant, and prevent the accused infringer from marketing its product by obtaining a preliminary injunction.<sup>2</sup> To obtain a preliminary injunction, a patentee must establish four factors: (1) a reasonable likelihood of success on the merits; (2) irreparable harm if the injunction were not granted; (3) the balance of the hardships, and (4) the impact of the injunction on the public interest.<sup>3</sup>

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<sup>2</sup> See, e.g., *Purdue Pharma L.P., v. Boehringer Ingelheim GMBH*, 237 F.3d 1359, 1363 (Fed. Cir. 2001) (affirming district court's grant of a preliminary injunction blocking marketing of a generic drug product).

<sup>3</sup> Relatively little case law exists to indicate the ease or difficulty for the brand-name company to obtain a preliminary injunction against an ANDA applicant. A few cases do suggest circumstances in which a preliminary injunction may be granted. When a patentee establishes a likelihood of success on the merits, it is entitled to a rebuttable presumption of irreparable harm. For example, when the brand-name company is able to show evidence of price erosion and its expected loss of market share caused by introduction of a competing drug product, or of a generic applicant's likely inability to pay the brand-name company's lost profit damages, a preliminary injunction may be granted. See, e.g., *Purdue Pharma L.P., v.*

## *Patent Listing Statute and Regulations*

The Hatch-Waxman Amendments describe the patent information that brand-name companies must file with any new drug application (NDA). Once the FDA approves the drug, it then lists the patents in the Orange Book. Specifically, the listing statute requires that an NDA filer "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 [new drug] application or which claims a method of using such drug and 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."<sup>4</sup>

The FDA has adopted regulations governing the types of patents that can be listed in the Orange Book.<sup>5</sup> The listing regulation is separated into 6 subsections below for ease of reading. Specifically, the brand-name company must list in the Orange Book each patent which:

[1] claims the drug or a method of using the drug that is the subject of the new drug application or amendment or

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*Boehringer Ingelheim GMBH*, 2000 U.S. Dist. LEXIS 6563 (S.D.N.Y. 2000), *aff'd* 237 F.3d 1359, 1363 (Fed. Cir. 2001); *Glaxo Group, Ltd v. Ranbaxy Pharms., Inc.*, 262 F.3d 1333, 1338 (Fed. Cir. 2001) (discussing district court's decision to grant preliminary injunction because generic manufacturer could not pay NDA holder's potential damages); see Chisum on Patents, § 20.04(e)(iv) (Matthew Bender).

<sup>4</sup> 21 U.S.C. § 355(b)(1).

<sup>5</sup> 21 C.F.R. § 314.53(b) (the "listing regulation").

supplement to it and

[2] with respect 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.

This portion of the listing regulation, requiring that a listed patent satisfy two independent prongs, is nearly identical to the governing statute, 21 U.S.C. § 355(b)(1), except that the regulation substitutes the term "drug product" for the term "drug" in the second prong. The FDA interprets the term "drug" in the statute's first prong to mean "drug product." A district court has affirmed this interpretation.<sup>6</sup> Thus, it is the drug product,<sup>7</sup> approved through the NDA, that controls the listing analysis of the two prongs ("claims the drug" and "a claim of patent infringement").

The remainder of the listing regulation elaborates on the meaning of the two independent prongs:

[3] For purposes of this part, such patents consist of drug substance (ingredient) patents, drug product (formulation and composition) patents, and method of use patents.

[4] Process patents are not covered by this section and information on process patents may not be submitted to FDA.

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<sup>6</sup> *Pfizer, Inc. v. FDA*, 753 F. Supp. 171 (D. Md. 1990).

<sup>7</sup> The FDA's regulations define "drug product" as "a finished dosage form, for example, a tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients." 21 C.F.R. § 210.3(4).

[5] For patents that claim a drug substance or drug product, the applicant shall submit information only on those patents that claim a drug product that is the subject of a pending or approved application, or that claim a drug substance that is a component of such a product.

[6] For patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use<sup>8</sup> of a pending or approved application.

### *Timing of Listing Later-Issued Patents*

Brand-name companies may list later-issued patents (*i.e.*, patents obtained from the U.S. Patent and Trademark Office after obtaining NDA approval) so long as they do so within 30 days of being granted the patent.<sup>9</sup> Two scenarios are possible, depending on whether a later-issued patent is listed *prior to* or *after* the generic applicant files its ANDA. If the later-issued patent is listed *prior to* a generic applicant's filing of an ANDA, then the generic applicant will certify regarding that patent along with all the other listed patents. A brand-name company's suit on those patents within 45 days will generate only one 30-month stay, despite the fact that multiple patents are at issue in the litigation.

If, however, the later-issued patent is listed *after* a generic applicant has filed its

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<sup>8</sup> *Id.*

<sup>9</sup> 21 U.S.C. § 355(c)(2). Of course, a brand-name company can list a patent more than 30-days after issuance; however, pending generic applicants do not have to re-certify to that patent.

ANDA with a paragraph IV certification, then the generic applicant must re-certify that its ANDA does not infringe the later-issued patent. If the brand-name company sues within 45 days of the generic applicant's *re-certification*, then a *second* 30-month stay will issue. Thus, a brand-name company can obtain an additional 30-month stay of FDA approval if it lists patents in the Orange Book *after* notice of an ANDA containing a paragraph IV certification, and then sues for patent infringement upon notice of the generic applicant's re-certification. It is not necessary for the multiple 30-month stays to run consecutively; it is possible for gaps to exist between the multiple 30-month stays. For example, the first stay may have expired without a decision of a court or FDA approval of the ANDA, but a later-issued patent triggers an additional 30-month stay.

### *Lack of Review of Patents in the Orange Book*

The FDA has stated that it lacks the resources and the expertise to review patents submitted with NDAs. The agency does not ensure that a submitted patent claims the approved drug before listing it in the Orange Book.<sup>10</sup> Moreover, the FDA has declined to enact any administrative procedures for resolving listing disputes. If a party disputes the accuracy of a listed patent, it may notify

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<sup>10</sup> 59 Fed. Reg. 50338, 50343 (Oct. 3, 1994) ("FDA does not have the expertise to review patent information. The agency believes that its resources would be better utilized in reviewing applications rather than reviewing patent claims."); Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28872, 28910 (1989) ("In deciding whether a claim of patent infringement could reasonably be asserted . . . the agency will defer to the information submitted by the NDA applicant.").

the FDA. The FDA then will request the brand-name company to confirm the correctness of the listed patent information. Unless the brand-name company voluntarily withdraws or amends its listed information, the FDA will not change the patent information in the Orange Book. If the information remains unchanged, generic applicants must certify to the disputed patent.<sup>11</sup> Two courts have upheld this policy.<sup>12</sup>

Several generic applicants have attempted to obtain court orders requiring the FDA or brand-name companies to delist certain patents from the Orange Book. When a patent is delisted, the 30-month stay will not run and, hence, the FDA is free to approve the ANDA, if other regulatory requirements are met. However, two recent court decisions have held that there is no private right of action under Hatch-Waxman.<sup>13</sup>

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<sup>11</sup> 21 C.F.R. § 314.53(f).

<sup>12</sup> See *aaiPharma v. Thompson*, 2002 WL 1473429 (4<sup>th</sup> Cir. Jul. 10, 2002); *Watson Pharmaceuticals v. Henney*, Civil Action No. 00-3516 (D. Md. Jan. 17, 2001).

<sup>13</sup> *Andrx Pharm, Inc. v. Biovail Corp.*, 276 F.3d 1368 (Fed. Cir. 2002); *Mylan Pharm, Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001). Nor do the patent laws permit an assertion of improper listing as a defense to patent infringement. *Mylan*, 268 F.3d at 1330-32. The Federal Circuit, however, has suggested that a generic applicant might sue the FDA under the Administrative Procedures Act to compel it to delist a patent and to approve an ANDA subject to a 30-month stay that flows from an improperly listed patent. *Andrx*, 276 F.3d at 1378-79. This suggestion contradicts the FDA's court-approved policy of not reviewing patents submitted with NDAs.

Box 4-2 discusses the BuSpar matter in which these holdings were made.

**Box 4-2 Private Parties Have No Right to Seek the Delisting of a Patent in the Orange Book**

The issue of whether a generic applicant could seek to delist a patent from the Orange Book was recently addressed in a court decision regarding BuSpar. Bristol-Myers Squibb ("BMS") had listed one patent in the Orange Book relating to buspirone (Patent No. 4,182,763 (the '763 patent)) when it had sought approval of its NDA. This patent was to expire on November 21, 2000.

Prior to expiration of this patent, Mylan Pharmaceuticals, among others, submitted an ANDA with a paragraph III certification, because it sought approval to market buspirone only after BMS's final patent covering BuSpar expired at 12:00 am on November 22, 2000. Only 12 hours before that time, however, the Patent Office issued Patent No. 6,150,365 (the '365 patent) to BMS; BMS immediately submitted the '365 patent to the FDA for listing in the Orange Book. This listing prevented FDA from granting final approval to any pending ANDA, including Mylan's.

Mylan sued BMS in the District Court for the District of Columbia, seeking an order requiring BMS to remove the patent from the Orange Book. The district court allowed the suit and agreed with Mylan that the '365 patent did not claim the drug product. Rather, the court held that the '365 patent claimed the buspirone metabolite, not buspirone itself, because BMS surrendered coverage of buspirone itself in order to convince the patent examiner to allow the patent. *Mylan v. Thompson*, 139 F.Supp. 1, 24-25 (D.D.C. 2001). The district court ordered BMS to delist the patent, which it did on March 28, 2001. This decision allowed generic buspirone to enter the market immediately. At this point, the '365 patent had delayed generic entry for about four months.

BMS appealed, however, and the Court of Appeals for the Federal Circuit reversed, holding that generic applicants have no private right of action to challenge an NDA holder's Orange Book listing as improper. Furthermore, the court ruled that Mylan's delisting suit was not a recognized patent infringement defense, but rather an attempt to assert a private right of action under Hatch-Waxman. *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001).

Following this decision, BMS chose not to relist the patent, although BMS continued to sue the generic applicants for patent infringement. *In re Buspirone Patent Litigation*, 185 F.Supp. 2d 363 (S.D.N.Y. 2002). As a result, generic buspirone remained on the market. Had BMS relisted the patent, however, the FDA could have revoked its approval of generic buspirone, thereby extending the effect of the '365 patent beyond the four month delay it initially created.

***Immunity From the Antitrust Laws for Listing Patents in the Orange Book***

The Commission recently has addressed whether the act of submitting a patent for listing in the Orange Book is immune from the antitrust laws, because it is a form of petitioning the government protected under the *Noerr Pennington* doctrine.<sup>14</sup> As discussed in Box 4-3, the

District Court for the Southern District of New York agreed with the Commission's argument that the act of listing patents in the Orange Book is not immune from the antitrust laws.

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anticompetitive impact of improper Orange Book listings in *American Bioscience, Inc. v. Bristol-Myers Squibb Co., et al.*, Dkt. No. CV-00-08577 (C.D. Cal. Sept. 7, 2000). See Federal Trade Commission Brief as *amicus curiae* available at

<http://www.ftc.gov/os/2000/09/amicusbrief.pdf>. In that case, the parties sought court approval of a settlement containing a specific factual finding that Bristol-Myers was required to list American Bioscience's patent for Bristol-Myers's branded drug Taxol in the Orange Book. The Commission was concerned that the court's approval of the settlement would amount to a judicial finding that the patent met the statutory requirements for listing in the Orange Book and would prejudice parties who may later challenge the listing.

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<sup>14</sup> *In re Buspirone Patent Litigation/In re Buspirone Antitrust Litigation*, Memorandum of Law of Amicus Curiae the Federal Trade Commission in Opposition to Defendant's Motion to Dismiss available at <http://www.ftc.gov/os/2002/01/busparbrief.pdf>. The Commission first raised concerns about the potential

### Box 4-3 Noerr-Pennington and Orange Book Listings

The *Noerr* doctrine – first articulated as an interpretation of the Sherman Act 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) – provides antitrust immunity for individuals “petitioning” government. Although the *Noerr* doctrine is an important limitation on the antitrust laws that protects the right of individuals to communicate with government entities, some courts have interpreted the doctrine broadly in ways that are inconsistent with Supreme Court precedent. The *Noerr* doctrine was never intended to protect what Robert Bork has characterized as “[p]redation through the misuse of government processes.” Robert H. Bork, *The Antitrust Paradox: A Policy at War with Itself* 364 (Free Press 1993) (1978).

In January 2002, several plaintiffs alleged that, through fraudulent patent filings with the FDA, BMS violated Section 2 of the Sherman Act by causing the FDA to list a patent in the Orange Book to block generic competition with its BuSpar product. In response, BMS moved to dismiss, claiming *Noerr-Pennington* immunity. On February 14, 2002, the court denied BMS’s motion to dismiss. *In re Buspirone Patent Litigation/In re Buspirone Antitrust Litigation*, 185 F.Supp.2d 363 (S.D.N.Y. 2002).

The court’s decision rejected BMS’s claim of *Noerr-Pennington* immunity on three independent and alternative grounds. The first, and perhaps most important, of these grounds was that Orange Book filings simply do not constitute protected “petitioning.” The court reasoned that an Orange Book filing is analogous to a tariff filing. In both cases, “the government does not perform an independent review of the validity of the statements, does not make or issue an intervening judgment, and instead acts in direct reliance on the private party’s representations.” 185 F.Supp.2d at 370. The court also stated that an Orange Book filing is not incidental to petitioning, holding that BMS could have listed its patent in the Orange Book “without subsequently bringing infringement suits . . . [and] could have brought these suits without relying on its Orange Book listing.” *Id.* at 372.

The court further concluded that, even if Orange Book filings were to constitute “petitioning,” application of two specific exceptions to the *Noerr* doctrine – the *Walker Process* and “sham” exceptions – would preclude a finding of antitrust immunity. Under *Walker Process*, a patent holder may be subject to antitrust liability for attempting to enforce a patent procured through fraudulent misrepresentations to the Patent and Trademark Office (“PTO”). *Walker Process Equipment, Inc. v. Food Machinery & Chemical Corp.*, 382 U.S. 172 (1965). The *Buspirone* court concluded that the Orange Book listing and patent prosecution processes were sufficiently analogous to warrant extension of the *Noerr* exception beyond the PTO context, and that plaintiffs’ allegations satisfied *Walker Process*. 185 F.Supp.2d at 372-75.

Under the “sham” exception, the opponent of *Noerr* immunity must demonstrate that defendant’s petitioning conduct – in this case, BMS’s patent filing with the FDA – was “objectively baseless.” *Professional Real Estate Investors, Inc. v. Columbia Pictures Industries, Inc.*, 508 U.S. 49, 60 (1993). After an examination of the prosecution history of BMS’s patent, as well as the specification and claims, the *Buspirone* court concluded that the filing was, indeed, “objectively baseless.” The court further observed that BMS’s argument to the contrary “ignores the law and tries to justify taking property that belongs to the public.”

In light of the *Buspirone* decision, and the underlying force of the court’s reasoning, the *Noerr-Pennington* doctrine may not prove as large an obstacle to using the antitrust laws to remedy improper Orange Book filings as some may have anticipated. It is worth noting, and indeed emphasizing, that *Buspirone* does not mean that all improper Orange Book filings will give rise to antitrust liability. Any antitrust liability must necessarily be predicated on a clear showing of a violation of substantive antitrust law. But, under *Buspirone*, Orange Book filings are not immune from those laws or exempt from their scrutiny.

### Definition of a “Court” Decision to Terminate the 30- Month Stay

Once a 30-month stay begins, FDA regulations govern what constitutes a decision of a “court” for purposes of terminating the 30-month stay. These regulations recently have changed. Originally, the FDA interpreted a decision of a “court” to mean “the court that enters final judgment from which no appeal can be or

has been taken.”<sup>15</sup> The FDA also used this definition of a decision of a “court” when it assessed whether the 180-day exclusivity had been triggered.<sup>16</sup>

In *TorPharm v. Shalala*,<sup>17</sup> the

<sup>15</sup> 21 CFR 314.107(e)(1) (1999).

<sup>16</sup> See Chapter 5 for further discussion of the 180-day exclusivity.

<sup>17</sup> *TorPharm, Inc. v. Shalala*, No. 97-1925, 1997 U.S. Dist. LEXIS 21983 (D.D.C. Sep. 15, 1997), appeal withdrawn and remanded, 1998 U.S. App. LEXIS 4681 (D.C. Cir. Feb. 5, 1998); vacated No. 97-1925 (D.D.C.

District Court for the District of Columbia found the FDA's interpretation of "court" to be inconsistent with the statute's plain meaning; the FDA was directed to approve an ANDA upon a decision of a *district court* finding a patent invalid, unenforceable, or not infringed.

To comply with this decision, the FDA has provided a "Guidance for Industry" that redefines "court" to be a district court. This definition applies, however, only to ANDAs containing paragraph IV certifications that were filed with the FDA after March 2000. If a generic applicant filed its ANDA with the paragraph IV certification prior to March 2000, the definition of a court will remain "the court that enters final judgment from which no appeal can be or has been taken."<sup>18</sup>

## Duration of Patent Infringement Litigation

Table 4-1 shows the average time it took to obtain a decision of a district court and, then, an appellate court in ANDA patent infringement cases involving the drug products included within the scope of the study. On average, the time between complaint and district court decisions in litigation with the first generic applicant was 25 months and 21 days. The time between complaint and an appellate decision was 38

months and 27 days. For ANDA infringement litigation with the second generic applicant, the time frames were slightly shorter as shown in Table 4-1. Table 4-1<sup>19</sup> also shows the average for litigation involving both first and second generic applicants.

**Table 4-1 Length of Patent Cases**

Average Time Period	First Generic Applicant	Second Generic Applicant	Weighted Average
Between Complaint and District Court Decision	25 months, 21 days (31 cases)	24 months, 29 days (22 cases)	25 months, 13 days (53 cases)
Between Complaint and Appellate Decision	38 months, 27 days (14 cases)	36 months, 4 days (12 cases)	37 months, 20 days (26 cases)

Several observations can be made from the data. First, patent infringement litigation over blockbuster drugs increasingly has involved more patents. Prior to 1998, for 8 out of the 9 blockbuster drug products as to which the brand-name company filed suit against the first generic applicant, the brand-name company alleged infringement of 1 or 2 patents. In the remaining case, the brand-name company alleged infringement of 3 patents. Since 1998, for only 3 out of the 8 blockbuster drug products as to which the brand-name company filed suit against the first generic applicant, the brand-name company alleged

Apr. 9, 1998).

<sup>18</sup> FDA, *Guidance for Industry, Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act (Mar 2000)*. This guidance document also discusses the definition of a court to trigger the 180-day exclusivity, *see* Chapter 5.

<sup>19</sup> Table 4-1 contains cases that resulted in a court opinion, including cases involving the same drug product, but a different dosage strength or generic applicant (if different generic applicants were first for different dosage strengths). It does not include stipulated dismissals or consent entered by the court pursuant to a patent settlement agreement.

infringement of 1 or 2 patents. In the remaining 5 instances, the brand-name company alleged infringement of 3 or more patents. For example, the brand-name company for blockbuster drug products such as Prilosec, Claritin, and Paxil sued the first generic applicant for patent infringement on six, three, and six patents, respectively. One drug product, Lupron, has 12 listed patents for which the brand-name company has alleged infringement.

Second, cases involving multiple patents appear to extend beyond the average time it took to resolve the patent infringement cases identified in Table 4-1. The data suggest that cases involving multiple patents take longer to resolve than those involving fewer patents. As of June 1, 2002, for 6 out of the 7 cases that have been pending for more than 30 months without a decision from a district court (*see* Figure 2-1), the brand-name company has alleged infringement of 3 or more patents.

Third, district courts have issued decisions about non-infringement in a shorter period of time than decisions of patent invalidity. The average time between the filing of the complaint against either the first or second generic applicant and a decision of non-infringement was 19 months, 23 days. By contrast, the average time to obtain a district court decision of patent invalidity was 33 months, 5 days.

### Multiple 30-Month Stays on Later-Issued Patents For Drug Products in the Study

The data revealed 8 drug products

(out of 104 in the study) for which the brand-name company listed a patent in the Orange Book *after* the first generic applicant had filed its ANDA.<sup>20</sup> In these cases, the brand-name company obtained one or more additional 30-month stays for the drug product. Table 4-2 shows that the majority of the second 30-month stays have issued since 1999.<sup>21</sup> In contrast to the discussion in Chapter 3 concerning settlement agreements, the discussion here is not anonymous because the Orange Book listings and patent information is readily available in the public domain.

**Table 4-2 Usage of Later-Issued Patents**

Year in Which 2 <sup>nd</sup> Stay Issued	Number of Drug Products	Drug Product(s)
1996	2	Hytrin (tablets); Platinol*
1997/98	0	
1999	1	Paxil
2000	4	Taxol; BuSpar; Neurontin (capsules); Neurontin (tablets)
2001 (thru 6/25/01)	1	Tiazac
<b>Total</b>	<b>8</b>	

\* The earlier-filed ANDAs contained paragraph III certifications, but the later-issued patent was listed in the Orange Book shortly before the underlying patents were to expire.

<sup>20</sup> This total does not include instances in which the brand-name company initiated suit on a different strength of the same drug product.

<sup>21</sup> There may be additional drug products that have obtained a second 30-month stay that are not included within this study because the first ANDA with a paragraph IV certification was filed after January 1, 2001. *See* Chapter 1 for the scope of the study.

Table 4-3 describes the total time per drug product during which the FDA was prohibited from approving a generic applicant's ANDA because of one or more 30-month stays generated by a later-listed patent. In most cases, the brand-name company companies only obtained one

additional 30-month stay, typically based on a formulation or method of use patent. Appendix G describes the relationship of these additional patents to the brand-name company's approved drug product. Appendix H describes issues about the listing of these patents in the Orange Book.

**Table 4-3 Multiple 30-Month Stays Caused by Patents Later-Issued Patents**

Drug Product/ Active Ingredient	Patent Claims in Original Lawsuit	Patent Claims in Subsequent Suit(s)	Total Number of Stays	Timing of Subsequent Stay(s)	Total Length of Stays	Net Sales in Year the Second Stay was Issued
Platinol (Cisplatin)	N/A, Paragraph III Certification	Formulation	1	Beginning 2 months prior to the last patent claiming the drug expired	30 months	Between \$100 and \$250 million
Hytrin – tablets (Terazosin)	Drug substance	Drug Substance	3	Beginning 43 months after the first stay began	70 months*	Between \$500 and \$750 million
Paxil (Paroxetine Hydrochloride)	Drug Substance, Formulation, Method of use	Drug Substance, Formulation, Method of Use	5	Beginning 17 months into the first stay	65 months	Over \$1 billion
Taxol (Paclitaxel)	Method of Use	Formulation	2	Beginning after 1 <sup>st</sup> 30-month stay had expired	Potentially 60 months**	Between \$750 million and \$1 billion
BuSpar (Buspirone)	Method of Use, Paragraph III Certification	Method of Use	2	Beginning the day the last patent claiming the drug expired	Potentially 30 months**	Between \$500 and \$750 million
Neurontin capsules (Gabapentin)	Drug Substance, Method of Use	Formulation	2	Beginning 23 months into first stay	53 months	Between \$250 and \$500 million
Neurontin tablets (Gabapentin)	Drug Substance, Method of Use	Formulation	2	Beginning 7 months into first stay	37 months	Between \$250 and \$500 million
Tiazac (Diltiazem)	Formulation	Formulation	2	Beginning 30 months after first stay began	Potentially 60 months**	Between \$100 and \$250 million

\* The time from the beginning of the first stay until the end of the final stay lasted approximately 70 months, but the stays were not overlapping. See Appendix G for a further discussion of Hytrin.

\*\* The actual total length of the stays were shorter because of the court actions in each of the cases, see discussion in Boxes 4-2, 4-3, and Appendix G.

In four instances (Hytrin (tablets), BuSpar, Paxil, and Tiazac), the brand-name company applied for the patents more than one year after the FDA had approved the drug product covered by the NDA, suggesting that the patents cannot cover the approved drug product and be valid, due to the "on sale bar" of patent law. The later-issued patents for Hytrin, Platinol, Taxol, and BuSpar were determined to be invalid patents or not infringed. The suit involving the later-issued patent listed for Tiazac was dismissed pursuant to the Commission's recent enforcement action described in Box

4-4. The infringement litigation involving the later-issued patents for the remaining drug products (Paxil, and Neurontin (tablets and capsules)) is still pending.

For Neurontin and Platinol, the second stay was generated by a patent that had been pending for an extended period in the Patent Office. In the case of Neurontin, the '482 patent had been pending for ten years. In the case of Platinol, U.S. Patent No. 5,562,925 had been pending for 26 years before it issued.

#### **Box 4-4 The FTC's Enforcement Action Involving Tiazac**

Tiazac is a drug for treatment of high blood pressure and chronic chest pain; it had annual sales in 2000 of almost \$200 million. Andrx filed the first ANDA for a generic version of Tiazac in June 1998 with a Paragraph IV certification regarding the only patent then claiming Tiazac, the '791 patent. Biovail filed a patent infringement lawsuit within 45-days of its notification, alleging that Andrx's generic Tiazac product would infringe the '791 patent. This lawsuit triggered a 30-month stay of final regulatory approval of Andrx's ANDA, which was to expire on February 26, 2001.

On March 6, 2000, the U.S. District Court presiding over the patent infringement suit found that Andrx's product did not infringe the '791 patent. *Biovail Corp. Int'l v. Andrx Pharm. Inc.*, 2000 WL 33354427 (S.D. Fla. Mar 6, 2000). Biovail appealed this decision to the U.S. Court of Appeals for the Federal Circuit. On February 13, 2001, the Federal Circuit affirmed the district court's ruling that Andrx's product did not infringe Biovail's '791 patent, thus ending the first 30-month stay.

Before the Federal Circuit issued its decision, however, Biovail, on January 8, 2001, listed a second patent in the Orange Book as claiming Tiazac. Biovail acquired this patent, U.S. Patent No. 6,162,463 ("the '463 patent"), from DOV Pharmaceuticals, Inc. through an exclusive licensing arrangement that also included plans to develop new diltiazem products jointly using the '463 patent. Because of this listing, Andrx was required to submit a second Paragraph IV certification asserting non-infringement of the '463 patent. After receiving Andrx's certification, Biovail filed another infringement suit, triggering a second 30-month stay, and further delaying the potential entry of Andrx's generic Tiazac product until at least June 2003 or until the '463 was declared invalid or not infringed.

The FTC's complaint alleged that Biovail was aware that the '463 patent did not claim the formulation of Tiazac that it had been marketing. Accordingly, Biovail did not need the '463 patent in order to make or sell its existing FDA-approved formulation of Tiazac, and it could have continued to do so without infringing the '463 patent. Moreover, in prosecuting the patent before the U.S. Patent and Trademark Office, DOV was required to distinguish the '463 patent from the prior art - including Biovail's Tiazac - before the patent examiner approved the patent. This fact suggests that the '463 patent could not simultaneously be valid and properly listed in the Orange Book for Tiazac.

The Commission alleged that Biovail misleadingly represented to the FDA that the new patent claimed existing-and-approved, rather than revised-and-unapproved, Tiazac, to avoid de-listing from the Orange Book and termination of the stay against Andrx. The Commission alleged that Biovail's patent acquisition, wrongful Orange Book listing, and misleading conduct before the FDA were acts in unlawful maintenance of its Tiazac monopoly, in violation of Section 5 of the FTC Act, and that the acquisition also violated Section 7 of the Clayton Act.

The proposed consent order would require Biovail to divest the illegally acquired patent to its original owner, except as to new product developments outside the Tiazac market; to dismiss its infringement case against Andrx, which would end the stay, thereby allowing entry of generic Tiazac to the benefit of consumers; and to refrain from any action that would trigger another 30-month stay on generic Tiazac entry. Further, the order prohibits Biovail from unlawfully listing patents in the Orange Book and requires Biovail to give the Commission prior notice of acquisitions of patents that it will list in the Orange Book for Biovail's FDA-approved products.

The patent listings involving GlaxoSmithKline's (GSK)<sup>22</sup> drug product Paxil illustrate the impact that multiple 30-month stays can have on the timing of FDA approval, and thus the beginning of generic competition. Four additional 30-month stays have prevented FDA approval of generic competition against Paxil for approximately 65 months.<sup>23</sup> GSK manufactures and distributes Paxil, which the FDA has approved for the treatment of depression, obsessive compulsive disorder, panic disorder, and social anxiety disorder.<sup>24</sup>

The FDA approved Paxil in December 1992. Patent No. 4,007,196 (the '196 patent) covering the active ingredient paroxetine hydrochloride had expired prior to this date and, therefore, was not listed in the Orange Book. However, GSK listed Patent No. 4,721,723 (the '723 patent) which claims paroxetine hydrochloride hemihydrate. (A hemihydrate is a form of the active ingredient that has one water molecule for every two paroxetine molecules incorporated into its crystalline structure.)

Apotex Corporation filed an ANDA for generic Paxil on March 31, 1998. With the ANDA, Apotex submitted a paragraph IV certification for the '723 patent, the only patent listed in the Orange Book at that time. GSK's infringement suit generated the first 30-month stay, which expired in approximately November 2000. Since March 1998, however, GSK has listed nine additional patents in the Orange Book and brought infringement suits against Apotex on four of them. The four infringement suits generated four additional 30-month stays that created an automatic stay on FDA approval of generic Paxil totaling over 5 years. Figure 4-1 depicts graphically the stay on FDA approval of Apotex's ANDA.

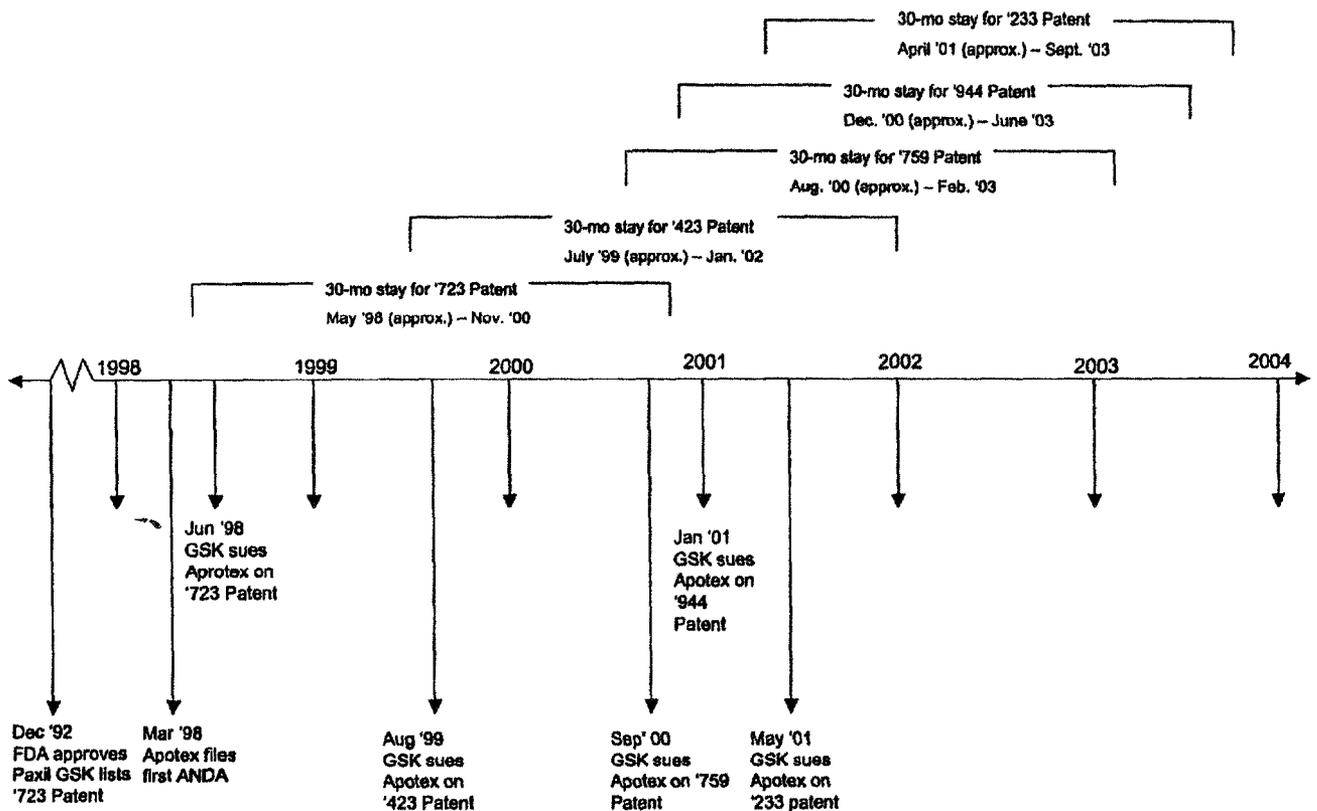
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<sup>22</sup> Before the merger of Glaxo Wellcome and SmithKline Beecham, Paxil was manufactured and distributed by SmithKline Beecham, which was also the original NDA holder. For simplicity, however, we will refer throughout to GSK.

<sup>23</sup> Apotex Corporation, Novartis (Geneva), Mylan, Alphapharm, IVAX, and Pentech have all filed ANDAs for generic Paxil. GSK sued each of them for infringing at least some of the patents discussed. For simplicity in demonstrating the effect of the more recently listed patents and the 30-month stays they generated, we will focus on the suits GSK brought against Apotex.

<sup>24</sup> *Physician's Desk Reference*, 55<sup>th</sup> ed. (2001) at 3114.

Figure 4-1 30-Month Stays Obtained for Paxil



### Analysis of Later-Issued Patents in the Orange Book

To gain some insight into patent listing issues, the FTC staff reviewed the patents listed for drug products as to which the responding generic companies indicated that they had challenged a listing in some way.<sup>25</sup> The analysis indicates that three categories of patents listed in the Orange Book raise significant listability issues – *i.e.*, issues concerning whether the listed patents fall within the statutorily defined class.

<sup>25</sup> See Appendix E, Question 4 for generic companies. These drug products encompass the eight products listed in Table 4-3 as subject to multiple 30-month stays.

Four points bear emphasizing as defining the class of listable patents according to the listing statute and regulation. First, a brand-name company may list only those patents that claim the approved drug product or a method of using the drug product described in its NDA. The key relationship governing whether a patent is properly listed in the Orange Book is the relationship between the patent and the brand-name drug product. *The relationship between the patent and any bioequivalent generic drug is irrelevant to the listing question.* As the discussion of litigation outcomes in Chapter 2 demonstrates, it is entirely possible, and in fact common, for a patent to claim the brand-name drug (and hence be listed in the Orange Book), but not

to be infringed by a bioequivalent generic product. Conversely, it is possible for a bioequivalent generic product to infringe a patent that does not claim the brand-name drug (and hence should not be listed in the Orange Book).<sup>26</sup>

Second, the Hatch-Waxman Amendments and listing regulations grant brand-name companies the 30-month stay *only* for those patents that claim its approved drug product or an approved use of that product. *The Amendments do not grant the protection of the 30-month stay to every patent that a bioequivalent generic product may infringe.* This does not mean, however, that a brand-name product is left vulnerable to infringing generic products. A brand-name company may obtain and enforce patents covering bioequivalent “design-around” formulations of its product. In fact, the brand-name company may bring its infringement suit at the time the generic files its ANDA, even when the patent is not listed in the Orange Book.<sup>27</sup> Moreover, just like

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<sup>26</sup> This is especially true for formulation patents, which cover composition of a drug product, rather than its active ingredient. A generic drug company may formulate its drug product differently than the brand-name product, but still produce a bioequivalent product. The generic’s different formulation may not infringe the brand’s patent covering its own formulation. *See, e.g., Biovail Corp. v. Andrx Pharma, Inc.*, 239 F.3d 1297 (Fed. Cir. 2001) (Andrx’s formulation did not infringe listed patent). On the other hand, a generic company’s own formulation may be sufficiently different to merit its own patent protection. *See U.S. Patent No. 5,567,441* (patent on diltizem formulation assigned to Andrx).

<sup>27</sup> 35 U.S.C. § 271(e)(2) makes it an act of infringement to submit an ANDA for a drug “claimed in a patent.” This statute allows infringement litigation based on the filing of an ANDA in spite of § 271(e)(1)’s safe harbor provision protecting activities related to obtaining FDA approval from infringement allegations. As one district court has recognized, nothing in the statute limits suits under § 271(e)(2) to those based on patents listed in

any patent holder, brand-name company companies may prevent initial marketing of a generic product by demonstrating entitlement to a preliminary injunction in patent infringement litigation. Thus, Orange Book listings control only whether a brand-name company may obtain an automatic 30-month stay, not whether and when it may obtain and assert patent protection.

Third, even after a patent satisfies the first prong of the statute (“claims the drug”), to be properly listed it must still satisfy the independent second prong, requiring that a “claim of patent infringement could reasonably be asserted” against the NDA holder’s approved drug product.<sup>28</sup> The analysis depends on whether the branded and approved drug product, rather than the generic product, infringes the patent, absent a license. Whether a patentee can “reasonably” assert a claim of patent infringement is not limited to infringement but also includes the validity and enforceability of the patent.

Fourth, the listing regulation requires

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the Orange Book. *In re Buspirone Antitrust Litigation*, 185 F. Supp. 2d 363, 372 (S.D.N.Y. 2002) (patentee could have brought its infringement suit without relying on its Orange Book listing); *see also Mylan Pharma, Inc. v. Thompson*, 268 F.3d 1323, 1331-32 (Fed. Cir. 2001) (rejecting argument that Mylan’s challenge to Orange Book listing could be viewed as a defense to Bristol’s assertion of patent infringement under 35 U.S.C. § 271(e)(2) suggesting that an infringement suit under § 271(e)(2) does not require that the asserted patent be listed in the Orange Book). In spite of this fact, one recent district court decision suggested that an Orange Book listing and a paragraph IV certification is a necessary predicate to a patent suit under § 271(e)(2). *Allergan Inc. v. Alcon Labs, Inc.*, 200 F.Supp.2d 1219 (C.D. Cal. 2002). To ensure that litigation can proceed upon the filing of an ANDA, without such an Orange Book listing and a paragraph IV certification, this decision should be overruled.

<sup>28</sup> 21 C.F.R. § 314.53(b).

that the patent “claim” the approved drug product.<sup>29</sup> The Court of Appeals for the Federal Circuit has explained that the term “claim” under the Hatch-Waxman Amendments has the standard meaning as understood in patent law.<sup>30</sup> A patent “claims” a product only when the written section of the issued patent labeled the “claims” define it. As the Federal Circuit stated, “the plain meaning of ‘claims’ is not the same as the plain meaning of infringement.”<sup>31</sup> Even though a drug product or its use may infringe a patent under the doctrine of equivalents,<sup>32</sup> or indirectly through theories of contributory infringement or inducement to infringe, that patent does not “claim” the product.<sup>33</sup> Consequently, a brand-name company may not list a patent in the Orange Book when its approved drug product infringes the patent

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<sup>29</sup> *Id.*

<sup>30</sup> *Hoechst-Roussel Pharms., Inc. v. Lehman*, 109 F.3d 756 (Fed. Cir. 1997) (interpreting the term “claims” in the Patent Term Restoration portion of the Hatch-Waxman Amendments at 35 U.S.C. § 156(a)). A district court has held that this interpretation of “claims” applies to the listing statute. *Mylan Pharma., 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).

<sup>31</sup> *Hoechst-Roussel Pharms., Inc.*, 109 F.3d at 759.

<sup>32</sup> If an accused device does not literally infringe a patent claim because it lacks some element of that claim, it may infringe under the doctrine of equivalents if it contains some element that is insubstantially different from the claim element which it lacks. *Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co.*, 520 U.S. 17, 35-36 (1997).

<sup>33</sup> *Hoechst-Roussel Pharms., Inc.*, 109 F.3d at 759 (“The relationship between infringement and the claims becomes even more tenuous under the doctrine of equivalents, where a product is deemed to infringe the patentee’s right to exclude even though the product does not fall within the scope of the patent’s claims.”).

only indirectly or under the doctrine of equivalents, and not directly and literally.

One general concern overlays all four points. One function of the Orange Book is to provide notice to ANDA applicants of relevant patents. There is, however, a trade-off between using the Orange Book to provide notice of all relevant patents and implementing a methodology that grants the protection of the 30-month stay to a defined class of patents, as does the current statutory methodology. One consequence of restricting the patents listed in the Orange Book is that the Orange Book would then not provide notice of every patent that an ANDA filer might infringe. For example, beyond those patents that do not claim the brand-name company’s drug product, the Orange Book also provides no notice of process patents. The importance of the notice function of the Orange Book is unclear, however. Many companies may not need an Orange Book listing to provide notice, given the sophistication of their patent searching techniques and the common practice of monitoring newly listed patents on a regular basis.<sup>34</sup>

The analysis identified three broad categories of patents that raise questions about whether they fall within the class the Hatch-Waxman Amendments defines as listable in the Orange Book. These categories, which are more fully explained in Appendix H, are:

1. Patents that may not be

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<sup>34</sup> *See, e.g.*, Testimony of Michael Kirschner, Immunex Corp., FTC Public Hearings: Competition and Intellectual Property Law and Policy in the Knowledge-Based Economy (Feb. 26, 2002) available at <<http://www.ftc.gov/opp/intellect/020226trans.pdf>>.

considered to claim the drug formulation or method of use approved through the NDA. For example:

- a. *Metabolite patents* that claim the chemical compound into which a patient's body converts the approved drug product;
  - b. *Drug intermediate patents* that claim a chemical compound used during production of the active ingredient, but not appearing in the final drug product; and
  - c. *Polymorph patents* that claim a crystalline form of the active ingredient that differs from the approved crystalline form;
2. Product-by-process patents that claim a drug product produced by a specified process; and
  3. Patents that constitute double-patenting because they claim subject matter that is obvious in view of the claims of another patent invented by the same person.

Several points emerge from the analysis in Appendices G and H comparing these patents to the class of patents defined as listable by the statute. The large majority of patents creating an additional 30-month stay raise some kind of listing issue. It is important to note that this patent analysis applies not only to late-issued patents, but also potentially to patents listed prior to the filing of ANDA. The patents generating the

first or sole 30-month stay have, on occasion, raised similar listability issues.

Determining whether these patents are appropriately listed sometimes involves an analysis of chemistry, patent law, and FDA law. Many of the listing issues concern the FDA's listing regulations, however, rather than interpretations of patent scope. For instance, the question of whether metabolite, drug intermediate, polymorph, and product-by-process patents may be listed appears to depend on interpretations of the listing regulations. As Appendix H details, the identification of individual patents as falling into one of those categories is usually relatively straightforward.

To the degree there is uncertainty about the scope of the listing regulations, they could be clarified by regulation or guidance. The FDA's clarification of these issues is important to antitrust challenges to improper Orange Book listings. The question of whether a patent claims some unapproved aspect (and hence should not be listed) may depend more on an interpretation of the NDA's scope of approval than an interpretation of the patent. A mechanism by which the FDA could comment on the scope of an NDA would be helpful in resolving some listing disputes, as occurred in the Tiazac situation described in Box 4-4. An antitrust suit involving complex elements beyond the propriety of the listing is the only current mechanism to challenge an Orange Book listing.

To clarify some of these issues (but not all), the FTC staff has submitted a Citizen Petition to the FDA that seeks guidance concerning the criteria that a patent

must meet before it can be listed in the Orange Book.<sup>35</sup> The requested guidance could eliminate uncertainty surrounding the appropriateness of listing some types of patents, in particular polymorph patents, in the Orange Book, but it will leave other issues unaddressed. The FTC staff Citizen Petition is pending.

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<sup>35</sup> Appendix F contains a copy of the FTC Staff Citizen Petition, *available at* <http://www.fda.gov/ohrms/docket/dailys/01/May01/052901/cpa.pdf>.

## Chapter 5 180-Day Marketing Exclusivity Under the Hatch-Waxman Amendments

### Introduction

The Hatch-Waxman Amendments provide 180 days of marketing exclusivity to the first generic application that seeks entry prior to expiration of the patents listed for the relevant brand-name drug product. The exclusivity allows this first generic applicant to sell the only generic substitute for a brand-name drug product for 180 days after either i) first commercial marketing by the first generic applicant, or ii) a decision of a court holding the relevant patents to be invalid or not infringed.<sup>1</sup> The grant of 180-day exclusivity to the first generic applicant creates an incentive for a generic company to challenge a brand-name company's drug product patents. One court has explained that 180-day exclusivity rewards the first generic applicant for the expense and effort involved with challenging a listed patent.<sup>2</sup>

If the 180-day exclusivity for the first generic applicant does not run, then the FDA may not approve any subsequent eligible generic applicants. Thus, if the first generic applicant agrees not to trigger the 180-day exclusivity, the possibility exists that no generic applicant may enter the market. The Commission's interest in 180-day exclusivity has focused on the agreements between brand-name and generic companies that have affected whether and when first generic applicants have triggered the running

of 180-day exclusivity. The Commission's antitrust law enforcement actions have alleged that certain brand-name and generic companies have entered into agreements that, among other things, have had the effect of delaying entry by the first generic that otherwise would trigger the running of the 180-day exclusivity, thereby creating a bottleneck for any subsequent eligible generic entry.<sup>3</sup>

The regulatory landscape implementing the 180-day exclusivity provision has shifted over the last several years, and this may have affected the frequency with which generic applicants obtain 180-day exclusivity. Before 1992 (a time period not included in the FTC's study), the FDA granted 180-day exclusivity to 3 generic applicants. From 1992 until 1998, the FDA granted 180-day exclusivity to no generic applicants. Since 1998, when the FDA changed its regulations in response to a court ruling,<sup>4</sup> and more ANDAs containing paragraph IV certifications have been filed, the FDA has granted 180-day exclusivity to the first generic applicant for 31 drug products.

For the drug products within the

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<sup>1</sup> 21 U.S.C. § 505(j)(5)(B)(iv).

<sup>2</sup> *Mova v. Shalala*, 140 F. 3d 1060, 1074 (D.C. Cir. 1998).

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<sup>3</sup> See *Abbott Laboratories*, No. C-3945 (May 22, 2000) (consent order), available at <<http://www.ftc.gov/os/2000/03/abbott.do.htm>> (this consent order related to 2 drug products: Hytrin tablets and Hytrin capsules).

<sup>4</sup> See *Mova*, *supra* n. 2.

scope of this study, the generic applicant's commercial marketing has triggered the 180-day exclusivity in 19 of 31 instances. The data show that when the brand-name company did not sue the first generic applicant for patent infringement (29 drug products, see Table 2-1), the first generic applicant began commercial marketing soon after receiving FDA approval.

The data show that 14 of the 20 final settlements obtained through the study (discussed in Chapter 3) had the potential, at the time they were executed, to "park" the first generic applicant's 180-day exclusivity for some period of time, thus preventing FDA approval of any eligible subsequent applicants. In addition to the 20 final settlement agreements, there were 4 interim settlement agreements pursuant to which the patent litigation continued, but the parties agreed upon certain conditions in the meantime. The Commission, as noted above, has challenged interim settlements for 3 drug products.

This chapter describes the 180-day provision in the Hatch-Waxman Amendments and details how FDA's rules governing 180-day exclusivity have evolved. The chapter examines how the 180-day exclusivity has been triggered, and it also reviews the agreements that were obtained through the study that affect the triggering of the 180-day exclusivity.

## The Shifting Regulatory Landscape Implementing the 180-Day Exclusivity Period

FDA rules implementing the 180-day exclusivity have changed over the last several years. This section describes the FDA's initial approach to implementing the 180-day exclusivity through the "successful defense" requirement and the current rules that no longer require a successful defense. The section then discusses the FDA's regulations governing what constitutes a decision of a "court" and "commercial marketing" sufficient to trigger the first generic applicant's 180-day exclusivity. Finally, it discusses recent developments surrounding the awarding of "shared" exclusivity to multiple generic applicants.

### *Successful Defense Requirement*

In October 1994, the FDA issued final regulations governing how it would award the 180-day exclusivity period to generic applicants.<sup>5</sup> FDA regulations required that, to obtain the 180-day exclusivity, the first generic applicant had to *defend successfully* against a patent claim of the brand-name company.<sup>6</sup> The FDA asserted that only those generic applicants that had devoted considerable time and money to defend successfully the patent infringement lawsuit were entitled to be the first and only generic company on the market for 180 days. The FDA reasoned that a first generic applicant that a brand-

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<sup>5</sup> See 59 Fed. Reg. 50338 *et seq.* (Oct. 3, 1994). Prior to this time, the FDA used an approach similar to that outlined in these regulations.

<sup>6</sup> See *id.*

name company had not sued might have an incentive to delay marketing. This delay would prolong the period of no generic competition, because other generic products may not be approved until the first generic product begins commercial marketing.<sup>7</sup>

These regulations were challenged in *Mova v. Shalala*, a case involving the brand-name drug product Glynase.<sup>8</sup> Mova Pharmaceuticals was the first generic applicant for Glynase. Pharmacia & Upjohn, the brand-name company, sued Mova for patent infringement within the requisite 45-day period, thus initiating the 30-month stay on FDA approval of Mova's application. Pharmacia did not sue the second generic applicant, Mylan Pharmaceuticals, for the same drug product within 45 days of being notified; thus, the 30-month stay was not triggered. FDA was about to approve Mylan's ANDA prior to the expiration of Mova's 30-month-stay, but before the district court had ruled on the merits of patent infringement case against Mova, the first generic applicant. Mova therefore sued the FDA to delay the effective date of the approval of Mylan's application until Mova had won its patent infringement suit or begun commercial marketing of its generic product.

The district court granted a preliminary injunction against the FDA on January 23, 1997, requiring the FDA to delay approval of Mylan until after Mova's 180 days of exclusivity took effect. This ruling rejected FDA's "successful defense" requirement as inconsistent with the plain

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<sup>7</sup> See 54 Fed. Reg. 28872 (Jul. 10, 1989).

<sup>8</sup> 955 F. Supp. 128 (D.D.C. 1997), *aff'd*, 140 F. 3d 1060 (D.C. Cir. 1998).

language of the Hatch-Waxman Amendments.<sup>9</sup> The Court of Appeals for the District of Columbia Circuit affirmed the District Court's ruling in its April 1998 decision.<sup>10</sup>

The FDA revoked the "successful defense" requirement and now makes exclusivity decisions on a case-by-case basis applying the literal words of the statute.<sup>11</sup> The FDA also has proposed new regulations to address issues that these court decisions have raised.<sup>12</sup> This rulemaking proceeding has been pending since August 1999.

### *Definition of the "Court" As Used in the 180-Day Marketing Exclusivity Provision*

The FDA originally interpreted the definition of a court that would trigger 180-day exclusivity to be "the court that enters final judgment from which no appeal can be or has been taken."<sup>13</sup> In *Mylan*

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<sup>9</sup> See *Mova*, 140 F.3d at 1069.

<sup>10</sup> The Court of Appeals also referenced *Granutec Inc. v. Shalala*, 139 F.3d 889, 1998 WL 153410 (4<sup>th</sup> Cir. 1998); 46 USPQ2d 1398 (4<sup>th</sup> Cir. 1998) (unpublished opinion), in dicta, "We note that the Fourth Circuit recently came to the same conclusion in an unpublished opinion." *Mova*, 140 F.3d at 1069.

<sup>11</sup> The FDA also subsequently published guidance for industry entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act" (June 1998), describing its approach to 180-day exclusivity in light of *Mova* and *Granutec*.

<sup>12</sup> 64 Fed. Reg. 42873 (Aug. 6, 1999).

<sup>13</sup> 21 CFR 314.107(e)(1) (1999).

*Pharmaceuticals, Inc. v. Shalala*,<sup>14</sup> the District Court for the District of Columbia found FDA's interpretation of "court" to be incorrect; the court instead held that "court" means "district court." The FDA amended its rules to implement the *Mylan* decision by defining the "court" decision that triggers the running of the 180-day marketing exclusivity period as the decision of a district court. This definition applies, however, only to ANDAs containing paragraph IV certifications filed with the FDA after March 2000. Thus, if a generic applicant filed its ANDA with the paragraph IV certification prior to March 2000, the definition of a court will remain "the court that enters final judgment from which no appeal can be or has been taken."<sup>15</sup>

## Triggers for the 180-Day Exclusivity Period

Prior to the *Mova* court of appeals decision on April 14, 1998, the FDA had granted the 180-day exclusivity to 3 generic applicants for drug products covered by 3 NDAs.<sup>16</sup> In each case, a court had decided that the patent was invalid or not infringed such that the generic applicant had "successfully defended" the patent litigation suit. Each of these grants of the 180-day

<sup>14</sup> *Mylan Pharmaceuticals, Inc. v. Shalala*, 81 F.Supp.2d 30 (D.D.C. 2000).

<sup>15</sup> FDA, Guidance for Industry, Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act (Mar 2000). This guidance document also discusses the definition of a court for purposes of when the 30-month stay expires, see Chapter 4.

<sup>16</sup> This information was provided by the FDA to the FTC staff.

exclusivity occurred prior to 1991 and involved drugs not included in the scope of the study.

Since *Mova*, the FDA has granted the 180-day exclusivity to the first generic applicant for 31 drug products.<sup>17</sup> Table 5-1 categorizes these grants of exclusivity by the triggering mechanism (either by commercial marketing or the decision of a court) as of June 1, 2002.

**Table 5-1: Marketing Exclusivity Triggering Event Since 1998<sup>18</sup>**

Triggering Event	Number of ANDAs
Commercial Marketing	19
Court Decision of Patent Invalidity or Non-Infringement	12
<b>Total</b>	<b>31</b>

<sup>17</sup> For 8 drug products, the FDA has provided two or more generic applicants the 180-day exclusivity for drug products covered by the same NDA, because different generic applicants had the first ANDA for a particular strength of the drug product (e.g., 30mg, 60 mg, and 90 mg tablets). To ensure no overcounting, the totals referred to in this section (and throughout the report unless otherwise noted) relate only to the number of NDAs for which 180-day exclusivity has been granted. For each drug product where this occurred, the same 180-day exclusivity was activated by the same trigger (i.e., commercial marketing or a court decision).

<sup>18</sup> For 2 drug products not included in Table 5-1 but within the scope of this study, the first generic applicant relinquished its eligibility for the 180-day exclusivity, thus eliminating any delay for subsequent generic applicants to market their generic products. In addition, for 3 other drug products not included in Table 5-1, but within the scope of the study, the FDA has indicated that certain generic applicants are eligible for 180-day exclusivity, but the period has not yet started to run, because neither trigger has been activated.

### *Trigger: Commercial Marketing*

For 19 of the 31 drug products in Table 5-1, the first generic applicant's commercial marketing triggered the running of the 180-day exclusivity period.

In 5 of the 19 instances, commercial marketing occurred when the FDA did not consider a *district court* decision sufficient to trigger the 180-day exclusivity. In these 5 instances, the generic applicants had prevailed at the district court and the 30-month stay period had expired, so that the FDA approved the generic applicant's ANDA. Rather than waiting for an appellate decision, the generic applicants began commercial marketing. In each of these instances, the generic applicant ultimately prevailed in the appellate court, but commercial marketing, not a court decision, triggered the 180-day exclusivity.

For another 5 of the 19 drug products in Table 5-1, the first generic applicant was not sued. Thus, the only available trigger for the 180-day exclusivity period was the first generic applicant's commercial marketing.<sup>19</sup>

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<sup>19</sup> There was one other drug product for which the first applicant was not sued, but its 180-day exclusivity was triggered by a court decision favorable to the second generic applicant. In this case, the FDA had not approved the first applicant's ANDA, but the second generic applicant appeared to be ready to market – except that it had to wait for the running of the first applicant's 180-day period. That the 180-day exclusivity had not run for the first generic applicant, because its ANDA had not yet been approved, delayed FDA approval of the second generic applicant's ANDA. To remedy this problem, the second generic applicant sought a court decision of non-infringement to activate the “court decision” trigger. The district court hearing this declaratory judgment action dismissed the case for lack of case or controversy, because the brand-name company indicated that it would not sue the generic applicant for infringement. The second generic

In each of these instances, the first generic applicant began commercial marketing soon after receiving FDA approval. For 3 of these 5 drug products, the second generic applicant was approved at the end of the 180-day exclusivity period, and there was not a second generic applicant for the other 2 drug products.

In 8 of the 19 instances, the brand-name company and the generic applicant settled the patent litigation and the generic applicant's commercial marketing triggered the 180-day exclusivity. These 8 settlements can be grouped into 4 categories:

- For 3 drug products, the generic applicant entered an interim settlement with the brand-name company. Following termination of the settlement and FDA approval, the generic applicant was granted 180-day exclusivity.<sup>20</sup>
- For 2 drug products, the generic applicant obtained a license to use the patents that were subject to the paragraph IV certification prior to the patent's expiration. The generic applicant then obtained FDA approval and began marketing the generic product that was the subject of its ANDA

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applicant argued that this constituted a “court decision” sufficient to trigger the 180-day period. The Court of Appeals for the District of Columbia agreed and ruled that a district court's earlier dismissal of the second generic applicant case for lack of case or controversy activated the court decision trigger and, thus, started the running of the first generic applicant's 180-day exclusivity. *See Teva Pharmaceuticals, USA, Inc. v. FDA*, 182 F.3d 1003 (D.C. Cir. 1999). There is some uncertainty regarding whether this reasoning would apply to trigger the 180-day exclusivity in the future.

<sup>20</sup> *See Abbott Labs., supra* n 3.

(see drug products A and C in Table 3-2).<sup>21</sup>

- For 2 drug products, the settlement involved a supply agreement allowing the generic applicant to market the brand-name company's product as a generic prior to patent expiration (see drug product K in Table 3-3,<sup>22</sup> and the description of the second supply agreement in the text of Chapter 3).<sup>23</sup>
- For 1 drug product, the settlement specified a date on which entry of the generic product could occur, which was prior to patent expiration (see drug product L in Table 3-3).<sup>24</sup>

In the last of the 19 instances in which commercial marketing triggered the 180-day exclusivity, commercial marketing began after the brand-name company

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<sup>21</sup> The generic applicant that was party to the remaining license agreements in Table 3-2 did not receive the 180-day exclusivity for one of 2 reasons: (1) the agreement was executed at a time when the FDA required the first applicant to defend successfully the patent infringement suit; having failed to do so, they were ineligible for 180-day exclusivity, or (2) the license has not yet taken effect, because of a waiting period in the agreement, such that commercial marketing has not yet occurred.

<sup>22</sup> See Letter to Deborah A. Jaskot, Teva Pharmaceuticals USA, FDA Docket No. 00P-1446/CP1 (Feb. 6, 2001).

<sup>23</sup> Although the 180-day exclusivity has run in these 2 instances, there is some uncertainty as to whether commercial marketing by the first generic applicant of the brand-name company's product will always activate the commercial marketing trigger.

<sup>24</sup> In most cases, the generic applicant that was the party to the remaining settlements in Table 3-3 (settlements with brand payments), did not obtain the 180-day exclusivity because entry did not occur until patent expiration, thus the generic applicant was ineligible for the 180-day exclusivity.

dismissed the patent suit upon determining the ANDA did not infringe the brand-name product.

### *Trigger: Court Decision*

For 12 out of the 31 drug products, the FDA granted 180-day exclusivity to a generic applicant following a court decision of patent invalidity or non-infringement. Other than the 2 drug products involved in the challenge to the FDA's successful defense requirement,<sup>25</sup> in most instances the court that activated the court decision trigger was an appellate court decision. More recently, in 2 of the 12 cases, a district court decision has triggered the running of the 180-day exclusivity. In one case, the FDA approved the ANDA after 21 days of the 180-day period had already run, and in the other case, FDA approval came 120 days into the 180-day period, thus shortening the effective life of the 180-day period.

### *Effect of 180-Day Exclusivity on FDA Approval of Subsequent Eligible Generic Applicants*

As noted in the introduction, in addition to encouraging entry by the first generic applicant, the 180-day exclusivity can delay when the FDA approves any subsequent eligible generic application that also contains a paragraph IV certification. If the 180-day exclusivity for the first generic applicant does not run, then the FDA may not approve any subsequent eligible generic applicants. Once the 180-day exclusivity

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<sup>25</sup> See *Mova* and *Granutec*, *supra* n. 8-10 and accompanying text.

runs, the FDA may approve any additional generic ANDAs that have been filed and meet regulatory requirements.

As discussed in Chapter 3, 14 of the 20 of the settlement agreements obtained through the study, at the time they were executed, had the potential to “park” the first generic applicant’s 180-day exclusivity for some period of time, thus preventing FDA approval of any subsequent eligible applicants.<sup>26</sup> These agreements include the 4 license agreements with a waiting period before the license took effect (drug products A, E, F, and H in Table 3-2), the 2 supply agreements described in the text of Chapter 3, and settlements with brand payments (drug products I through P in Table 3-3). Ten brand-name companies and 10 generic companies used agreements with respect to 14 drug products.

In addition to the 20 final settlement agreements, there were 4 interim settlement agreements pursuant to which the patent

litigation continued, but the parties agreed upon certain conditions until the patent litigation was resolved. The Commission has challenged interim settlements for 3 drug products. In those agreements, the Commission alleged that the brand-name drug company paid the first generic applicant not to enter the market, thereby retaining its (unused) 180-day marketing exclusivity and precluding the FDA from approving any eligible subsequent generic applicants.<sup>27</sup>

Between April 1999 (shortly after FTC investigations in this area became public) and the end of the period covered by this study, brand-name companies and first generic applicants have not entered agreements similar to the interim agreements challenged by the FTC.

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<sup>26</sup> Whether FDA was actually prevented from approving subsequent eligible generic applicants depends on a number of factors, including whether there were subsequent generic applicant(s) and the result of any patent litigation with those applicants.

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<sup>27</sup> See *supra*. n. 3.



## Chapter 6 FDA Citizen Petitions and Generic Drug Applications

### Introduction

This chapter reviews FDA regulations concerning the use of citizen petitions. It also examines the citizen petitions that brand-name companies have filed about drug products in this study, and discusses their effect on the development of generic drug competition for these drug products.

The FDA has generally resolved the issues raised by the citizen petitions that brand-name companies file about drug products in this study in a timely manner, and in most instances prior to a district court ruling on the merits of the patent infringement litigation. Thus, for drug products in the study, citizen petitions that have been answered by the FDA have not delayed generic competition.

No general conclusions about the use of citizen petitions can be drawn from this study, however, because it did not examine citizen petitions filed in connection with ANDAs that contained paragraph I, II, or III certifications. Citizen petitions may have a greater potential to delay generic competition in those circumstances, in which no 30-month stay would be applicable.

### FDA Regulations Governing Citizen Petitions

The FDA has several informal and formal mechanisms by which it can be contacted on a particular issue (including via

letter, fax, email or meeting). A formal procedure, which has been used by both brand-name and generic pharmaceutical companies, is the filing of a citizen petition.<sup>1</sup> The FDA can be petitioned on any matter or issue which is within the Agency's jurisdiction.

The petition can request that the Commissioner issue, amend, or revoke a regulation or order, or take or refrain from taking any other form of administrative action. The Commissioner must furnish a response to a petitioner within 180 days of receipt of the petition.<sup>2</sup> The FDA's reply must approve, deny, or provide a tentative response. If the FDA provides a tentative response, it must indicate why the agency has been unable to reach a decision on the petition and may indicate when a final response may be furnished.<sup>3</sup> Unlike ordinary correspondence, the FDA treats the response to a citizen petition as the official position of the agency.<sup>4</sup>

Individuals and companies often use the formal citizen petition process to raise issues regarding the safety and efficacy of pharmaceuticals. Brand-name companies, for example, have petitioned the FDA on issues relating to bioequivalence for particular generic drugs.

The FTC staff has commented to the

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<sup>1</sup> 21 C.F.R. § 10.30.

<sup>2</sup> *Id.* at 10.30(e)(2).

<sup>3</sup> *Id.*

<sup>4</sup> *Id.* at § 10.45(d).

FDA on the potential for such petitions, on occasion, to mask anticompetitive strategies. The FTC staff has suggested changes to the FDA's proposed rules governing citizen petitions that might reduce the potential for regulatory abuse.<sup>5</sup> The FTC staff comment explained there is a potential for anticompetitive abuse of nearly any regulatory process.<sup>6</sup> To delay competition may be a lucrative strategy for an incumbent, especially in an industry in which entry is regulated, such as pharmaceuticals. Improper petitioning may be appealing in part because it can be used against any size firm, regardless of relative resources of the parties. The cost of filing an improper citizen petition may be trivial compared to the value of securing a delay in a rival's entry into a lucrative market.<sup>7</sup>

The Noerr-Pennington doctrine often protects participation in the regulatory process from antitrust scrutiny.<sup>8</sup> As discussed in Chapter 4, in its simplest terms, the Noerr-Pennington doctrine shields private parties from antitrust liability when they engage in concerted but genuine efforts to influence governmental action, even though the conduct is undertaken with an

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<sup>5</sup> Comment of the Staff of the Bureau of Competition and the Office of Policy Planning of the Federal Trade Commission, *Citizen Petitions; Actions That Can be Requested by Petition; Denials, Withdrawals, and Referrals for Other Administrative Action*, FDA Docket No. 99N-2497 (Mar. 2, 2000) (FTC Staff Comment on Citizen Petitions).

<sup>6</sup> Robert H. Bork, *The Antitrust Paradox* 347 (1978) ("The modern profusion of [ . . . ] governmental authorities offers almost limitless possibilities for abuse.").

<sup>7</sup> *Id.* at 348.

<sup>8</sup> *Eastern Railroad Presidents Conference v. Noerr Motor Freight, Inc.*, 365 U.S. 127 (1961); *United Mine Workers v. Pennington*, 381 U.S. 657 (1965).

anticompetitive intent and purpose. If regulatory intervention (or a series of interventions) is used, however, to impede competition, antitrust concerns may be raised if not shielded by Noerr-Pennington.<sup>9</sup>

One of the recommendations in the FTC Staff Comment on Citizen Petitions was that the FDA consider requiring notification of whether the citizen petitioner has received, or will receive, consideration for filing the citizen petition and identification of the party furnishing the consideration. This information may be important in evaluating the competitive effect of the petition.

### **The Use of Citizen Petitions About Drug Products for Which an ANDA Containing a Paragraph IV Certification Was Filed**

Each brand-name company was required to state, for each drug product included in the study for which the company has been notified that an ANDA containing a paragraph IV certification has been filed with the FDA, whether the company has filed, or contributed to the filing of, in whole or in part (e.g., provided funds, legal or regulatory assistance to support the filing), a citizen petition with FDA concerning an ANDA related to that drug product and to identify the FDA docket number assigned to such citizen petition.

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<sup>9</sup> *Professional Real Estate Investors, Inc. v. Columbia Pictures Indus. Inc.*, 508 U.S. 49 (1993); see also Bork, *see n. 5*, at 354.

Of the 104 drug products included in this study, brand-name companies filed citizen petitions relating to generic versions of 12 drug products. The data showed that for 1 drug product, the brand-name company filed 3 citizen petitions against different generic applicants; each petition sought different relief. For 2 other drug products, the brand-name company filed 2 citizen petitions, each seeking different relief. Thus, brand-name companies filed a total of 16 separate citizen petitions relating to the 104 drug products included in the study.

In each case, the brand-name company was the author of the petition and there was no effort on behalf of the company to withhold its identity from the FDA.

For 11 of the 12 drug products covered by citizen petitions, the brand-name company that had filed the citizen petition also had either settled the patent infringement litigation with an agreement that contained a brand payment (*see* Chapter 3), filed a late-issued patent to obtain a second 30-month stay (*see* Chapter 4), or has patent litigation pending in which the brand company has claimed the ANDA infringes more than one patent (*see* Chapter 4).

Table 6-1 breaks down the type of request that was included in each petition.

**Table 6-1 Brand-Name Company Use of Citizen Petitions**

Relief Requested by the Brand-name Company in the Citizen Petition	Number of Citizen Petitions
Additional bioequivalence studies or safety studies	7
Additional patent certifications	3
FDA to classify the NDA as a different dosage form	2
Other	4

Almost 50 percent of the citizen petitions requested that the FDA require additional bioequivalence studies before approving the generic applicant's ANDA. Of these 7 petitions regarding bioequivalence, the FDA denied 3 of these petitions, granted 1, granted and denied 1 in part, and 2 petitions were pending as of June 1, 2002. In each case in which the petition was denied, the brand-name company also had initiated patent infringement litigation against the generic applicant.

In the 5 cases in which the FDA ruled on the merits of the bioequivalence issues raised by the petition, it did so prior to a district court ruling on the merits of the infringement litigation and prior to the expiration of the 30-month stay. Thus, the filing of the citizen petition in these cases did not affect the generic product's entry. For the other 2 bioequivalence petitions, the FDA has not yet approved the generic applicant's ANDA.

In the second category of citizen petitions described in Table 6-1, brand-name companies requested the FDA refrain from approving a generic version of the drug product unless the generic company certified

to a new patent that was listed after the generic applicant had filed its ANDA. The FDA denied one of the petitions, and in the other two, the petitions were withdrawn because of a merger or because the generic applicant made the requisite patent certification. In each case, the citizen petition did not affect when the FDA approved (if it did) the generic applicants' ANDAs.

In the third category of citizen petitions described in Table 6-1, brand-name companies requested FDA redefine dosage forms with varying release mechanisms as distinct dosage forms. If the FDA were to grant this category of petitions, the generic applicant also would have been required to file a suitability petition that sought an FDA ruling that the two dosage forms were bioequivalent. In other words, it would have been procedurally more difficult for the generic applicant to have its ANDA approved in a timely manner.

The FDA denied both of these petitions. In each case, the brand-name company had sued the generic applicant for patent infringement, and the citizen petition was resolved by the FDA within the 30-month stay period. Thus, the petition had no effect on the timing of generic drug approval.

The last 4 citizen petitions dealt with issues unique to the underlying drug product. In one case, the petition was withdrawn, in another the FDA responded to the petition in an informal manner that satisfied the parties involved, in the third instance, the petition was denied, and in the fourth case, the petition was pending as of June 1, 2002. In the first 3 cases, the

resolution of the citizen petition did not effect market entry by the generic applicant.

## **Conclusions**

The citizen petitions related to drug products in the study that have been resolved did not affect the timing of generic entry. The FDA has addressed the issues raised by those citizen petitions in a timely manner and prior to the expiration of the 30-month stay related to the underlying patent infringement litigation.

No general conclusions about the use of citizen petitions, however, can be drawn from this study, however, because it only examined citizen petitions filed in connection with ANDAs that contained paragraph IV certifications.

## **Appendix A: Glossary of Terms**

“ANDA” means Abbreviated New Drug Application.

“Drug product” means the finished dosage form of a drug approved through an NDA or ANDA.

“Generic applicant” means those companies that have filed an ANDA containing a paragraph IV certification.

“Brand-name company” is synonymous with the NDA holder.

“180-day exclusivity” is the grant of 180 days of exclusive marketing to the first generic applicant that files an ANDA containing a paragraph IV certification after either i) first commercial marketing by the first generic applicant, or ii) a decision of a court holding the relevant patents to be invalid or not infringed.”

“NDA” means New Drug Application. Pursuant to the Federal Food, Drug, and Cosmetic Act, a brand-name company seeking to market a new drug product must first obtain FDA approval by filing an NDA.

“Orange Book” means the FDA’s publication entitled “Approved Drug Products with Therapeutic Equivalence,” in which the patents claiming a drug product approved through an NDA are listed.

“Paragraph I certification” means a certification that a generic applicant seeks FDA approval of its ANDA for a relevant NDA for which no patent information has been filed in the Orange Book.

“Paragraph II certification” means a certification that a generic applicant seeks FDA approval of its ANDA for a relevant NDA for which a patent filed in the Orange Book has expired.

“Paragraph III certification” means a certification that a generic applicant seeks FDA approval of its ANDA as of the date a patent listed in the Orange Book for a relevant NDA expires.

“Paragraph IV certification” means a certification that a patent listed in the Orange Book is invalid or will not be infringed by the generic drug for which the ANDA applicant seeks approval.

“Settlements” means agreements settling patent litigation between brand-name companies and a generic applicant that has filed an ANDA containing a paragraph IV certification.

“30-month stay” prohibits the FDA from approving an ANDA with a paragraph IV certification for 30 months if the relevant brand-name company brings a patent infringement suit within 45 days of notice of the generic applicant’s paragraph IV certification. The 30-month stay is terminated by (1) the expiration of the patents; (2) a final determination of non-infringement or patent invalidity by a court in the patent litigation; or (3) the expiration of thirty months from the receipt of notice of the Paragraph IV certification.

**Appendix B:**  
**Relevant Provisions of the Hatch-Waxman Amendments**  
**21 USCA § 355 (a), (b) and (j)**

**(a) Necessity of effective approval of application**

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.

**(b) Filing application; contents**

**(1)** Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application

**(A)** full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use;

**(B)** a full list of the articles used as components of such drug;

**(C)** a full statement of the composition of such drug;

**(D)** a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

**(E)** such samples of such drug and of the articles used as components thereof as the Secretary may require; and

**(F)** specimens of the labeling proposed to be used for such drug. The applicant 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 and 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. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

**(2)** An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include -

**(A)** a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section -

**(i)** that such patent information has not been filed,

**(ii)** that such patent has expired,

**(iii)** of the date on which such patent will expire, or

**(iv)** that such patent is invalid or will not be infringed by the manufacture, use, or sale of the

new drug for which the application is submitted; and

- (B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3)

- (A) An applicant who makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give the notice required by subparagraph (B) to -
  - (i) each owner of the patent which is the subject of the certification or the representative of such owner designated to receive such notice, and
  - (ii) the holder of the approved application under subsection (b) of this section for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.
- (B) The notice referred to in subparagraph (A) shall state that an application has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification. Such notice shall include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed.
- (C) If an application is amended to include a certification described in paragraph (2)(A)(iv), the notice required by subparagraph (B) shall be given when the amended application is submitted.

(4)

- (A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 262 of title 42, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.
- (B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 262 of title 42 if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.
- (C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except -
  - (i) with the written agreement of the sponsor or applicant; or
  - (ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.
- (D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue

involved.

- (E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.
- (F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.
- (G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 262 of title 42 (including all scientific and medical matters, chemistry, manufacturing, and controls).

(j) Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2)

(A) An abbreviated application for a new drug shall contain -

- (i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a "listed drug");
- (ii)
  - (I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;
  - (II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or
  - (III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 321(p) of this title, and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;
- (iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;
- (iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the active ingredients of the new drug

are of the same pharmacological or therapeutic class as those of the listed drug referred to in clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

- (v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;
- (vi) the items specified in clauses (B) through (F) of subsection (b)(1) of this section;
- (vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) of this section -
  - (I) that such patent information has not been filed,
  - (II) that such patent has expired,
  - (III) of the date on which such patent will expire, or
  - (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and
- (viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

**(B)**

- (i) An applicant who makes a certification described in subparagraph (A)(vii)(IV) shall include in the application a statement that the applicant will give the notice required by clause (ii) to -
  - (I) each owner of the patent which is the subject of the certification or the representative of such owner designated to receive such notice, and
  - (II) the holder of the approved application under subsection (b) of this section for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.
- (ii) The notice referred to in clause (i) shall state that an application, which contains data from bioavailability or bioequivalence studies, has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of such drug before the expiration of the patent referred to in the certification. Such notice shall include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed.
- (iii) If an application is amended to include a certification described in subparagraph (A)(vii)(IV), the notice required by clause (ii) shall be given when the amended

application is submitted.

- (C) If a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application. The Secretary shall approve or disapprove a petition submitted under this subparagraph within ninety days of the date the petition is submitted. The Secretary shall approve such a petition unless the Secretary finds -
- (i) that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug; or
  - (ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application.

(3)

- (A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.
- (B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of bioavailability and bioequivalence studies needed for approval of such application. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of such studies. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant.
- (C) Any agreement regarding the parameters of design and size of bioavailability and bioequivalence studies of a drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except -
  - (i) with the written agreement of the sponsor or applicant; or
  - (ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.
- (D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.
- (E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance office personnel unless such field or compliance office personnel demonstrate to the reviewing division why such decision should be modified.
- (F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.
- (G) For purposes of this paragraph, the reviewing division is the division responsible for the review of

an application for approval of a drug under this subsection (including scientific matters, chemistry, manufacturing, and controls).

- (4) Subject to paragraph (5), the Secretary shall approve an application for a drug unless the Secretary finds -
- (A) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;
  - (B) information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application;
  - (C)
    - (i) if the listed drug has only one active ingredient, information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;
    - (ii) if the listed drug has more than one active ingredient, information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug, or
    - (iii) if the listed drug has more than one active ingredient and if the application is for a drug which has an active ingredient different from the listed drug, information submitted with the application is insufficient to show -
      - (I) that the other active ingredients are the same as the active ingredients of the listed drug, or
      - (II) that the different active ingredient is an active ingredient of a listed drug or a drug which does not meet the requirements of section 321(p) of this title,or no petition to file an application for the drug with the different ingredient was approved under paragraph (2)(C);
  - (D)
    - (i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration, dosage form, or strength of the listed drug referred to in the application, information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug, or
    - (ii) if the application is for a drug whose route of administration, dosage form, or strength of the drug is different from that of the listed drug referred to in the application, no petition to file an application for the drug with the different route of administration, dosage form, or strength was approved under paragraph (2)(C);
  - (E) if the application was filed pursuant to the approval of a petition under paragraph (2)(C), the application did not contain the information required by the Secretary respecting the active ingredient, route of administration, dosage form, or strength which is not the same;
  - (F) information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application or, if the application was filed pursuant to a petition approved under paragraph (2)(C), information submitted in the application is insufficient to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in paragraph (2)(A)(i) and that the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of

use referred to in such paragraph;

- (G) information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application except for changes required because of differences approved under a petition filed under paragraph (2)(C) or because the drug and the listed drug are produced or distributed by different manufacturers;
- (H) information submitted in the application or any other information available to the Secretary shows that
  - (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or
  - (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;
- (I) the approval under subsection (c) of this section of the listed drug referred to in the application under this subsection has been withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section, the Secretary has published a notice of opportunity for hearing to withdraw approval of the listed drug under subsection (c) of this section for grounds described in the first sentence of subsection (e) of this section, the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (6), or the Secretary has determined that the listed drug has been withdrawn from sale for safety or effectiveness reasons;
- (J) the application does not meet any other requirement of paragraph (2)(A); or
- (K) the application contains an untrue statement of material fact.

(5)

- (A) Within one hundred and eighty days of the initial receipt of an application under paragraph (2) or within such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.
- (B) The approval of an application submitted under paragraph (2) shall be made effective on the last applicable date determined under the following:
  - (i) If the applicant only made a certification described in subclause (I) or (II) of paragraph (2)(A)(vii) or in both such subclauses, the approval may be made effective immediately.
  - (ii) If the applicant made a certification described in subclause (III) of paragraph (2)(A)(vii), the approval may be made effective on the date certified under subclause (III).
  - (iii) If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval shall be made effective immediately unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. If such an action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that -
    - (I) if before the expiration of such period the court decides that such patent is invalid or not infringed, the approval shall be made effective on the date of the

court decision,

- (II) if before the expiration of such period the court decides that such patent has been infringed, the approval shall be made effective on such date as the court orders under section 271(e)(4)(A) of title 35, or
- (III) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective on the date of such court decision.

In such an action, each of the parties shall reasonably cooperate in expediting the action. Until the

expiration of forty-five days from the date the notice made under paragraph (2)(B)(i) is received, no action may be brought under section 2201 of title 28, for a declaratory judgment with respect to the patent. Any action brought under section 2201 shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(iv) If the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection continuing such a certification, the application shall be made effective not earlier than one hundred and eighty days after -

- (I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
- (II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed, whichever is earlier.

(C) If the Secretary decides to disapprove an application, the Secretary shall give the applicant notice of an opportunity for a hearing before the Secretary on the question of whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(D)

(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this

section, except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

- (iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section for such drug.
  - (iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section.
  - (v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted or which refers to a change approved in a supplement to the subsection (b) application effective before the expiration of two years from September 24, 1984.
- (6) If a drug approved under this subsection refers in its approved application to a drug the approval of which was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under this paragraph or which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons, the approval of the drug under this subsection shall be withdrawn or suspended -
- (A) for the same period as the withdrawal or suspension under subsection (e) of this section or this paragraph, or
  - (B) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.
- (7)
- (A)
    - (i) Within sixty days of September 24, 1984, the Secretary shall publish and make available

to the public -

- (I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) of this section before September 24, 1984;
  - (II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and
  - (III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published.
- (ii) Every thirty days after the publication of the first list under clause (i) the Secretary shall revise the list to include each drug which has been approved for safety and effectiveness under subsection (c) of this section or approved under this subsection during the thirty-day period.
  - (iii) When patent information submitted under subsection (b) or (c) of this section respecting a drug included on the list is to be published by the Secretary, the Secretary shall, in revisions made under clause (ii), include such information for such drug.
- (B) A drug approved for safety and effectiveness under subsection (c) of this section or approved under this subsection shall, for purposes of this subsection, be considered to have been published under subparagraph (A) on the date of its approval or September 24, 1984, whichever is later.
  - (C) If the approval of a drug was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under paragraph (6) or if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list -
    - (i) for the same period as the withdrawal or suspension under subsection (e) of this section or paragraph (6), or
    - (ii) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

A notice of the removal shall be published in the Federal Register.

(8) For purposes of this subsection:

- (A) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.
- (B) A drug shall be considered to be bioequivalent to a listed drug if -
  - (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or
  - (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug

is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

- (9) The Secretary shall, with respect to each application submitted under this subsection, maintain a record of -
- (A) the name of the applicant,
  - (B) the name of the drug covered by the application,
  - (C) the name of each person to whom the review of the chemistry of the application was assigned and the date of such assignment, and
  - (D) the name of each person to whom the bioequivalence review for such application was assigned and the date of such assignment.

The information the Secretary is required to maintain under this paragraph with respect to an application submitted under this subsection shall be made available to the public after the approval of such application.

(k) Records and reports; required information; regulations and orders; access to records

- (1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section. Regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.
- (2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(l) Public disclosure of safety and effectiveness data

Safety and effectiveness data and information which has been submitted in an application under subsection (b) of this section for a drug and which has not previously been disclosed to the public shall be made available to the public, upon request, unless extraordinary circumstances are shown -

- (1) if no work is being or will be undertaken to have the application approved,
- (2) if the Secretary has determined that the application is not approvable and all legal appeals have been exhausted,
- (3) if approval of the application under subsection (c) of this section is withdrawn and all legal appeals have been exhausted,
- (4) if the Secretary has determined that such drug is not a new drug, or
- (5) upon the effective date of the approval of the first application under subsection (j) of this section which refers to such drug or upon the date upon which the approval of an application under subsection (j) of this section which refers to such drug could be made effective if such an application had been submitted.

**(m) "Patent" defined**

For purposes of this section, the term "patent" means a patent issued by the United States Patent and Trademark Office.

**(n) Scientific advisory panels**

- (1) For the purpose of providing expert scientific advice and recommendations to the Secretary regarding a clinical investigation of a drug or the approval for marketing of a drug under this section or section 262 of title 42, the Secretary shall establish panels of experts or use panels of experts established before November 21, 1997, or both.
- (2) The Secretary may delegate the appointment and oversight authority granted under section 394 of this title to a director of a center or successor entity within the Food and Drug Administration.
- (3) The Secretary shall make appointments to each panel established under paragraph (1) so that each panel shall consist of -
  - (A) members who are qualified by training and experience to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs;
  - (B) members with diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions;
  - (C) a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel; and
  - (D) two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated.

Scientific, trade, and consumer organizations shall be afforded an opportunity to nominate individuals for

appointment to the panels. No individual who is in the regular full-time employ of the United States and engaged in the administration of this chapter may be a voting member of any panel. The Secretary shall designate one of the members of each panel to serve as chairman thereof.

- (4) Each member of a panel shall publicly disclose all conflicts of interest that member may have with the work to be undertaken by the panel. No member of a panel may vote on any matter where the member or the immediate family of such member could gain financially from the advice given to the Secretary. The Secretary may grant a waiver of any conflict of interest requirement upon public disclosure of such conflict of interest if such waiver is necessary to afford the panel essential expertise, except that the Secretary may not grant a waiver for a member of a panel when the member's own scientific work is involved.
- (5) The Secretary shall, as appropriate, provide education and training to each new panel member before such member participates in a panel's activities, including education regarding requirements under this chapter and related regulations of the Secretary, and the administrative processes and procedures related to panel meetings.
- (6) Panel members (other than officers or employees of the United States), while attending meetings or conferences of a panel or otherwise engaged in its business, shall be entitled to receive compensation for each day so engaged, including traveltime, at rates to be fixed by the Secretary, but not to exceed the daily equivalent of the rate in effect for positions classified above grade GS-15 of the General Schedule. While serving away from their homes or regular places of business, panel members may be allowed travel expenses (including per diem in lieu of subsistence) as authorized by section 5703 of title 5, for persons in the Government service employed intermittently.

- (7) The Secretary shall ensure that scientific advisory panels meet regularly and at appropriate intervals so that any matter to be reviewed by such a panel can be presented to the panel not more than 60 days after the matter is ready for such review. Meetings of the panel may be held using electronic communication to convene the meetings.
- (8) Within 90 days after a scientific advisory panel makes recommendations on any matter under its review, the Food and Drug Administration official responsible for the matter shall review the conclusions and recommendations of the panel, and notify the affected persons of the final decision on the matter, or of the reasons that no such decision has been reached. Each such final decision shall be documented including the rationale for the decision.

**Appendix C:  
New Drug Applications Examined in Study**

	<b>NDA Number</b>	<b>Active Ingredient</b>	<b>Proprietary Name</b>	<b>Dosage Form</b>
1	019872	Acetaminophen	Tylenol	650 mg extended-release tablets
2	020802	Acetaminophen/Aspirin/Caffeine	Excedrin	250/65 mg tablets
3	018603	Acyclovir Sodium	Zovirax	injection
4	020560	Alendronate Sodium	Fosamax	5, 10, 40 mg tablets
5	018276	Alprazolam	Xanax	0.25, 0.5, 1, 2 mg tablets
6	018240	Atenolol	Tenormin	25, 50, 100 mg tablets
7	020711	Bupropion Hydrochloride	Zyban	150 mg extended-release tablets
8	020358		Wellbutrin SR	150 mg extended-release tablets
9	018644		Wellbutrin	100 mg tablets
10	018731	Buspirone HCl	Buspar	5, 10, 15, 30 mg tablets
11	019890	Butorphanol Tartrate	Stadol	nasal spray
12	018874	Calcitriol	Calcijex	injection
13	018343	Captopril	Capoten	50, 100 mg tablets
14	020234	Carbamazepine	Tegretol XR	100, 200, 400 mg extended-release tablets
15	019856	Carbidopa/ Levodopa	Sinemet	25/100 and 50/200 mg extended-release tablets
16	012365	Carisoprodol/ASA	Soma compound	325/200 mg tablets
17	012366	Carisoprodol/ASA/Codeine Phosphate	Soma compound w/ Codeine	325/200/16 mg tablets
18	019537	Ciprofloxacin Hydrochloride	Cipro	100, 200, 500, 750 mg tablets
19	018057	Cisplatin	Platinol & Platinol AQ	injection
20	018938	Desmopressin Acetate	DDAVP	injection
21	017922		DDAVP	nasal spray
22	020713	Desogestrel; Ethinyl Estradiol	Mircette	0.01, 0.02, 0.15 mg tablets
23	019471	Diltiazem Hydrochloride	Cardizem SR	60, 90, 120 mg extended-release capsules
24	020092		Dilacor XR	120, 180, 240 mg extended-release capsules
25	020062		Cardizem CD	120, 180, 240, 300 mg extended-release capsules
26	020401		Tiazac	120, 180, 240, 300, 360, 420 mg extended-release capsules
27	018723	Divalproex Sodium	Depakote	125, 250, 500 mg delayed-release tablets
28	019668	Doxazosin Mesylate	Cardura	1, 2, 4, 8 mg tablets
29	018998	Enalapril Maleate	Vasotec	2.5, 5, 10, 20 mg tablets
30	020375	Estradiol	Climara	transdermal
31	020584	Etodolac	Lodine XL	400, 500, 600 mg extended-release tablets
32	019462	Famotidine	Pepcid	20, 40 mg tablets
33	020325		Pepcid AC	10 mg tablets
34	020801			10 mg chewable tablets
35	019834	Felodipine	Plendil ER	2.5, 5, 10 mg extended-release tablets
36	019304	Fenofibrate	Tricor	67, 134, 200 mg capsules
37	018830	Flecainide Acetate	Tambocor	50, 100, 150 mg tablets
38	019949	Fluconazole	Diflucan	50, 100, 150, 200 mg tablets
39	018148	Flunisolide	Nasalide	nasal spray
40	018936	Fluoxetine Hydrochloride	Prozac	10, 20, 40 mg capsules
41	020974			10 mg tablets
42	020101			oral solution
43	018554			Flutamide
44	020235	Gabapentin	Neurontin	100, 300, 400 mg capsules
45	020882			600, 800 mg tablets
46	020051	Glyburide	Glynase	1.5, 3, 6 mg tablets
47	020716	Hydrocodone Bitartrate and Ibuprofen	Vicoprofen	7.5/200 mg tablets
48	020516	Ibuprofen	Children's Motrin	oral suspension
49	019842		Motrin	oral suspension
50	020476			

	NDA Number	Active Ingredient	Proprietary Name	Dosage Form
51	019771	Ibuprofen and Pseudoephedrine Hydrochloride	Advil Cold & Sinus	200/30 mg tablets
52	019763	Ifosfamide / Mesna	IFEX Mesna Kit	injection
53	074464	Indomethacin	Indocin SR	75 mg extended-release capsule
54	019732	Leuprolide Acetate	Lupron Depot	injection
55	020606	Loperamide Hydrochloride and Simethicone	Imodium Advanced	2/125 mg chewable tablets
56	019658	Loratadine	Claritin	10 mg tablets
57	020641			oral syrup
58	020704		Claritin Reditabs	10 mg disintegrating tablets
59	020470	Loratadine Pseudoephedrine Sulfate	Claratin D-24 Hour	10/240 mg extended release tablets
60	019670		Claratin-D	5/120 mg extended-release tablets
61	020264	Megestrol Acetate	Megace	oral suspension
62	019583	Nabumetone	Relafen	500, 750 mg tablets
63	020353	Naproxen Sodium	Naprelan	375, 500, 750 mg extended-release tablets
64	020152	Nefazodone Hydrochloride	Serzone	50, 100, 150, 200, 250 mg tablets
65	020076	Nicotine	Habitrol	extended-release transdermal film
66	020198	Nifedipine	Adalat CC	30, 60, 90 mg extended-release tablets
67	019684		Procardia XL	30, 60, 90 mg extended-release tablets
68	020144	Nitroglycerin	Transderm-Nitro	extended-release transdermal film
69	020145		Transderm/Nitro-Dur	extended-release transdermal film
70	019508		Nizatidine	Axid
71	018985	Norethindrone/ Ethinyl Estradiol	Ortho-Novum 7/7/7-21	0.035/0.035/0.035/0.5/1/0.75 mg tablets
72	019697	Norgestimate/ Ethinyl Estradiol	Ortho Tri-Cyclen	0.035/0.035/0.035/0.18/0.215/0.25 mg tablets
73	020592	Olanzapine	Zyprexa	2.5, 5, 7.5, 10, 15, 20 mg tablets
74	019810	Omeprazole	Prilosec	10, 20, 40 mg delayed-release capsules
75	015539	Oxazepam	Serax	10, 15, 30 mg capsules
76	020553	Oxycodone Hydrochloride	Oxycontin	10, 20, 40, 80 mg extended-release tablets
77	020262	Paclitaxel	Taxol	injection
78	020036	Pamidronate Disodium	Aredia	injection
79	020031	Paroxetine Hydrochloride	Paxil	10, 20, 30, 40 mg tablets
80	019385	Pergolide Mesylate	Permax	0.25, 0.5, 1 mg tablets
81	019439	Potassium Chloride	K-Dur	10, 20 meq extended-release tablets
82	019898	Pravastatin Sodium	Pravachol	10, 20, 40, 80 mg tablets
83	019157	Prednisolone Sodium Phosphate	Pediapred	oral solution
84	019627	Propofol	Diprivan	injection
85	019885	Quinapril Hydrochloride	Accupril	5, 10, 20, 40 mg tablets
86	019090	Ranitidine	Zantac	injection
87	019675			oral syrup
88	020095		Zantac 150 & 300	300 mg capsule
89	018703			150, 300 mg tablets
90	020520		Zantac 75	75 mg tablets
91	019839	Sertraline Hydrochloride	Zoloft	25, 50, 100 mg tablets
92	020478	Sevoflurane	Ultane	liquid inhalation
93	019766	Simvastatin	Zocor	5, 10, 20, 40, 80 mg tablets
94	017970	Tamoxifen Citrate	Nolvadex	10, 20 mg tablets
95	019057	Terazosin Hydrochloride	Hytrin	1, 2, 5, 10 mg tablets
96	020347			1, 2, 5, 10 mg capsules
97	018949	Terfenadine	Seldane	tablets
98	019979	Ticlopidine Hydrochloride	Ticlid	250 mg tablets
99	018086	Timolol Maleate	Timoptic	ophthalmic drops
100	018207	Trazodone Hydrochloride	Desyrel	50, 100, 150, 300 mg tablets
101	018776	Vecuronium Bromide	Norcuron	injection
102	019614	Verapamil Hydrochloride	Verelan	120, 180, 240, 360 mg extended-release capsules
103	014103	Vincristine Sulfate	Oncovin	injection
104	019655	Zidovudine	Retrovir	100 mg capsules

**Appendix D:  
Brand-Name Companies Served Special Orders**

Abbott Laboratories  
Alcon Laboratories, Inc.  
American Home Products Corporation  
AstraZeneca, PLC  
Aventis Pharmaceuticals, Inc.  
Bayer Corporation  
Berlex Laboratories, Inc.  
Biovail Corporation  
Bristol-Myers Squibb Company  
Carter-Wallace, Inc.  
Celltech Americas, Inc.  
Elan Pharmaceutical Research Corporation  
Eli Lilly and Company  
Glaxo Wellcome, Inc.  
Hoffman-La Roche Inc.  
Johnson & Johnson  
Knoll Pharmaceutical Company  
Merck & Company, Inc.  
Minnesota Mining and Manufacturing Company  
Novartis Pharmaceuticals Corporation  
Organon Inc.  
Pfizer Inc.  
Pharmacia Corporation  
The Proctor & Gamble Company  
Purdue Pharma L.P.  
Schering-Plough Corporation  
SmithKline Beecham, Inc.  
TAP Pharmaceutical Products, Inc.

## Generic Companies Served Special Orders

Aesgen, Inc.  
Alphapharm Pty Ltd  
Alpharma USPD Inc.  
American Pharmaceutical Partners, Inc.  
Amide Pharmaceutical, Inc.  
Andrx Corporation  
Ascent Pediatrics, Inc.  
Barr Laboratories, Inc.  
Bausch and Lomb, Inc.  
Baxter Healthcare Corporation  
Ben Venue Laboratories, Inc.  
Brightstone Pharma, Inc.  
Duramed Pharmaceuticals, Inc.  
Elan Corporation, PLC  
Endo Pharmaceuticals Inc.  
Eon Labs Manufacturing, Inc.  
Faulding Pharmaceuticals Inc.  
Geneva Pharmaceuticals, Inc.  
Genpharm Inc.  
Gensia Sicor Pharmaceuticals, Inc.  
Hi Tech Pharmacal Company Inc.  
IMPAX Laboratories, Inc.  
Invitrogen Corporation  
Inwood Laboratories, Inc.  
IPR Pharmaceuticals, Inc.  
IVAX Corporation  
Kremers Urban Development Company  
L. Perrigo Company  
Lek USA, Inc.  
Morton Grove Pharmaceuticals, Inc.  
MOVA Laboratories, Inc.  
Mutual Pharmaceutical Company, Inc.  
Mylan Pharmaceuticals, Inc.  
Oakwood Laboratories, L.L.C.  
Ohm Laboratories, Inc.  
Par Pharmaceutical, Inc.  
Pentech Pharmaceuticals, Inc.  
Person and Covey, Inc.  
Pharmaceutical Formulations, Inc.  
Pharmachemie U.S.A., Inc.  
Ranbaxy Pharmaceuticals, Inc.  
Reddy-Cheminor, Inc.  
Roxane Laboratories, Inc.  
Sano Corporation  
Stason Pharmaceuticals, Inc.

Teva Pharmaceuticals USA, Inc.  
TorPharm, Inc.  
Upsher-Smith Laboratories, Inc.  
Warner Chilcott, Inc.  
Watson Pharmaceuticals, Inc.  
WE Pharmaceuticals, Inc.  
Whitney Pharmaceuticals Inc.

**Appendix E:**  
**Specifications in the Special Orders Sent to Brand-Name Companies**

In addition to routine questions about the name, address, and incorporation date of the responding company and its subsidiaries, and the name, business address, and official capacity of the official supervising the company's response, the FTC asked brand-name companies (the company) to provide answers to the following five questions about specific drugs:

1. Submit all agreements between the company and any person<sup>1</sup> (including corporations or other business entities acquired since the agreement(s) was (were) executed) executed after December 31, 1994,<sup>2</sup> relating to<sup>3</sup> an ANDA involving any Drug Product,<sup>4</sup> where the company holds the rights to the NDA corresponding to the ANDA that is the subject of the agreement. Examples of such agreements include, but are not limited to: (a) patent litigation settlements (full or partial) between the company and persons that have filed an ANDA involving any Drug Product; (b) agreements related to the filing (or non-filing) of an ANDA by any applicant (or potential applicant) involving any Drug Product; (c) licensing agreements between the company and persons that have filed an ANDA involving any Drug Product; and (d) agreements related to any acquisition, divestiture, joint venture, alliance, license or merger by the company of any business involving the research, development, manufacture or sale of any Drug Product that is the subject of an ANDA. The company is not required to submit purchase orders for raw material supplies, equipment and facility contracts, or employment or consulting contracts, nor is the company required to submit agreements executed after the generic manufacturer had begun commercial marketing of the generic Drug Product corresponding to the ANDA for which it had received FDA approval. The company also is not required to submit information that has already been submitted to the Commission pursuant to the Premerger Notification Rules (16 CFR 801-803 (1998)) and Section 7A of the Clayton Act (15 U.S.C. 18a), or Sections 6, 9, 13, and 20 of the Federal Trade Commission Act (15 U.S.C. 46, 49, 53, and 57b-1), although the company must identify such information as having been previously submitted. For any such agreement submitted, also submit all studies, surveys, analyses and reports which were prepared by or for any officer(s) or director(s) of the company (or, in the case of unincorporated entities, individuals exercising similar functions) that evaluate or analyze the reasons for making such agreement (or any of the provisions in such agreement), and indicate (if not contained in the document itself) the date of preparation, and the name and title of each individual who prepared each such document.

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<sup>1</sup> The term "person" means any natural person, corporate entity, partnership, association, joint venture, or trust which is engaged in research and development, planning and design, production and manufacturing, distribution, or sales and marketing of any Drug Product.

<sup>2</sup> As well as such agreements that were executed prior to January 1, 1995 but remain in force as of the date of the information collection request.

<sup>3</sup> The term "relating to" means in whole or in part constituting, containing, concerning, discussing, describing, analyzing, identifying or stating.

<sup>4</sup> The term "Drug Product" means each finished dosage form of the drug the company has listed in the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") (regardless of whether the Drug Product is currently listed in the Orange Book) and specifically includes those Drug Products including the following active ingredients: (a list of such active ingredients will be tailored specifically for each company).

2. Identify all patents that the company has filed in the Orange Book and the date of listing (regardless of whether currently listed in the Orange Book) relating to each Drug Product for which the company has been notified of the filing of an ANDA by another person. Also indicate if the patent(s) was (were) filed in the Orange Book after the company received approval of the New Drug Application, as defined under 21 U.S.C. 355(b) et seq., for the Drug Product. Also submit a copy of each such patent identified and identify whether the patent is owned by, assigned to, or licensed to the company.

3. Identify and list all lawsuits (including the court, date filed, docket number, parties, current or final status (including dates), current or final docket sheet, any reporter cites; and any appellate history relating to the lawsuit) to which the company is or was a party that involve an ANDA paragraph IV certification related to any Drug Product. Submit the complaint, the answer, any motion(s) for summary judgment, any pretrial memoranda, and any court orders and opinions on any dispositive issue for each such lawsuit.

4. For each Drug Product for which the company has been notified that an ANDA containing a paragraph IV certification had been filed with the FDA, state the company's sales,<sup>5</sup> in units and dollars, by each finished dosage form for each calendar year since, and including, the year the company was notified of the filing of such ANDA. If the company has its own generic version of the Drug Product, separate the sales for the brand-name product and the generic product.

5. For each Drug Product for which the company has been notified that an ANDA containing a paragraph IV certification has been filed with FDA, state whether the company has filed, or contributed to the filing of, in whole or in part (e.g., provided funds, legal or regulatory assistance to support the filing), a citizen petition with FDA concerning an ANDA related to that Drug Product and identify the FDA docket number assigned to such citizen petition.

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<sup>5</sup> The term "sales" means net sales, i.e., total sales after deducting discounts, returns, allowances and excise taxes. "Sales" includes sales of the Drug Product whether manufactured by the company itself or purchased from sources outside the company and resold by the company in the same manufactured form as purchased.

## Specifications in the Special Orders Sent to Generic Companies

In addition to routine questions about the name, address, and incorporation date of the responding company and its subsidiaries, and the name, business address, and official capacity of the official supervising the company's response, the FTC asked generic companies (the "company") to provide answers to the following five questions:

1. Submit all agreements between the company and any person<sup>6</sup> (including corporations or other business entities acquired since the agreement(s) was (were) executed after December 31, 1994,<sup>7</sup> relating to<sup>8</sup> any ANDA involving any Drug Product.<sup>9</sup> Examples of such agreements include, but are not limited to: (a) patent litigation settlements (either full or partial) between the company and any Brand-Name Company<sup>10</sup>; (b) agreements between the company and any other person related to the filing (or non-filing) of an ANDA by the company involving any Drug Product; (c) licensing agreements entered into with any Brand-Name Company; and (d) agreements related to any acquisition, divestiture, joint venture, alliance, license or merger by the company of any business involving the research, development, manufacture or sale of any Drug Product that is the subject of an ANDA. The company is not required to submit purchase orders for raw material supplies, equipment and facility contracts, or employment or consulting contracts, nor is the company required to submit agreements executed after the company had begun commercial marketing of the generic Drug Product corresponding to the ANDA for which it had received FDA approval. The company also is not required to submit information that has already been submitted to the Commission pursuant to the Premerger Notification Rules (16 CFR 801-803 (1998)) and Section 7A of the Clayton Act (15 U.S.C. 18a), or Sections 6, 9, 13, and 20 of the Federal Trade Commission Act (15 U.S.C. 46, 49, 53, and 57b-1), although the company must identify such information as having previously submitted. For any such agreement submitted, also submit all studies, surveys, analyses and reports which were prepared by or for any officer(s) or director(s) (or, in the case of unincorporated entities, individuals exercising similar functions) that evaluate or analyze the reasons for making such agreement (or any of the provisions in such agreement), and indicate (if not contained in the document itself) the date of preparation, and the name and title of each individual who prepared each such document.

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<sup>6</sup> The term "person" means any natural person, corporate entity, partnership, association, joint venture, or trust which is engaged in research and development, planning and design, production and manufacturing, distribution, or sales and marketing of any Drug Product.

<sup>7</sup> As well as such agreements that were executed prior to January 1, 1995 but remain in force as of the date of the information collection request.

<sup>8</sup> The term "relating to" means in whole or in part constituting, containing, concerning, discussing, describing, analyzing, identifying or stating.

<sup>9</sup> The term "Drug Product" means each finished dosage form of the drug listed in the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") (regardless of whether the Drug Product is currently listed in the Orange Book) and specifically includes those Drug Products including the following active ingredients: (a list of such active ingredients will be tailored specifically for each company).

<sup>10</sup> The term "Brand-Name Company" means each person or company (including its predecessors in interest, subsidiaries, affiliates, successors, and assigns) that has filed a New Drug Application (NDA), as defined under 21 U.S.C. § 355(b) et seq. for any Drug Product, or holds the rights to any such NDA.

2. Identify and list all lawsuits (including the court, date filed, docket number, parties, current or final status (including dates), current or final docket sheet, and any reporter cites) to which the company is or was a party involving an ANDA containing a paragraph IV certification. In those cases in which the company is not the sole defendant, describe how litigation expenses are or have been distributed among the defendants.

3. Identify when the company first began commercial marketing of a generic version of any Drug Product approved by the FDA, by each finished dosage form (or, if applicable, indicate that no such commercial marketing has occurred). Identify when the company received tentative and final approvals from the FDA for such Drug Product.

4. Identify each instance in which the company has asserted before a court or before the FDA that a patent was improperly or untimely listed in the Orange Book as defined in 21 U.S.C. 355(b) or (c). For each such assertion, submit the pleading(s) in which such assertion was made and any responsive pleading(s).

5. For each Drug Product for which the company has filed an ANDA containing a paragraph IV certification, state the company's sales<sup>11</sup> (if any), in units and dollars, by each finished dosage form for each calendar year since, and including, the year the company received FDA approval of such ANDA.

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<sup>11</sup> The term "sales" means net sales, *i.e.*, total sales after deducting discounts, returns, allowances and excise taxes. "Sales" includes sales of the Drug Product whether manufactured by the company itself or purchased from sources outside the company and resold by the company in the same manufactured form as purchased.

**Appendix F:  
FTC Staff's Citizen Petition on the Listability of  
Certain Patents in the Orange Book**

May 16, 2001

Dockets Management Branch  
Food and Drug Administration  
Department of Health & Human Services  
Room 1-23  
12420 Parklawn Drive  
Rockville, MD 20857

**CITIZEN PETITION**

The Bureau of Competition and Policy Planning Staff of the Federal Trade Commission ("FTC") submit this Citizen Petition to the Commissioner of Food and Drugs pursuant to 21 C.F.R. §§ 10.25(a) and 10.30 concerning certain issues relating to patent listings in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"). We request that the FDA clarify these issues, on an expedited basis, via industry guidance or other means that the FDA considers appropriate.

In recent years, the FTC has gained significant experience concerning competition in the pharmaceutical industry. In particular, the Commission has brought a number of antitrust enforcement activities affecting both the branded and generic drug industries. Last year, the Commission announced plans to conduct an extensive study pursuant to Section 6(b) of the FTC Act, 15 U.S.C. § 46(b) of U.S. generic drug competition (the "Study"). The Study will enable the FTC to provide a more complete picture of how generic drug competition has developed under the Hatch-Waxman Act. *See* 66 Fed. Reg. 12512 (Feb. 27, 2001); 65 Fed. Reg. 61334 (Oct. 17, 2000); "FTC to Study Generic Drug Competition," (Oct. 11, 2000)

<<http://www.ftc.gov/opa/2000/10/genericdrug.htm>>. The Office of Management and Budget ("OMB") cleared the Study on April 6, 2001, following the closure of two public comment periods. The FTC will obtain factual information for the Study from name-brand pharmaceutical and generic drug manufacturers through interrogatories and document requests.

The Study seeks information concerning a variety of practices that may have an impact on competition in the pharmaceutical industry, including the possible improper or untimely listing of patents by name-brand pharmaceutical companies in the Orange Book. In this connection, the Study requests name-brand companies to "[i]dentify all patents that the company has filed in the Orange Book and the date of listing (regardless of whether currently listed in the Orange Book) relating to each Drug Product for which the company has been notified of the filing of an ANDA by another person [, and indicate] if the patent(s) was (were) filed in the Orange Book after the company received approval of the New Drug Application. . . ." 66 Fed. Reg. at 12520. The Study also requests generic drug companies to

“[i]dentify each instance in which the company has asserted before a court or before the FDA that a patent was improperly or untimely listed as defined in 21 U.S.C. § 355(b) or (c).” *Id.* at 12521. This information is crucial to determine how often and when name-brand companies have filed new patents after the FDA has approved the drug product. *Id.* at 12517. The consequences of such filings are significant, because as “long as the patent remains listed, ANDA applicants must still make a paragraph IV certification, potentially triggering the 30-month stay of FDA approval of generic drug applications.” *Brief of Federal Trade Commission as Amicus Curiae In American Bioscience, Inc., v. Bristol-Myers Squibb Company* (Sept. 1, 2001) at 10, <<http://www.ftc.gov/os/2000/09/amicusbrief.pdf>>. Thus, such listings can affect when generic competition starts. 66 Fed. Reg. at 12517.

During the public comment period prior to OMB approval of the Study, the FTC received several comments that supported the Commission’s proposed examination of Orange Book patent listing practices. For example, Microbix indicated that generic competition can be delayed on name-brand drug products if name-brand companies newly list “irrelevant and undefendable” patents in the Orange Book near the expiration of the name-brand drug product’s original patents. Generic competition is delayed because the FDA is prohibited from approving a generic version of the name-brand product for 30 months in order to resolve litigation over the newly-listed patents. Microbix Comment at 2 (Dec. 18, 2000). *See also* General Motors Comment (Dec. 18, 2000) at 2, NACDS Comment at 1-2 (Dec. 18, 2000). These comments are available on the FTC’s website at <<http://www.ftc.gov/os/comments/genericdrugstudy/index.htm>>.

As the FTC proceeds with the Study and continues to investigate methods of competition in the pharmaceutical industry, it would be helpful if the FDA provided further guidance concerning the proper application of its regulations that require certain patents to be listed in the Orange Book. We describe below our interpretation of the pertinent statutory provisions, regulations, and the FDA statements regarding particular drug products. We seek your views on our interpretations. For example, we seek clarification of the FDA’s response to a prior Citizen Petition submitted on behalf of Apotex concerning its pending abbreviated new drug application (“ANDA”) for the marketing of a generic form of Paxil, which is marketed by GlaxoSmithKline (“GSK”, formerly SmithKline Beecham). The Apotex Citizen Petition was submitted to the FDA on February 3, 2000 in Docket No. 00P-0499/CP1. The FDA responded to that petition on November 21, 2000 (the “Citizen Petition Response” (attached)).

### Two-Prong Listing Test

First, we seek guidance concerning the criteria that a patent must meet before it can be listed in the Orange Book. We understand that the governing regulation, 21 C.F.R. § 314.53(b), and the statutes on which it is based, 21 U.S.C. §§ 355(b)(1), (c)(2), require that a patent satisfy both of two independent prongs before qualifying for Orange Book listing. To satisfy the first prong, a patent must claim a drug product<sup>1</sup> or method of using a drug product that is the subject of a new drug application (“NDA”) or an amendment or supplement to it. To satisfy the second prong, the patentee must be able to reasonably assert a claim for infringement of the listed patent against someone who manufactures, uses or sells the drug product that is the subject of the NDA. In addition, we understand that the language in 21 C.F.R.

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<sup>1</sup> The interpretation in this regulation of the term “drug” as meaning the “drug product” is consistent with the FDA’s position in *Pfizer v. FDA*. 753 F. Supp. 171 (D. Md. 1989).

§ 314.53(b) that follows the two-prong test (*i.e.*, the text following the first full sentence of that section) is merely explanatory language and does not expand the scope of this regulation. Please comment on whether our understanding comports with the FDA's interpretation of 21 C.F.R. § 314.53(b) and 21 U.S.C. §§ 355(b)(1), (c)(2).

*Listing of Patents Claiming an Unapproved Aspect of an Approved Drug*

Second, we seek guidance concerning whether under the first prong, an NDA holder can list a patent claiming an unapproved aspect of an approved drug. The regulation requires that a patent must "claim[] the drug or a method of using the drug that is the subject of the new drug application . . ." 21 C.F.R. § 314.53 (b). We read this provision to require that after a drug is approved, a listed patent must claim the drug product as approved by the FDA *in all respects*. We understand that any patent claiming only an unapproved component, an unapproved formulation, or an unapproved use of a drug product cannot satisfy the first prong. Similarly, we understand that any patent claiming an aspect of an approved drug that would require prior FDA approval (*e.g.*, a supplemental NDA) before incorporation or implementation in a marketed drug product such as a component of the drug, its formulation, a condition of use, an indication, or labeling information cannot satisfy the first prong.

We note that the FDA made statements consistent with this position in a recent patent listing dispute in federal court between Biovail (name-brand) and Andrx (generic) concerning Biovail's Tiazac product.<sup>2</sup> In that court proceeding, the FDA stated its preliminary conclusion that Biovail was required to file a supplement to its NDA for a change in manufacturing process and formulation that had not been previously approved. The FDA further clarified that the patent at issue must claim the approved formulation of Tiazac to be properly listed in the Orange Book. According to the FDA, to the extent the patent claimed only the new, unapproved formulation, it was not properly listed.

With respect to the listing of patents on unapproved aspects of an approved drug product, we also are seeking elaboration concerning the statement in the Citizen Petition Response that "[p]atents must be listed if they claim the drug substance, or active ingredient, of an approved drug product, or if they claim a drug substance that is the component of such a product." (Response at 6.) We understand the FDA's statement to be simply a restatement of the first prong and consistent with our understanding of the first prong and the criteria for listing drug substance patents set forth above. We understand that any patent claiming only an unapproved component cannot satisfy prong one. Likewise, we understand that if a drug substance patent claims only a chemical compound which the FDA has not approved as a component of an approved drug product, that patent may not be listed. In particular, we understand this to be the case even when the claimed unapproved chemical compound differs only in its water of hydration from an approved component.

Please comment on whether our understanding comports with the FDA's interpretation of 21 C.F.R. § 314.53(b) and 21 U.S.C. §§ 355(b)(1), (c)(2), and the related statements in the Citizen Petition Response.

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<sup>2</sup> See "Federal Defendant's Notice of Change in Position," *Andrx Pharmaceuticals, Inc., v. Biovail Corp.* (Case No. 01-6194-CV-DIMITROULEAS) (S.D. Fla.) (pleading filed on Feb. 28, 2001).

### Definition of "Drug Product"

Third, we seek guidance on the meaning of the term "drug product" as defined in 21 C.F.R. § 314.3(b) and as applied in 21 C.F.R. § 314.53(b), and the effect of that definition on the analysis of the second prong. We understand that the relevant "drug product" is only that product which is the subject of the NDA as approved by the FDA. Consequently, in analyzing "whether a claim of patent infringement can reasonably be asserted" against a drug product, one may only consider the drug product in the form approved by the FDA. We understand that for any aspect of a drug product which is subject to FDA approval including for instance, a drug product's components, formulation, a condition of use, an indication, or labeling information only the aspects as approved may be considered in the infringement analysis of the second prong. Please comment on whether our understanding comports with the FDA's interpretation of 21 C.F.R. § 314.53(b) and 21 U.S.C. §§ 355(b)(1), (c)(2).

### Listing of Drug Substance Patents

Finally, we seek guidance on whether a patent claiming only a chemical compound that the FDA has not approved for use as the drug substance in an approved drug product may be listed. The regulation requires that in order for a drug substance patent to be listed, it must claim a drug substance that is a component of a drug product that is the subject of a pending or approved NDA. See 21 C.F.R. § 314.53(b) and 21 U.S.C. §§ 355(b)(1), (c)(2). We understand that if a drug substance patent claims only a chemical compound which the FDA has not approved as a component of an approved drug product, that patent may not be listed.

For example, the Citizen Petition Response states "[p]lease note that for purposes of the same active ingredient requirement in 505(j), FDA considers anhydrous and hemihydrous forms of drug substances to be pharmaceutical equivalents and to contain the same active ingredient." (Response at 6, n. 16.) We understand the FDA's statement to be limited to the issue of whether a drug product, submitted for approval through an ANDA, satisfies the requirement of 21 U.S.C. § 355(j) that it contain the "same active ingredient" as the reference listed drug, even when the active ingredient of the ANDA product and the listed drug differ by water of hydration. For example, in the case of Paxil, the statement is limited to whether the anhydrate and hemihydrate forms of paroxetine hydrochloride are pharmaceutically equivalent and considered to be the same active ingredient for purposes of 21 U.S.C. § 355(j).

We do not read this statement in the Citizen Petition Response as having any bearing on the requirements for listing patents in the Orange Book as set out in 21 U.S.C. §§ 355(b)(1), (c)(2) and 21 C.F.R. § 314.53 (b). In particular, we understand the fact that the FDA may consider one chemical compound pharmaceutically equivalent to, or the same active ingredient as, another chemical compound for purposes of 21 U.S.C. § 355(j) does not alter the requirement of 21 C.F.R. § 314.53(b) that a listed drug substance patent must claim a component of an approved drug product. We further understand that it is possible for a chemical compound to be pharmaceutically equivalent to an approved active ingredient and considered the same active ingredient for purposes of 21 U.S.C. § 355(j), but not itself be approved as a component of the drug product. For example, although the FDA considers the anhydrous form of paroxetine hydrochloride to be the same active ingredient as the hemihydrous form of paroxetine

hydrochloride for purposes of 21 U.S.C. § 355(j), the anhydrous form is not an approved component of the drug product, Paxil.

Please comment on our understanding of 21 C.F.R. § 314.53(b) and 21 U.S.C. §§ 355(b)(1), (c)(2), and the related statements in the Citizen Petition Response.

We appreciate your consideration of this matter.

Respectfully submitted,

Molly S. Boast  
Director  
Bureau of Competition

Susan S. DeSanti  
Director  
Policy Planning

## Appendix G: Orange Book Listing and Analysis

This appendix describes the patent listing and litigation history for each of the eight drug products listed in Tables 4-2 and 4-3 that obtained multiple 30-month stays. The relationship of the litigated patents creating the stays to the approved drug product (as detailed in the *Physician's Desk Reference*) is also described.

### *BuSpar (buspirone)*

Box 4-2 describes Bristol-Myer Squibb's listing of Patent No. 6,150,365 (the '365 patent), which caused the additional 30-month stay for BuSpar, and the ensuing litigation. Reported court decisions related to this listing can be found at:

- *Watson Pharm., Inc. v. Henney*, Civil Action No. 00-3516 (D. Md. Jan. 17, 2001) (dismissing suit against the FDA seeking delisting because the FDA need not review Orange Book listings);
- *Mylan Pharmaceuticals, Inc. v. Thompson*, 139 F. Supp. 2d 1 (D.D.C. 2001), *rev'd* 268 F.3d 1323 (Fed. Cir. 2001) (ordering delisting of '365 patent because patent did not satisfy statutory listing criteria);
- *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001) (reversing district court decision ordering delisting of '365 patent because ANDA filer had no private right of action to challenge listing);
- *In re Buspirone Patent Litigation*, 185 F. Supp.2d 340 (S.D.N.Y. 2002) (holding that ANDAs did not infringe '365 patent);
- *In re Buspirone Antitrust Litigation*, 185 F. Supp. 2d 363 (S.D.N.Y. 2002) (holding that Orange Book listings were not petitioning activity subject to *Noerr-Pennington* immunity).

### *Hytrin (terazosin hydrochloride)*

Abbott Laboratories ("Abbott") distributes terazosin hydrochloride (known by the brand name Hytrin), which is approved for the treatment of hypertension and symptomatic benign prostatic hyperplasia.<sup>1</sup> The FDA approved the Hytrin tablet NDA on August 7, 1987, and the capsule NDA on December 14, 1994. Abbott sells the dihydrate form of terazosin hydrochloride (having two associated water molecules).<sup>2</sup>

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<sup>1</sup> *Physician's Desk Reference*, 55<sup>th</sup> ed. (2001), hereinafter "PDR" at 461.

<sup>2</sup> *Id.*; see also *Abbott Labs. v. Geneva Pharma.*, 182 F.3d 1315, 1316 (Fed. Cir. 1999).

Geneva Pharmaceuticals, Inc. filed its ANDAs for terazosin hydrochloride tablets in January 1993 and for capsules in December 1995, seeking approval to market "Form IV" anhydrous (having no associated water) terazosin hydrochloride.<sup>3</sup> Over the course of several years, Abbott brought five lawsuits involving several patents that it had listed in the Orange Book. The priority dates<sup>4</sup> of patents-at-issue in the third, fourth and fifth suits are later than Abbott's first marketing of Hytrin, suggesting that these patents might not cover Hytrin and be valid, because of the "on-sale bar" of patent law.

Initially Abbott sued Geneva in February 1992, alleging infringement of U.S. Patent No. 4,251,532 (the '532 patent), thereby generating the first 30-month stay. The '532 patent claims the dihydrate form of terazosin hydrochloride approved by the FDA for sale as Hytrin. Almost nine months later, in November 1993, the court dismissed the suit without prejudice, ending the stay. Abbott brought another suit against Geneva in September 1994, although it dismissed that suit less than a year later.<sup>5</sup> Abbott filed its third suit in November 1995, alleging infringement of U.S. Patent Nos. 4,112,097 (the '097 patent) and 5,412,095 (the '095 patent), presumably generating another stay. The '097 patent claimed a pharmaceutical composition containing terazosin hydrochloride, while the '095 patent claims the Form III anhydrate of terazosin hydrochloride (not the dihydrate). Shortly thereafter, in February 1996, the court dismissed the '095 patent from the suit without prejudice.<sup>6</sup> Litigation continued with respect to the '097 patent, however, for nearly another year. Although the '097 patent had originally expired in 1995, before Abbott filed suit, Abbott argued that the Uruguay Round Agreements Act extended its term to January 21, 1997. Geneva ultimately prevailed in district court and on appeal by asserting that the patent expired October 14, 1995.<sup>7</sup>

Abbott filed its fourth suit against Geneva in March 1996, alleging infringement of U.S. Patent No. 5,294,615 by Geneva's capsule ANDA. The '615 patent claims an anhydrous form of terazosin hydrochloride, not the dihydrate form sold by Abbott. Again, shortly after filing, the court dismissed the suit without prejudice.<sup>8</sup> Abbott's listing of the '615 patent and other patents claiming the anhydrous

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<sup>3</sup> *Id.* at 1317.

<sup>4</sup> A priority date is the earliest filing date to which the patent is entitled.

<sup>5</sup> Presumably the second suit, *Abbott Labs. v. Geneva Pharma.*, Civil Action No. 94-5634 (N.D. Ill.), related to U.S. Patent No. 5,294,615 (the '615 patent), which claimed an anhydrous form of terazosin hydrochloride, not the dihydrate form sold by Abbott. Because the '615 patent was untimely listed in the Orange Book after Geneva had filed its tablet ANDA, any suit by Abbott on the patent would not generate a 30-month stay as to Geneva's tablet ANDA. 21 C.F.R. §314.94(a)(12)(vi); see *Abbott Labs. v. Zenith Labs., Inc.*, 934 F. Supp.2d 925, 935-36 (N.D. Ill. 1995)(discussing Abbott's late listing of '615 patent and its effect on pending ANDAs).

<sup>6</sup> The FDA's Approval Letter to Geneva Pharma. for ANDA No. 74-315 (indicating dismissal date of suit related to '095 patent), posted at <[www.fda.cder.approval.index.htm](http://www.fda.cder.approval.index.htm)>

<sup>7</sup> *Abbott Labs. v. Novopharm, Ltd.*, 104 F.3d 1305 (Fed. Cir. 1997).

<sup>8</sup> Docket Sheet for *Abbott Labs. v. Geneva Pharma.*, Civil Action No. 96-1762 (N.D. Ill.)(indicating dismissal of Civil Action 96-1762 in May 1996); FDA's Approval Letter to Geneva Pharma. for ANDA No. 74-823 (indicating dismissal of Civil Action No. 96-1762 on '615 patent), posted at <[www.fda.cder.approval.index.htm](http://www.fda.cder.approval.index.htm)>

form of terazosin hydrochloride raises questions concerning the listing of polymorph patents described in Appendix H.

Abbott filed its fifth suit on June 4, 1996, alleging infringement of U.S. Patent No. 5,504,207 (the '207 patent) by Geneva's tablet ANDA. The '207 patent claimed the Form IV anhydrate of terazosin, used by Geneva in its tablets and capsules, but not by Abbott in Hytrin. Although Geneva had filed a paragraph IV certification with respect to the '207 patent for both its capsule and tablet ANDAs, Abbott failed to sue based on the capsule ANDA. Accordingly, the suit only initiated a 30-month stay on FDA approval of Geneva's tablet ANDA. That stay expired in October 1998, nearly 70 months after Abbott initiated its first suit against Geneva. The district court held the '207 patent invalid under the statutory on-sale bar, and the Federal Circuit affirmed on July 1, 1999.<sup>9</sup>

Because no 30-month stay prevented it, the FDA approved Geneva's capsule ANDA in March 1998. Rather than begin marketing, Geneva entered an agreement with Abbott whereby Geneva agreed not to market its generic tablets or capsules until the '207 patent litigation was finally concluded. In exchange, Abbott paid Geneva \$4.5 million per month.<sup>10</sup> Ultimately, Geneva began marketing its capsules in August 1999. The Geneva-Abbott agreement, however, gave rise to an FTC investigation, which concluded in a consent agreement with both Geneva and Abbott.<sup>11</sup>

#### *Neurontin (gabapentin) Tablets and Capsules*

Pfizer Warner-Lambert (Pfizer) distributes gabapentin tablets and capsules<sup>12</sup> (known by the brand name Neurontin), which is approved for treating seizures caused by epilepsy.<sup>13</sup> Pfizer's patent listings in the Orange Book and related patent infringement suits demonstrate that the lengthy pendency of a patent application can generate overlapping 30-month stays that prevent FDA approval of generic products for more than 30 months in the case of Neurontin capsules, about 53 months.

Pfizer's patents covering the gabapentin molecule and the only approved use of gabapentin have expired. The generic applicants did not challenge the validity of either patent or attempt to enter before their expiration. Pfizer had already listed Patent Nos. 4,894,476 (the '476 patent) and 5,084,479 (the '479 patent) in the Orange Book at the time the generic applicants first filed ANDAs for the capsule

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<sup>9</sup> See *Abbott*, 182 F.3d at 1318.

<sup>10</sup> *In re Terazosin Hydrochloride Antitrust Litigation*, 164 F. Supp. 1340, 1346 (D.C. Fla. 2000).

<sup>11</sup> *Abbott Laboratories*, No. C-3945 (May 22, 2000) (consent order), complaint available at <http://www.ftc.gov/os/2000/05/c3945complaint.htm>

<sup>12</sup> Before the merger of Pfizer and Warner-Lambert Co., Parke Davis, a division of Warner-Lambert, distributed Neurontin. PDR. at 2459. We refer to Pfizer Warner-Lambert (Pfizer) throughout, but some of the activity discussed was carried out by its predecessor Warner-Lambert.

<sup>13</sup> PDR at 2459.

form of gabapentin in 1998. Pfizer's suits for infringement of the '476 patent,<sup>14</sup> brought against Faulding and Apotex Corp.<sup>15</sup> in June and July 1998, generated the first 30-month stays, which expired in about December 2000.<sup>16</sup>

The subject matter claimed in the '476 and the '479 patents differs from Neurontin as manufactured and sold by Pfizer. Pfizer sells the *anhydrate* form of gabapentin (having no associated water molecules),<sup>17</sup> but the '476 patent claims a *monohydrate* form of gabapentin (having one associated water molecule). The patent explains that the monohydrate is a "novel" form of gabapentin as compared to the known, anhydrate form. Thus, Pfizer obtained the '476 patent by asserting that the new monohydrate is patentably distinct from the anhydrate that it has FDA approval to sell. The listed '479 patent claims "a method for treating neurodegenerative diseases" such as Alzheimer's, Huntington's and Parkinson's diseases with gabapentin, even though the FDA has approved gabapentin only for treatment of epilepsy.

Pfizer received Patent No. 6,054,482 (the '482 patent) on April 25, 2000, based on the fourth in a string of continuation applications<sup>18</sup> claiming priority back to 1989, and listed it in the Orange Book. Consequently, FDA regulations required the ANDA filers to re-certify to the '482 patent.<sup>19</sup> The infringement suits Pfizer brought in June and July 2000 based on those paragraph IV certifications generated second 30-month stays that extended nearly two years beyond the first stay, until

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<sup>14</sup> Presumably, the FDA did not require the generic applicants to file paragraph IV certifications for the '479 patent, which claims a method of treating neurodegenerative diseases, such as Alzheimer's, Huntington's and Parkinson's diseases, because the generic applicants did not seek approval for these uses. 21 U.S.C. § 355(j)(2)(A)(viii) (if an ANDA applicant does not seek approval for a method of use claimed in a listed patent, he may submit a statement to that regard, rather than certify to the patent). Apotex did submit a paragraph IV certification for the '479 patent and Pfizer brought suit. *Warner-Lambert Co. v. Apotex Corp.*, 2001 U.S. Dist. LEXIS 14592 (N.D. Ill. Sept. 14, 2001). Pfizer also sued Purepac for infringement of the '479 patent. *Warner-Lambert Co. v. Purepac Pharmaceutical*, Docket No. 98-CV-2749 (D. N.J.).

<sup>15</sup> At least three other generic companies have filed ANDAs for generic gabapentin following Purepac and Apotex. Pfizer has sued most for patent infringement.

<sup>16</sup> The district court granted summary judgment of no infringement for Apotex on April 2, 2001 for the '476 patent and on September 13, 2001 for the '479 patent. *Warner-Lambert v. Apotex*, 2001 U.S. Dist. LEXIS 14592 (N.D. Ill. Sept. 14, 2001). Pfizer's appeal of the '479 decision is pending. *Warner-Lambert Co. v. Apotex Corp.*, Docket No. 98-CV-4293 (N.D. Ill.). Pfizer's case against Purepac for infringement of the '476 and '479 patents is pending. *Warner-Lambert Co. v. Purepac Pharmaceutical*, Docket No. 98-CV-2749 (D. N.J.).

<sup>17</sup> PDR at 2458.

<sup>18</sup> A continuation patent is one filed during the pendency of another, earlier patent application, which contains the same disclosure as the earlier application. The continuation refers back to the earlier application and receives the benefit of its earlier filing date for purposes of identifying prior art and determining patentability. 35 U.S.C. § 120; *Transco Prods., Inc. v. Performance Contr., Inc.*, 38 F.3d 551, 555-56 (Fed. Cir. 1994).

<sup>19</sup> Faulding also was the first generic applicant for the tablet form of gabapentin, which is approved by the FDA under a different NDA. Faulding filed its ANDA for tablets 16 months later than the one for capsules. When Pfizer listed the '482 patent in the Orange Book, it did so for both capsules and tablets. Thus the additional 30-month stay relating to tablets resulted in a shorter total stay period, 37 months, than the one for capsules of 53 months.

approximately December 2002.<sup>20</sup> The relationship between the '482 patent, which claims a purified formulation of gabapentin, and Neurontin as sold by Pfizer cannot be determined from public sources such as the *Physician's Desk Reference*.

*Paxil (paroxetine hydrochloride)*

The section of Chapter 4 entitled "Orange Book Patent Listing Practices and Use of Multiple 30-Month Stays" describes GlaxoSmithKline's (GSK)<sup>21</sup> patent listings and infringement suits that caused the multiple 30-month stays for Paxil. As explained in Chapter 4, GSK has sued an ANDA filer, Apotex, for infringement of five patents, thereby generating five overlapping 30-month stays totaling over five years. This appendix examines the Orange Book listings by comparing the scope of the five patents-in-suit to Paxil.

The first patent which GSK listed and sued on was Patent No. 4,721,723 (the '723 patent), which claims paroxetine hydrochloride hemihydrate, the form of the active ingredient contained in Paxil. (The hemihydrate has one water molecule for every two paroxetine molecules incorporated into its crystalline structure.)

The second and third patents on which GSK sued Apotex were anhydrate patents. The second was Patent No. 5,872,132 (the '132 patent), which claims paroxetine hydrochloride *anhydrate* (having no associated water molecules) and so differs from the *hemihydrate* form sold by GSK. In fact, the hemihydrate form is prior art to this patent and, thus, GSK represented to the Patent Office that the anhydrate is patentably distinct from the hemihydrate. GSK also sued on Patent No. 6,080,759 (the '759 patent), which claims the anhydrate made according to a specified process. The '132 and '759 patents raise the issue of whether polymorph patents should be listed in the Orange Book, discussed in Appendix H.

The fourth and fifth patents on which GSK sued Apotex were product-by-process patents, raising the listing issues described in Appendix H. GSK's fourth suit was for infringement of Patent No. 6,113,944 (the '944 patent), which claims tablets containing paroxetine made according to a specified process. The fifth suit was for infringement of Patent No. 6,172,233 (the '233 patent), which claims paroxetine hydrochloride made according to specified processes. The '233 patent acknowledges that paroxetine hydrochloride was well known at the time GSK applied for the patent. Likewise the '944 patent acknowledges that paroxetine tablets were known. In both cases, only the recited process for making the tablets or compound is asserted to be new. Moreover, GSK applied for the '233 patent

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<sup>20</sup> Pfizer's suits for infringement of the '482 patent have been consolidated in multi-district litigation and are pending. *In re Gabapentin Patent Litigation*, MDL No. 1384 (D.N.J.).

<sup>21</sup> Before the merger of Glaxo Wellcome and SmithKline Beecham, Paxil was manufactured and distributed by SmithKline Beecham, which was also the original NDA holder. For simplicity, we will refer throughout to GSK.

several years after it began marketing Paxil. Therefore, Paxil is prior art to this patent, and it can only be valid if it claims a process other than the FDA-approved process used to make Paxil.<sup>22</sup>

### *Platinol (cisplatin)*

Bristol-Myers Squibb Co. (Bristol) distributes cisplatin (known by the brand names of Platinol and Platinol-AQ<sup>23</sup>), which is approved for treatment of testicular, ovarian and bladder cancer.<sup>24</sup> Bristol's patent listings in the Orange Book and related patent infringement suits demonstrate that double-patenting and lengthy pendency of a patent application can generate an automatic 30-month stay on FDA approval of generic products close to their otherwise expected approval date.

Bristol holds the exclusive license<sup>25</sup> to two patents related to cisplatin, Patent Nos. 4,177,263 (the '263 patent) and 5,562,925 (the '925 patent). The '263 patent issued on December 4, 1979, and Bristol eventually listed it in the Orange Book. That patent claims a method of treating tumor cells by administering cisplatin. Prior to expiration of the '263 patent on December 4, 1996, three generic companies<sup>26</sup> filed ANDAs for cisplatin containing paragraph III certifications stating that they did not seek FDA approval for their generic versions until the '263 expired. On October 8, 1996, shortly before the '263 expired, however, the Patent Office issued the '925 patent. Bristol listed this patent in the Orange Book, which forced the generic applicants to file paragraph IV certifications. Bristol then brought infringement suits against the generic applicants, triggering an automatic 30-month stay lasting until approximately May 1999.<sup>27</sup>

The '925 patent issued from the tenth application in a series of continuation applications originating with an application filed on April 20, 1970, more than 26 years before the '925 patent's issuance. The '263 patent issued from the fourth application in the same family, making the '925 patent

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<sup>22</sup> Sale of a product made by a process, even when the process cannot be discerned from the product, raises the on-sale bar of 35 U.S.C. § 102 with regard to a claimed process. *Woodland Trust v. Flowertree Nursery, Inc.*, 148 F.3d 1368, 1370-71 (Fed. Cir. 1998).

<sup>23</sup> Platinol is sold as a freeze-dried (lyophilized) form of cisplatin, which is dissolved in water prior to injection. Platinol AQ is sold as a solution of cisplatin with the water already added. Bristol received approval to market Platinol in 1978 and Platinol AQ in 1988.

<sup>24</sup> PDR at 1055-56.

<sup>25</sup> *Research Corp. Tech. v. Gensia Labs., Inc.*, 2001 U.S. App. LEXIS 4444 (Fed. Cir. 2001) (unpublished).

<sup>26</sup> Pharmachemie BV, American Pharmaceutical Partners, Inc. and Ben Venue Laboratories, Inc. filed ANDAs prior to expiration of the '263 patent. Gensia Laboratories, Inc. filed an ANDA shortly thereafter.

<sup>27</sup> This first suit was against American Pharmaceutical Partners, Inc., which received FDA approval on July 16, 1999 and began marketing its generic cisplatin in November 1999. *American Pharmaceutical Partners Announces Exclusive Cisplatin Launch*, *Bristol's Cisplatin Patent Ruled Invalid*, PR Newswire (Nov. 13, 1999).

a direct decedent of the '263. Because of its lengthy pendency, the '925 was able to issue and generate a 30-month stay just as its direct predecessor, the '263, was about to expire.<sup>28</sup>

The generic applicants successfully defended the patent infringement suits by asserting that the '925 patent was invalid for "obviousness-type double patenting" in light of the '263 patent. The '925 patent claims "a therapeutic composition comprising" cisplatin. The generics argued that this "therapeutic composition" was obvious in light of the method of treating tumors using cisplatin claimed by the '263 patent. (Appendix H explains double-patenting and the surrounding listing issues.) The district court agreed, and the Court of Appeals for the Federal Circuit affirmed on March 23, 2001<sup>29</sup> (after the 30-month stays had expired).

### *Taxol (paclitaxel)*

Bristol-Myers Squibb Co. manufactures and distributes paclitaxel (brand name, Taxol, and generically known as taxol), which the FDA has approved for treatment of ovarian, breast and lung cancers and AIDS-related Kaposi's sarcoma.<sup>30</sup> Bristol's patent listings in the Orange Book and the related patent infringement suits demonstrate that invalid patents in combination with the lengthy pendency of a patent application can potentially generate an additional 30-month stay.

During the 1980's, the National Cancer Institute (NCI) sponsored research and clinical trials of taxol's effects on numerous cancers. Eventually, the agency sought a commercial partner to bring a taxol-based drug to market, and in 1991 the NCI entered a Cooperative Research and Development Agreement ("CRADA") with Bristol.<sup>31</sup> Bristol filed an NDA for taxol on July 22, 1992, which the FDA approved five months later.<sup>32</sup> At that time, it was widely expected that generic pharmaceutical companies would submit ANDAs for generic taxol in December 1997, at the conclusion of Bristol's five-year new chemical entity (NCE) exclusivity awarded by the Hatch-Waxman Amendments.<sup>33</sup>

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<sup>28</sup> Pursuant to section 534 of Pub. L. 103-465, the term of a patent granted on an application filed on or after June 8, 1995, that is a continuation of an earlier filed application, will be 20 years from the date on which the earliest such application was filed. 35 U.S.C. § 154. The application which issued as the '925 patent was filed June 2, 1994, prior to the effective date of this provision. Therefore, the term of the '925 patent is 17 years from the date of issuance (October 8, 2013), but the term of the patent extending beyond May 8, 2012 was disclaimed.

<sup>29</sup> *In re Research Corporation Technologies, Inc. Patent Litigation*, 1999 U.S. Dist. LEXIS 22589 (D.N.J. Oct. 21, 1999), *aff'd* *Research Corp. Tech. v. Gensia Labs., Inc.*, 2001 U.S. App. LEXIS 4444 (Fed. Cir. 2001) (unpublished).

<sup>30</sup> PDR at 1062.

<sup>31</sup> *Bristol-Myers Squibb Co. v. IVAX Corp.*, 77 F. Supp. 2d 606, 609 (D.N.J. 2000).

<sup>32</sup> *Bristol-Myers Squibb Co. v. Ben Venue Labs.*, 90 F. Supp. 2d 522, 524 (D.N.J. 2000).

<sup>33</sup> 21 U.S.C. § 355(j)(5)(D)(ii) states that the FDA may not accept an ANDA for a generic version of any approved drug product containing a "new chemical entity" (i.e., an active ingredient for which the FDA has never before granted marketing approval) until five years after the approval of that NCE. The expectation that generic taxol would be available was created, in part, by Bristol's statements before Congressional committees in 1991 and 1993 that "near-term generic competition for Taxol is a certainty because Taxol is not a patented product." *Bristol-Myers Squibb Co.*, 77 F. Supp. 2d at 616.

In August 1992, Bristol filed a patent application, which resulted in Patent Nos. 5,641,803 (the '803 patent) and 5,670,537 (the '537 patent). Those patents claim an FDA-approved method of administering a specified amount of taxol to a patient over the course of three hours. Bristol listed both patents in the Orange Book and sued the generic ANDA applicants, who had filed paragraph IV certifications. The patent infringement suit against IVAX Corp., the first paragraph IV filer, triggered a 30-month stay on FDA approval that lasted until June 2, 2000. In March 2000, the district court hearing the infringement suit entered summary judgment that both patents were invalid in light of references reporting on government-sponsored clinical trials of taxol.<sup>34</sup> The Court of Appeals for the Federal Circuit affirmed that decision as to the majority of asserted claims in April 2001.<sup>35</sup>

Although the '803 and '537 patents no longer blocked generic competition at the time the 30-month stay expired in June 2000, the FDA had not yet approved any generic version of taxol for marketing. For that reason, when American Biosciences, Inc. (ABI) obtained Patent No. 6,096,331 (the '331 patent) on August 1, 2000, and Bristol listed it in the Orange Book as explained below, the patent had the potential to create a second 30-month stay on generic entry. Due to a series of tangled legal maneuvers, this never came to pass, however, and the '331 patent delayed FDA approval of a generic product for only a few weeks.

The story of the '331 patent is complex. It claims priority back to an original application filed in 1993, seven years before its issuance. The majority of the claims in the patent cover taxol "substantially free of cremophor," the solvent used for dissolving and administering the FDA-approved version of taxol. Hence, these claims do not cover the approved version of taxol and cannot support listing. However, a small number of broad claims recite a "vessel" containing a specified amount of a taxol ranging from 33 mg to 3000 mg. These claims arguably cover, for instance, a bag for intravenous administration of taxol as approved by the FDA, but a district court has also invalidated the claims based on this interpretation.<sup>36</sup>

At the time the '331 patent issued, ABI approached Bristol, asking that it list the '331 patent in the Orange Book. Bristol initially refused, so ABI sought and obtained a temporary restraining order on August 11, 2000 from the district court for the Central District of California requiring Bristol to list the patent.<sup>37</sup> Bristol later agreed to list the patent, and the parties requested that the court enter their settlement agreement, but on September 7, 2000, the district court refused, and instead dismissed the case on the grounds that ABI had no private right of action seeking listing of a patent in the Orange Book. Thus, the district court dissolved the TRO and ordered Bristol to delist the patent by September

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<sup>34</sup> *Bristol-Myers Squibb Co. v. Boehringer Ingelheim Corp.*, 86 F. Supp. 2d 433 (D.N.J. 2000).

<sup>35</sup> *Bristol-Myers Squibb Co. v. Ben Venue Labs. Inc.*, 246 F.3d 1368 (Fed. Cir. 2001). The Federal Circuit vacated the district court's invalidity decision regarding the remaining asserted claims with a suggestion that those too might be held invalid after further development of the record. Bristol chose not to pursue these remaining claims.

<sup>36</sup> See claims 31, 36, 39, 41 and 42 of the '331 patent. *American Biosciences, Inc. v. Baker Norton Pharmaceuticals, Inc.*, 2000 WL 54627 (C.D. Cal. 2002), *aff'd on reconsideration*, 2000 WL 655272.

<sup>37</sup> *American Bioscience*, 142 F. Supp. 2d at 4-5.

14.<sup>38</sup> Also on September 7, ABI brought a patent infringement suit against IVAX and asserted to the FDA that the suit barred approval of IVAX's ANDA for 30 months.<sup>39</sup>

On September 11, 2000, Bristol, without referring to the earlier listing, informed the FDA that it wished to list the '331 patent. Bristol again communicated with the FDA on September 14, this time stating that it was de-listing the '331 patent "to the extent that listing was compelled by the TRO," but that it did not mean to "affect the continued and continuous listing of the patent."<sup>40</sup> The FDA considered Bristol's August 11 listing ineffective and its September 11 listing to be late, because it occurred more than 30 days after the patent issued.<sup>41</sup> For that reason, the FDA did not require the ANDA applicants to submit paragraph IV certifications regarding the '331 patent or view ABI's infringement suit as creating a 30-month stay. On September 15, the FDA granted final approval to IVAX's generic taxol.<sup>42</sup> ABI sought review of this decision in the D.C. district court, which sided with the FDA on October 3, 2000.<sup>43</sup> IVAX began marketing about three weeks later and remains on the market. At least two other generic manufacturers have subsequently entered.

In November 2001, the D.C. Circuit Court of Appeals reversed the district court's affirmance of FDA's decision to consider Bristol's September 11 listing untimely and to grant final approval to IVAX. Moreover, the Court of Appeals ordered the FDA to vacate its approval of IVAX's ANDA, effective January 24, 2002.<sup>44</sup> This never occurred, however, because Bristol decided against relisting the '331 patent<sup>45</sup> following the January 11, 2002 decision by the district court holding that the asserted patents

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<sup>38</sup> *American Bioscience, Inc. v. Bristol Myers Squibb Co.*, 2000 WL 1278348 (C.D. Cal. 2000) (an action to enforce the FDCA may only be brought by the United States pursuant to 21 U.S.C. § 337(a)).

<sup>39</sup> A recounting of this history can be found in *American Bioscience, Inc. v. Shalala*, 142 F. Supp. 2d 1 (D.D.C. 2000), *vacated*, 243 F.3d 579 (D.C. Cir. 2001).

<sup>40</sup> *Id.* at 6.

<sup>41</sup> 21 U.S.C. § 355(c)(2) requires that an NDA holder submit a patent for listing within 30 days of the date of issue. If the NDA holder lists a patent more than 30 days after issuance, any ANDAs on file need not certify to the patent. 21 C.F.R. § 314.94(a)(12)(vi).

<sup>42</sup> The FDA had granted "tentative approval" to IVAX two weeks earlier, on August 28, because it had completed its substantive review of the ANDA, but could not issue final approval until the questions about the '331 patent had been resolved. *American Bioscience, Inc.*, 142 F. Supp. 2d at 6. Thus, the dispute over the '331 patent delayed final approval of generic taxol about 18 days.

<sup>43</sup> *American Bioscience, Inc.*, 142 F. Supp. 2d 1.

<sup>44</sup> *American Biosciences, Inc. v. Thompson*, 269 F.3d 1077 (D.C. Cir. 2001).

<sup>45</sup> *FDA Status Resolved - IVAX' Generic Paclitaxel On the Market to Stay*, Business Wire, Jan. 25, 2002.

claims were invalid.<sup>46</sup> (The same claims supported the listing.) Had Bristol not delisted, the D.C. Circuit court's decision might have forced generic taxol off the market.

*Tiazac (diltizem hydrochloride)*

Box 4-4 describes Biovail's listing of Patent No. 6,162,463 (the '463 patent),<sup>47</sup> which caused the second 30-month stay for Tiazac, and the FTC's related enforcement action. Court decisions related to this listing can be found at:

- *Biovail Corp., Int'l v. Andrx Pharm., Inc.*, 2000 WL 33354427 (S.D. Fla. March 6, 2000), *aff'd* 239 F.3d 1297 (Fed. Cir. 2001) (holding that Andrx's ANDA did not infringe Patent No. 5,529,791 (the '791 patent), the first listed patent covering the Tiazac formulation).
- *Andrx Pharm., Inc. v. Biovail Corp.*, 175 F. Supp. 2d 1362 (S.D. Fla. 2001) *vacated*, 276 F.2d. 1368 (Fed. Cir. 2002) (dismissing Andrx's challenge to the '463 listing because it had no private right of action, but shortening the 30-month stay because Biovail's actions "were done to impede or delay the expeditious resolution of the patent actions between Biovail and Andrx . . .").<sup>48</sup>
- *Andrx Pharm., Inc. v. Biovail Corp.*, 276 F.2d. 1368 (Fed. Cir. 2002) (holding that the district court had no authority to shorten 30-month stay based on Biovail's allegedly improper conduct before the FDA).
- [www.ftc.gov/opa/2002/04/biovailtiazac.html](http://www.ftc.gov/opa/2002/04/biovailtiazac.html) (FTC proposed consent decree requiring delisting).

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<sup>46</sup> The court held that the use of Taxol as marketed by Bristol prior to the effective filing date of the '331 patent anticipated the claims and rendered them invalid under 35 U.S.C. § 102. *American Biosciences, Inc. v. Baker Norton Pharmaceuticals, Inc.*, 2000 WL 54627 (C.D. Cal. 2002), *aff'd on reconsideration*, 2000 WL 655272 (holding claims 31, 36, 39, 41 and 42 of the '331 patent invalid).

<sup>47</sup> The '463 patent claims a diltiazem formulation containing both slow-release beads, of the type found in Tiazac, and "at least 1% free diltiazem." Because Tiazac is prior art to the '463 patent, the patent cannot cover Tiazac and be valid. See *In re Buspirone Patent Litigation*, 185 F. Supp. 2d at 360-62.

<sup>48</sup> *Id.* at 1374. The district court rejected Biovail's argument that the court's authority to limit the 30-month stay could be based only on the filing of the '463 infringement action because "[s]uch a myopic approach to each listed patent would lead to a potentially endless listing of patents to prolong FDA approval of a generic competitor." *Id.* at 1375.

## Appendix H: Orange Book Patent Analysis

This appendix describes and analyzes three categories of patents that raise Orange Book listability questions and provides examples of patents falling into those categories. The appendix also suggests ways in which the listability questions might be addressed. The FTC Staff identified the patent categories and examples by reviewing all patents listed for drug products for which the responding generic companies indicated that they had challenged a listing in some way. The cited examples are not exhaustive. They only illustrate a category. Chapter 4 of this report describes the statutory and regulatory scheme governing Orange Book listings and underlying this analysis.

### *Patents Not Claiming the Approved Drug Substance, Drug Formulation or Use*

As explained in Chapter 4, the listing regulation requires that those patents listed in the Orange Book claim the drug product that is the subject of the NDA, or an approved use of that product. The regulation allows the listing of drug substance patents, drug formulation patents, and method of use patents. One court has pointed out that the scope of the NDA, and not the brand-name company's drug as marketed, controls the listing analysis.<sup>49</sup> Normally, the scope of the approved NDA will closely align with the marketed drug, given that almost all changes to a drug's formulation or labeling require supplemental FDA approval.<sup>50</sup> Therefore, in most cases, one can compare a patent with the FDA approved, marketed drug to analyze whether the patent listing is appropriate. In this analysis, the FTC Staff compared the listed patent to the drug product as described in the *Physician's Desk Reference*, 55<sup>th</sup> ed. (2001). It is possible, however, that resolution of a listing dispute might depend on an interpretation of the scope of approval granted through the NDA, and a mechanism for addressing this issue could be valuable.

Some patents listed in the Orange Book claim a formulation that differs from the formulation approved through the NDA. For instance, the FTC has alleged that Patent No. 6,162,463, listed for Tiazac (diltiazem) claims a formulation comprising slow release beads and free diltiazem but that the Tiazac formulation approved through the NDA contains only slow release beads.<sup>51</sup> Other listed patents claim only unapproved uses of the drug. For example, Patent No. 5,084,479, listed for Neurontin (gabapentin), claims the use of gabapentin to treat neurodegenerative diseases. The FDA has approved gabapentin only for treating epilepsy, which is not a neurodegenerative disease. Other patents falling into this category are those that claim a method of using a drug substance other than the approved drug substance, such as Patent No. 4,621,077, listed for Fosamax (alendronate sodium), which claims a method of using the acid form of alendronate. Only the sodium form of alendronate is sold.

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<sup>49</sup> *Andrx Pharm., Inc. v. Biovail Corp.*, 276 F.3d 1378, 1376 (Fed. Cir. 2002).

<sup>50</sup> 21 C.F.R. § 314.70(b).

<sup>51</sup> The FTC accepted for public comment a proposed consent order on April 23, 2002, available at <http://www.ftc.gov/opa/2002/04/biovailtiazac.htm>.

Brand-name companies also have listed patents that claim a drug substance differing from the approved drug substance in some way. These patents generally fall into three subcategories: metabolites, polymorphs, and intermediates. Each subcategory raises its own specific issues, as elaborated below.

*(i) Metabolite Patents*

Of the drug products for which the FTC Staff examined listed patents, there are at least two instances where brand-name companies have listed and sued generic companies for infringement of metabolite patents.<sup>52</sup> A metabolite is the chemical compound into which a patient's body metabolizes or converts the active ingredient of a drug product. Often the metabolite, rather than the active ingredient itself, produces the drug's therapeutic effect in the body. Only patients, and not the generic applicant, can directly infringe a metabolite patent; they do so by ingesting the approved drug product and then metabolizing it into the claimed compound. Typically, the patentee charges that the generic applicant will induce or contribute to the infringement of the metabolite patent by selling its drug to patients who then metabolize it.<sup>53</sup>

One district court explicitly has held that a brand-name company may not list a metabolite patent in the Orange Book, because the metabolite patent does not "claim the drug," as required by the listing statute.<sup>54</sup> The court looked to the precedent, *Hoechst-Roussel Pharms., Inc. v. Lehman*,<sup>55</sup> 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.

Whether a brand-name company appropriately may list patents claiming metabolites or the use of metabolites in the Orange Book could be clarified through FDA regulation or guidance.

*(ii) Polymorph Patents*

Another category of patents that raises listing questions includes those patents claiming a chemical compound that differs by water-of-hydration or that forms a crystalline structure different from the active ingredient approved by FDA through the NDA. For instance, the FDA has approved the *anhydrate* form of gabapentin (having no water) but the Orange Book contains a patent claiming the

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<sup>52</sup> Two examples are Prilosec (omeprazole, Patent No. 4,636,499) and BuSpar (buspirone Patent No. 6,150,365). The generic applicants in the omeprazole litigation moved for summary judgment that they did not contribute to or induce infringement of the '499 patent. The district court granted that motion based, in part, on the argument of the generic applicants that the patent could not cover a patient's ingesting and metabolizing omeprazole because that activity was prior art to the patent. *In re Omeprazole Patent Litigation*, 2001 WL 585534 (S.D.N.Y. 2001).

<sup>53</sup> *In re Omeprazole Patent Litigation*, 2001 WL 585534 (S.D.N.Y. 2001); *see also*, *Zenith Labs. v. Bristol-Myers Squibb*, 10 F.3d 1418, 1422 (Fed. Cir. 1994) (infringement may occur if the administered product is converted *in vivo* in to the claimed product); 35 U.S.C. § 271(b), (c) (one who induces or contributes to infringement of a patent is liable as an infringer).

<sup>54</sup> *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).

<sup>55</sup> 109 F.3d 756 (Fed. Cir. 1997).

monohydrate form of gabapentin (having one water molecule in its crystalline structure for each gabapentin molecule). Compounds differing in this way, or by the way in which the individual molecules arrange in a crystalline structure, are called polymorphs. Some drugs having patents listed which claim a form of the active ingredient differing by water of hydration from the approved form include Hytrin (terazosin hydrochloride), Paxil (paroxetine hydrochloride) and Neurontin (gabapentin).

The FDA typically grants approval through an NDA to a brand-name company to sell only one polymorph of an active ingredient. The company may not sell other versions of the active ingredient without FDA approval. Thus, one view is that these different polymorphs of the approved active ingredient are not part of the approved drug product, and patents claiming the different polymorphs do not claim the approved drug product, thus making the listing of such patents questionable.

An alternative view recognizes that under certain circumstances, the FDA will treat a compound differing by water-of-hydration or crystalline structure from an approved active ingredient as the same active ingredient. The FDA will allow the active ingredient of a generic product to differ in these ways if the generic applicant demonstrates that its product is bioequivalent to the brand-name company's product.<sup>56</sup> For this reason, some have argued that patents claiming compounds that differ by water-of-hydration or crystalline structure from the approved active ingredient claim the "same" active ingredient and therefore should be listable.<sup>57</sup>

A response to this argument is based on the fact that often the form of the active ingredient used in the approved drug product is prior art to the later-issued polymorph patent. This is the case for Hytrin, Paxil, and Neurontin. That means that the patentee argued, and the Patent Office agreed, that the different polymorph was sufficiently distinct from the FDA-approved polymorph to be patentable. This fact highlights the difficulty in treating the two compounds as the "same" for purposes of the patent analysis required by Orange Book listings. Listable patents are those that "claim" the approved drug product (a concept based on patent principles), and not every patent that a bioequivalent product might infringe. The listing analysis is rooted in patent concepts, and the ability of two polymorphs to form bioequivalent products is not decisive to that analysis. If the ability of two polymorphs to form bioequivalent products made them the "same" for patent purposes (as opposed to FDA purposes), the brand-name company could never obtain the later polymorph patent in the first place because the earlier, approved polymorph would invalidate it.

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<sup>56</sup> See FDA, Preface to Twenty First Edition of Approved Drug Products with Therapeutic Equivalence Evaluation, available at <<http://www.fda.gov/cder/orange/adp.htm>>.

<sup>57</sup> One district court addressed the issue and agreed. In *Zenith Laboratories, Inc. v. Abbott Laboratories*, 1996 WL 33344963 (D.N.J. 1996), the court denied Zenith's request that the court order Abbott, the holder of an approved NDA on terazosin dihydrate (Hytrin), to de-list four patents claiming anhydrous terazosin. Contrary to FDA regulations stating that the agency does not review the propriety of a listing, the court stated, "the FDA approved Abbott's [anhydrate] patents for listing. Such approval demonstrates that the FDA believed that those patents are covered by an approved drug product." *Id.* at \*9. Zenith appealed that decision to the Court of Appeals for the Federal Circuit, but the parties settled following oral argument and before the court issued an opinion, with Abbott paying Zenith, who agreed to stay off the market. *In re Terazosin Antitrust Litigation*, 164 F. Supp.2d 1340, 1346 (S.D. Fla. 2000).

Whether a brand-name company may appropriately list polymorph patents, or those claiming a use or formulation containing a polymorph, could be clarified through FDA regulation or guidance. This is the subject of the FTC Staff's Citizen Petition.

### *(iii) Drug Intermediate Patents*

The "intermediate" patents listed in the Orange Book present a category that may 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.

In the patent litigation concerning Aredia (pamidronate disodium), the district court held that a brand-name company may list intermediate patents in the Orange Book. The generic applicant challenged the listing of a patent claiming a compound used in the manufacture of its product, which the brand-name company admitted was not present in Aredia.<sup>58</sup> The district court held that the brand-name company could maintain the listing, however, on the basis that the claimed compound was a "component" of Aredia because it was used in the manufacture of that drug product.<sup>59</sup> For support, the court looked to the FDA's listing regulations that allow listing of a patent claiming a "component" of an approved drug product,<sup>60</sup> and the FDA's regulations on good manufacturing practices defining "component" to mean "any ingredient for use in the manufacture of a drug product, including those that may not appear in such a drug product."<sup>61</sup> The court did not address whether a patent claiming an intermediate compound claims the approved drug product.

Whether a brand-name company may appropriately list intermediate patents could be clarified through FDA regulation or guidance.

### *Product-by-Process Patents*

A simple example of the claims of a chemical product-by-process patent, and a comparison with product and process patents, is necessary to understanding the listing issues surrounding these patents. A *product* patent claim would recite "such and such substance." A related *process* patent claim would recite "a process for making such and such substance by performing steps (a) and (b)." A corresponding

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<sup>58</sup> The brand-name company admitted that Aredia was sold as the anhydrous (lacking water) form of pamidronate, not the pentahydrate form, which contains five water molecules for every pamidronate molecule. *Ben Venue Labs., Inc. v. Novartis Pharm. Corp.*, 10 F. Supp. 2d 446, 454 (D. N.J. 1998) (the court did not address whether the generic applicant had a private right of action to challenge the listing).

<sup>59</sup> *Id.* at 457-58.

<sup>60</sup> *Id.* at 455-58; see 21 C.F.R. § 314.53(b) ("For patents that claim a drug substance or drug product, the applicant shall submit information only on those patents that claim a drug product that is the subject of a pending or approved application, or that claim a drug substance that is a component of such a product.").

<sup>61</sup> *Id.* at 456 (quoting 21 C.F.R. § 210.3(b)(3)).

*product-by-process* patent claim would simply rearrange words of the process claim to recite “such and such substance made by the process of performing steps (a) and (b).”

Two arguments support the position that product-by-process claims may not be listed. First, although the FDA’s listing regulation does not address product-by-process patents, it specifically defines three categories of listable patents: drug substance (ingredient) patents, drug product (formulation and composition) patents, and method of use patents. Product-by-process patents do not comprise a category of listable patents under the FDA’s listing regulation. Second, the listing regulation and Hatch-Waxman’s legislative history prohibit the listing of process patents,<sup>62</sup> and product-by-process claims are arguably similar to process patents than are product patents. As seen above, the wording of the product-by-process claim more closely resembles that of the process claim, not the product claim. Moreover, the scope of patent coverage afforded by a product-by-process patent for small-molecule pharmaceuticals typically is identical to that afforded by the corresponding process patent.

An examination of two listed product-by-process patents illustrates this latter point. Patent Nos. 6,063,927 (the ‘927 patent) and 6,172,233 (‘233) both claim paroxetine hydrochloride made according to specified processes. In each case, the patent itself acknowledges that paroxetine hydrochloride was well known at the time the brand-name company applied for the patents. The brand-name company represented to the Patent Office in the patent document that the recited process was new and made the claims patentable. Therefore, if valid, these patents cover only those products (paroxetine hydrochloride) made according to the specified process,<sup>63</sup> just as process patents cover products made according to the specified process.<sup>64</sup> In contrast, product patents, such as listable drug substance and formulation patents, cover a product regardless of the process by which it is made.<sup>65</sup> Thus, product-by-

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<sup>62</sup> 21 C.F.R. § 314.53(b). Examples of “product-by-process” patents are the three patents listed for Paxil (paroxetine hydrochloride).

<sup>63</sup> *Atlantic Thermoplastics Co. v. Faytex Corp.*, 970 F.2d 834, 844 (Fed. Cir. 1992).

<sup>64</sup> A process claim covers performance of the process steps, but it also provides patent coverage to products made according to the recited process. 35 U.S.C. § 271(g) (“Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a patented process in the United States shall be liable as an infringer . . .”).

<sup>65</sup> A counter-argument is that, based on a statement in the Federal Circuit opinion, *Scripps Clinic & Research Foundation v. Genentech, Inc.*, the process limitations of these patent claims must be ignored, effectively making them listable product claims. In that case the court stated “the correct reading of product-by-process claims is that they are not limited to a product prepared by the process set forth in the claims.” 927 F.2d 1565, 1583 (Fed. Cir. 1991). A later case, *Atlantic Thermoplastics*, held that process limitations must be considered. 970 F.2d 834, 844 (Fed. Cir. 1992). However, the two cases can be reconciled in this context. If the patentee depended on the novelty of the process limitations in obtaining these patents, it is then estopped from ignoring those limitations. *Atlantic Thermoplastics Co. v. Faytex Corp.*, 974 F.2d 1279, 1280 (J. Rich, dissent from denial of reh’g en banc) (patentee admitted that product-by-process claim was limited to the process and claim must be interpreted accordingly); *Id.* at 1299 (J. Lourie, same). When the product is old, but the process is new, as is generally the case with patents related to small-molecule pharmaceutical compounds, the claim is a process claim, not a true product-by-process claim of the type discussed in *Scripps*. “The *Scripps* class of product-by-process claims is quite different from claims [which are] allowed when the process is found patentable.” *Id.* at 1282 (J. Newman, same). Under this analysis, an interpretation of the listed product-by-process patents as process patents is completely consistent with the *Scripps* case. Moreover, any argument that ignores the process limitations in an attempt to support the Orange Book listing on the grounds that these are product patents would necessarily invalidate the patents, thereby suggesting that a claim of patent infringement could not “reasonably be asserted” under this claim interpretation, as required for listing under 21 U.S.C. § 355(b)(1).

process patents in which only the novelty of the process supports patentability arguably are characterized more accurately as process patents.

Whether a brand-name company may appropriately list such patents could be clarified through FDA regulation or guidance.

### *Double Patenting*

When a patent applicant obtains a second patent claiming subject matter that is the same as or obvious in light of the claims of an earlier issued patent, it is called "double-patenting." The patent statute and the judicially-created doctrine of "obviousness-type double patenting" renders such patents invalid. The doctrine of double patenting prevents the patentee from extending the patent right beyond the statutorily granted time limit.<sup>66</sup> The Platinol example, as described in Appendix G, provides an example of a 30-month stay created by a patent invalid for double-patenting. The brand-name company obtained a 30-month stay by obtaining, listing and suing on Patent No. 5,562,925. The Federal Circuit eventually invalidated that patent for double patenting -- 45 months after the generic applicant challenged the validity of the patent.<sup>67</sup> The '925 patent effectively generated an additional 30 months of exclusivity even though it claimed nothing new.

In some circumstances a patentee may obtain a second patent that is obvious in view of its own earlier patent. The Patent Office typically allows a patent applicant to obtain such a patent only if the applicant files a "terminal disclaimer" for the later patent, disclaiming the term of the later patent that extends beyond the term of original patent, so that both patents expire on the same day. In those cases in which the brand-name company files a terminal disclaimer for the later patent, the later patent does not provide rights beyond those of the earlier patent because both expire on the same day. This is the rationale behind the Patent Office's allowing the later patent. The later patent does provide additional protection from generic competition, however, if it generates a second, later-expiring 30-month stay.

Fosamax provides an example of how double-patenting with a terminal disclaimer may result in multiple 30-month stays. The brand-name company listed and initially sued on the earlier patent, No. 5,849,726 (the '726 patent), which claims "a method for treating and/or preventing bone loss" using the anhydrate form of alendronate sodium. The later patent, No. 6,008,207 (the '207 patent), was a continuation of the '726 patent.<sup>68</sup> It claims "a method for treating bone resorption" and "a method for

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<sup>66</sup> *In re Lonardo*, 119 F.3d 960, 965 (Fed. Cir. 1997); *See In re Goodman*, 11 F.3d 1046, 1052 (Fed. Cir. 1993). The Patent Office allows a terminal disclaimer to cure an obviousness-type double patenting rejection only when the same entity owns both patents.

<sup>67</sup> *Research Corp. Techs. v. Gensia Labs., Inc.*, 10 Fed. Appx. 856 (Fed. Cir. 2001)(unpublished).

<sup>68</sup> A continuation patent is one filed during the pendency of another, earlier patent application, which contains the same disclosure as the earlier application. The continuation refers back to the earlier application and receives the benefit of its earlier filing date for purposes of identifying prior art and determining patentability. A continuation application generally claims the same invention claimed in the earlier application, although there may be some variation in the scope of the subject matter claimed. The term "parent" refers to the immediately preceding application upon which a continuing application claims priority. 35 U.S.C. § 120; *Transco Prods., Inc. v. Performance Constr., Inc.*, 38 F.3d 551, 555-56 (Fed. Cir. 1994).

inhibiting bone resorption” using the anhydrate form. As the patents explain, however, “a method for treating and/or preventing bone loss” is the same thing as “a method for treating and/or inhibiting bone resorption.”<sup>69</sup> The brand-name company filed a terminal disclaimer on the ‘207 patent, presumably to overcome or avoid a rejection based on double patenting. The brand-name company sued for infringement of the ‘207 patent based on a paragraph IV certification approximately four months after suing based on the ‘726 patent.

In theory, the later-issued ‘207 patent provides no additional patent protection beyond the ‘726 patent because both expire on the same day. However, the ‘207 patent generated a second, later-expiring 30-month stay because it issued later, thus triggering a later paragraph IV certification and a later suit. Consequently, the later-issued ‘207 patent did provide an additional exclusionary right beyond the ‘726 patent that potentially had the ability to delay generic entry by an additional four months. That delay never materialized because the court dismissed the suits on both patents by stipulation of the parties before the first 30-month stay expired, thereby extinguishing the 30-month stays generated by both the ‘207 and the ‘726 patents.<sup>70</sup>

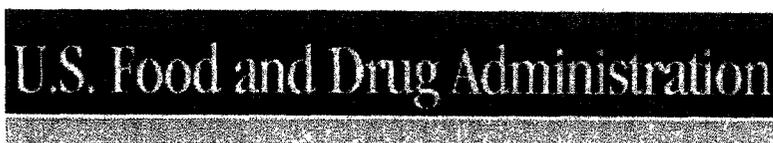
Whether a brand-name company may appropriately list additional patents claiming subject matter that is the same as or obvious in light of the claims of an earlier-issued patent for the same drug product could be clarified through FDA regulation or guidance.

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<sup>69</sup> Specifically, the patents state, “The term ‘inhibition of bone resorption’ as used herein, refers to treatment and prevention of bone loss . . . .” U.S. Patent No. 6,008,207, col. 2, lines 28-29.

<sup>70</sup> Publicly available information does not provide a reason for the stipulated dismissal.

**ATTACHMENT B**



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## Greater Access to Generic Drugs

### New FDA initiatives to improve drug reviews and reduce legal loopholes

By Michelle Meadows

You might think that lower cost means lower quality, but that's not the case with prescription drugs, says Gary Buehler, R.Ph., director of the Food and Drug Administration's Office of Generic Drugs. "The FDA ensures a rigorous review of all drugs, and consumers can be assured that generic drugs are as safe and effective as brand-name drug products," he says.

Generic drugs are copies of brand-name drugs and are available in both over-the-counter (OTC) and prescription form. For example, ibuprofen is the generic version of the OTC pain medicine Advil. Last year, the FDA approved the first generic of the prescription anti-seizure drug Neurontin (gabapentin). Generics have the same quality, safety, and strength as branded medicines. But for an average brand-name drug that costs \$72, the generic version costs about \$17.

At roughly one-third the price of brand-name medications, generics can bring consumers significant savings. A 2002 study by the Schneider Institute for Health Policy at Brandeis University in Waltham, Mass., concluded that if Medicare increased the rate of generic usage to that of similar high-performing private sector plans, its 40 million beneficiaries could see potential savings of \$14 billion in 2003.

The FDA has made it a priority to encourage the availability of generic drugs. FDA experts say there is no question that brand-name drugs are also essential.

"Generic drugs are possible only as a result of the development of new innovative drugs, and this innovation requires significant investment," says former FDA Commissioner Mark B. McClellan, M.D., Ph.D. "Without fair compensation from meaningful patent protection, drug research and development would slow or stop." According to the Boston-based Tufts Center for the Study of Drug Development, the cost to develop a new drug averages \$897 million. The Pharmaceutical Research and Manufacturers of America (PhRMA) reports that its member companies invested about \$32 billion in 2002 in discovering and developing new medicines.

A brand-name company submits information to the FDA on patents it holds on a drug and their expiration dates. Then the agency lists patents on new drugs in the publication *Approved Drug Products with Therapeutic Equivalence*, also known as the Orange Book. Patent protection gives brand-name companies, also known as "innovator" companies, the sole right to sell a drug for a certain period of time. This allows them to fairly recoup their

investment costs. Patent protection for drugs typically lasts an average of 11 years. A generic drug can only enter the market after the brand-name patent or other marketing exclusivities have expired and FDA approval is granted.

But rising drug costs remain a major challenge for consumers, especially older Americans. "This is where generics play an essential role," McClellan says. "Once the appropriate patent protection has expired, generic medicines give patients an alternative."

On Dec. 8, 2003, the Medicare Prescription Drug Improvement and Modernization Act of 2003 was enacted. Title XI of that Act provides for, among other things, limits on certain court actions that could delay availability of generic drugs. The move is expected to save consumers billions of dollars, as well as lower costs for government and employer-provided coverage.

In addition, the FDA also continues initiatives to improve access to generic drugs. These initiatives involve revamping the FDA's review process to put generic drugs into consumers' hands more quickly. The fiscal year 2005 FDA budget request includes increases in funding for the FDA's generic drug program. The additional funds would go toward increased staff and other improvements to speed up generic drug reviews. The FDA routinely evaluates the generic drug review program to find ways to increase efficiency and get quality products into the hands of consumers to improve the public health.

#### **How Generics Get on the Market**

The main reason generic drug companies can market their drugs at lower prices is that they don't face the same development costs as brand-name companies. Under the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, generic drug companies don't have to repeat expensive clinical trials.

"The Hatch-Waxman Act essentially created the generic drug industry," says Buehler. Roughly two decades ago, generics made up only 12 percent of all prescriptions. Now, generics represent over 50 percent of all prescriptions in the United States, according to the Generic Pharmaceutical Association (GPhA). "The law paved the way for many more generic drugs because rather than repeating research, generic drug companies instead must show the FDA that their drugs are bioequivalent to the brand-name drug," Buehler says.

When a drug is "bioequivalent" to another, it means that its active ingredient works in the same way and in the same amount of time as the brand-name drug. Scientists measure a generic drug's bioavailability--the amount of the generic drug in the bloodstream and how long it takes to get there. Then they compare that measurement to the brand-name drug. While innovator companies submit full new drug applications, generic companies submit what are known as abbreviated new drug applications (ANDAs). Along with showing that a generic drug has the same bioavailability as the brand-name drug, generic companies must prove that their products have the same active ingredient, follow the same quality manufacturing standards, and have similar labeling. ([See "FDA Requirements for Generic Drugs."](#))

The competition encouraged by the Hatch-Waxman Act helps to keep drug costs down and also spurs innovator firms to develop more new drugs, Buehler says. "The law aims to protect the intellectual property rights of innovator companies, while also encouraging the development of generic drugs," he says. As an incentive for generic drug firms to submit ANDAs to the FDA, the first generic challenger of patents is awarded a period of marketing exclusivity.

#### **Reducing Legal Barriers**

The Medicare Modernization Act will close legal loopholes in the Hatch-Waxman Act that delay generic drug approval. For example, only one 30-month "stay" is allowed under the Act if an innovator company sues a generic company over patent issues. This may occur

after a generic applicant certifies that an innovator's patent will not be infringed. Unless the innovator sues within 45 days after such notice, there is no 30-month stay. The innovator can still sue, but no 30-month stay results.

A stay is the term for the delay in generic approval that occurs when a brand-name company files a patent infringement lawsuit. This delay is meant to be a time to resolve issues about whether a generic drug company is infringing a drug patent. During the stay the FDA cannot approve the generic drug.

A limit of one 30-month stay is in line with recommendations from the Federal Trade Commission (FTC). According to an FTC study released July 30, 2002, there were cases involving several brand-name drugs between 1994 and 2000 in which repeated 30-month stays delayed access to generic drugs.

Access to generic drugs has sometimes been delayed from four to 44 months when drug companies have used various methods to get repeated 30-month stays. Examples of delaying tactics include submitting patent information on the color of the pill bottle, ingredient combinations, and other minor matters that don't affect the drug's effectiveness or safety.

Such strategies have been seen only in a minority of drug firms. And, according to PhRMA, stays are rare. But the FTC concluded that multiple stays can have substantial financial impact and are "harmful to consumers." President Bush has said, "Our message to brand-name manufacturers is clear: You deserve the fair rewards of your research and development; you do not have the right to keep generic drugs off the market for frivolous reasons."

A new regulation that went into effect Aug. 18, 2003, implements another FTC recommendation, to tighten the patent submission and listing process so that only appropriate patents are submitted to the FDA. To help prevent unfair competition, the regulation clarifies the types of patents that must be submitted to the FDA. Companies must submit patent information on active ingredients, drug formulations and compositions, and approved uses of a drug. Certain patents, such as those for packaging claims, are among those that cannot be submitted. More detailed information will now be required on patent submissions, and false statements could lead to criminal charges.

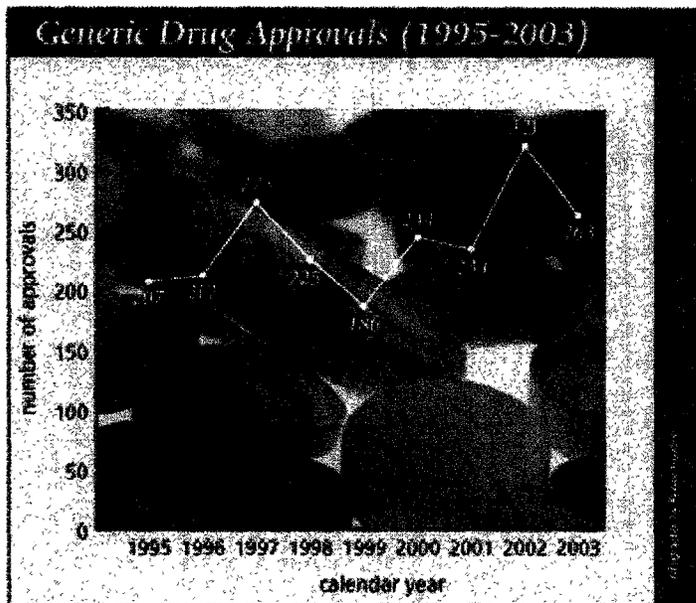
Kathleen Jaeger, GPhA president and chief executive officer, praised the announcement of the generic drug regulation and said it complements generic drug access provisions of the Medicare Modernization Act.

"GPhA strongly believes that the administration's initiatives, coupled with substantial legislative measures in the compromise legislation, will ensure that American health care becomes more affordable," Jaeger said in a statement. The legislation overlaps with the FDA's regulation in one area in that it would also prevent multiple 30-month stays in the approval of generic drugs.

In testimony before the Senate Judiciary Committee on June 17, 2003, Bruce N. Kuhlik, PhRMA's senior vice president and general counsel, cautioned against changes that could "undermine incentives for continued pharmaceutical innovation." He said, "The Hatch-Waxman Act of 1984 is achieving its purpose of speeding market entry of generic drugs."

Kuhlik pointed out that since the law was enacted, the generic share of the drug market has soared, and so has the expense of developing new drugs. "Our patent laws and regulations provide a key incentive for continued innovation in medicines," Kuhlik said. "Better treatments and new cures can come only from pharmaceutical research companies, and only if patent incentives are maintained."

#### **More Efficient Reviews**



approval

indicates that final approval of the application is delayed due to patent or exclusivity issues. In 2003, 479 applications were submitted for review. This is up from 392 the year before.

It takes 20 months on average for a new generic drug to be approved by the FDA, and it usually involves multiple review cycles. Very few applications are approved on the first cycle, but about a third are approved on the second cycle. Sometimes multiple review cycles can't be avoided, but the FDA has identified the lack of early communication between generic drug companies and the FDA as one cause for multiple review cycles. With the proposed increases for the generics budget, the FDA plans to increase resources that would make earlier communications possible.

The agency plans to hire more review experts to help speed up the review of generic drug applications so that review time can be reduced by at least two months. The goal is to provide guidance to industry to allow for submission of more complete applications the first time they are submitted, rather than going through multiple review cycles because of problems. Each round of review generally means many months delay in approval.

The new resources, along with other improvements, such as adding another chemistry review division, are expected to reduce the total time to approval for most new generic drugs by three months or more over the next three to five years. One new approach will be to develop an FDA standard for giving generic companies initial feedback on obvious minor deficiencies within 10 days after the first review cycle is completed. Applicants will have an opportunity to respond and amend an application to try to avoid a whole new review cycle.

#### Getting the Word Out

"Generic Drugs: Safe. Effective. FDA Approved." That's one of the slogans featured in an FDA consumer education program to promote consumer confidence in generic drugs. The FDA messages have been featured in newspaper articles, posters, and brochures highlighting the safety and effectiveness of generic drugs. Public service announcements have appeared in major magazines and journals, as well as on the radio. Posters and brochures are being distributed at major pharmacies throughout the country. Advertisements rolled around on buses in Chicago, Los Angeles, and New York, and have appeared on billboards in Michigan.

Consumers want lower-cost options for drugs, according to AARP, a nonprofit organization that addresses the needs of people ages 50 and older. In a recent AARP survey of 1,046 people ages 45 and up, 84 percent said generic drugs are important for controlling drug costs. Most also said they usually choose generics over brand names when generics are

available. And 24 percent reported not being able to afford a prescription drug when no generic was available.

Richard Cole, senior vice president of corporate communications at Blue Cross Blue Shield of Michigan, says in a statewide survey he conducted in the summer of 2001, most people said they believe generic drugs are equivalent to brand-name drugs. "In the past, the conventional wisdom was that if we increased education about generic drugs, it would look like our only motives were to save money for the company," Cole says. "But consumers reported that they saw it as our job to tell them about generic drug options."

In the fall of 2001, Blue Cross Blue Shield invited all Michigan pharmacies to participate in a competition to increase generic dispensing rates. The goal was to increase generic use among Michigan Blues members by one percentage point, which would result in a \$17 million savings for both the company and the customers, Cole says.

Blue Cross Blue Shield challenged pharmacies to develop in-store campaigns and tracked generic dispensing rates. More than 1,000 Michigan pharmacies competed. The prize for the stores with the highest rates: featured spots in a \$1 million advertising campaign with the slogan "Generic Drugs--The Unadvertised Brand." Rite Aid won for the retail chain category and Grand Value Drugs of Detroit won for the independent pharmacy category. Cole estimates that the annual savings for Michigan Blues members was more than \$30 million.

"People don't want a less expensive drug if they think the quality isn't good," Cole says. "When you or a member of your family gets sick, you don't want second best. But you don't have to worry about that with generic drugs."

The FDA's Center for Drug Evaluation and Research would like to hear from organizations interested in partnering with the FDA on its generic drug education program. For more information about a potential partnership, call (301) 827-7503.

### **For More Information**

[FDA's Office of Generic Drugs](#)

[Generic drugs final rule](#)

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### **FDA Requirements for Generic Drugs**

- Generic drugs must have the same active ingredients and the same labeled strength as the brand-name product.
- Generic drugs must have the same dosage form (for example, tablets, liquids) and must be administered in the same way.
- Generic drug manufacturers must show that a generic drug is bioequivalent to the brand-name drug, which means the generic version delivers the same amount of active ingredients into a patient's bloodstream in the same amount of time as the brand-name drug.
- Generic drug labeling must be essentially the same as the labeling of the brand-name drug.
- Generic drug manufacturers must fully document the generic drug's chemistry, manufacturing steps, and quality control measures.
- Firms must assure the FDA that the raw materials and finished product meet specifications of the U.S. Pharmacopoeia, the organization that sets standards for drug purity in the United States.

- Firms must show that a generic drug will remain potent and unchanged until the expiration date on the label before it can be sold.
  - Firms must comply with federal regulations for good manufacturing practices and provide the FDA a full description of facilities they use to manufacture, process, test, package, and label the drug. The FDA inspects manufacturing facilities to ensure compliance.
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### **Approvals for 2003**

Examples of recent first-time generic equivalent approvals for brand-name drugs:

- paroxetine (Paxil) for depression
- gabapentin (Neurontin) for certain kinds of seizures
- mirtazapine (Remeron) for depression
- quinapril (Accupril) for high blood pressure

*(Infographic by Renée Gordon)*

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**ATTACHMENT C**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

FEB 24 2003

Gilbert's  
Attention: Mr. Tim Gilbert  
49 Wellington Street East  
Toronto, Canada M5E 1C9

OGD Control # 03-107

Dear Mr. Gilbert:

This responds to your January 31, 2003, letter regarding FDA's treatment of ANDAs for mirtazapine in light of the agency's January 28, 2003, decision regarding 180-day exclusivity for pending ANDAs for gabapentin. Both the gabapentin and mirtazapine ANDAs raise questions related to whether an ANDA applicant may be eligible for 180-day exclusivity under section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act) with respect to a patent that does not claim an approved use of the listed drug. Your concern is that FDA is treating these ANDAs - which you believe are similarly situated - in an inconsistent fashion. The agency has reviewed the record concerning the gabapentin and mirtazapine ANDAs, and your analysis, and has concluded that the decisions are warranted by the facts and are not inconsistent.

The agency is aware that on February 14, 2003, Torpharm sued FDA in the U.S. District Court for the District of Columbia over FDA's decisions related to the approval of gabapentin ANDAs. This response to your January 31, 2003, letter is being issued subsequent to that lawsuit. However, you should be aware that the agency had prepared its response regarding the differences between the gabapentin and mirtazapine situations before the February 14, 2003, lawsuit was filed. A February 13, 2003, letter from Organon requesting delisting of the '099 patent delayed issuance of the letter while the agency considered the effect, if any, of this request on 180-day exclusivity. The agency revised its letter to address the delisting issue, as described below.

As you know, FDA has determined that no gabapentin ANDA applicant is eligible for 180-day exclusivity as to U.S. Patent Number 5,084,479 (the '479 patent). FDA's determination that no ANDA applicant is eligible for 180-day exclusivity as to the '479 patent was based upon its conclusion that no applicant could legally maintain its paragraph IV certification as to that patent (and thus the patent could be removed from the Orange Book). This outcome is a consequence of the representation by Pfizer, Inc., the holder of the approved NDA for gabapentin capsules and the '479 patent, to FDA on December 13, 2002, disavowing any claim that the '479 patent covered the approved use of gabapentin - epilepsy (as opposed to the unapproved use - neurodegenerative diseases). This representation was confirmed in later correspondence with Pfizer, as well as in the findings of Judge Huvelle in *Purepac Pharmaceutical Co. v. Thompson*, No. 02-1657 (D.D.C. Dec. 16, 2002). The Federal Circuit also confirmed that the '479 patent

Tim Gilbert  
Page 3

from the Orange Book, as requested by Organon, or require a change from paragraph IV certification to section viii statement for mirtazapine ANDA applicants on the basis of a district court decision of non-infringement, where that decision was the result of the ANDA applicant's submission of a paragraph IV certification and successful litigation of the patent claim. In the normal course, FDA would require ANDA applicants with paragraph IV certifications to maintain the certification and leave the patent in the Orange Book for the 180-day period beginning with the court decision, even when the patent holder requests that the patent be removed from the Orange Book, as has happened with Organon.<sup>1</sup>

In the gabapentin case, Torpharm prevailed on January 16, 2003, in its paragraph IV litigation on the '479 patent in *Warner-Lambert* and thus might appear to be entitled to exclusivity. Thus, although Pfizer notified FDA on January 17, 2003, that it agreed to withdraw the '479 patent, FDA reexamined, in its January 28 letter, Torpharm's entitlement to 180-day exclusivity on that patent before delisting it. See 21 C.F.R. § 314.94 (a)(12)(viii)(B). As noted in FDA's January 28 letter, Pfizer clarified in its December 13 letter that the '479 patent claims the use of gabapentin to treat neurodegenerative diseases, not epilepsy. All of the relevant ANDAs seek approval for gabapentin products labeled for use in treating epilepsy. In light of Pfizer's December 13 clarification, no gabapentin ANDA applicant could retain a paragraph IV certification to the '479 patent. This conclusion was consistent with Judge Huvelle's findings. As FDA pointed out in its January 28 letter, if the '479 patent had remained in the Orange Book, Judge Huvelle's decision would have enabled every gabapentin ANDA applicant to submit a section viii statement to that patent. Thus, even if Torpharm could retain its paragraph IV certification, every other ANDA applicant could change a paragraph IV certification to a section viii statement, and thus deny Torpharm any exclusivity.

Therefore, the agency reaffirms that no ANDA applicants are eligible for exclusivity as to the now delisted '479 patent for gabapentin. Moreover, the '099 patent will remain in the Orange Book for the 180-day period following the district court decision, and mirtazapine ANDA applicants remain eligible for exclusivity as to that patent.

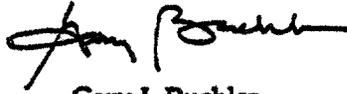
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<sup>1</sup> The mirtazapine ANDAs are governed by the "new" definition of the court decision trigger, which is described in FDA's *Guidance Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act*, March 2000. As to mirtazapine, the December 18, 2002, district court decision in *Organon v. Teva* triggers the running of exclusivity. In contrast, if any gabapentin ANDA applicant were eligible for exclusivity as to the '479 patent, such exclusivity would have been triggered by the *Warner-Lambert* appellate decision, as the gabapentin ANDAs are governed by the "old" definition of court decision as described in the guidance.

Tim Gilbert  
Page 4

If you have questions regarding these issues, please contact Ms. Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, (301) 827-5845.

Sincerely yours,



Gary J. Buehler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

cc: Marcy Macdonald, U.S. Agent for TorPharm/Apotex  
Arthur Y. Tsien, counsel for Torpharm/Apotex  
William A. Rakoczy, counsel for Torpharm/Apotex  
Charles J. Raubicheck, counsel for Purepac  
Andrew M Berdon, counsel for Purepac  
Daniel E. Troy, OCC

**ATTACHMENT D**



MAY 28 2003

Daniel J. Tomasch, Esq.  
Orrick, Herrington & Sutcliffe LLP  
666 Fifth Ave.  
New York, NY 10103

Dear Mr. Tomasch:

This responds to your letter of May 23, 2003, on behalf of Alcon Laboratories, Inc., regarding 180-day exclusivity under Section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act with respect to the patents listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) as protection for Allergan's Alphagan (brimonidine tartrate) Ophthalmic Solution. Alcon has a pending ANDA for brimonidine, as does Bausch & Lomb.

Alcon's position is that no 180-day exclusivity should attach to any of the patents listed for brimonidine, because certain court decisions have found that none of those patents claim approved uses of Alphagan, and thus they should not have been listed in the Orange Book. More importantly, given the posture of this matter, Alcon argues that no party is eligible for 180-day exclusivity for U.S. Patent No. 6,465,464 ('464 patent'). FDA has reviewed your submission and disagrees with your analysis.

**I. Background on Brimonidine Patent Litigation.**

Your letter cites recent private patent litigation as a basis for denying 180-day exclusivity as to the '464 patent for brimonidine. Allergan initially obtained U.S. Patents 6,194,415 ('415 patent) and 6,248,741 ('741 patent) which claimed a method of using brimonidine as a neuroprotective agent to treat glaucoma. After Alcon and Bausch & Lomb filed ANDAs for brimonidine with paragraph IV certifications to the '415 and '741 patents, Allergan separately sued Alcon and Bausch & Lomb for patent infringement in the U.S. District Court for the Central District of California. On May 8, 2002, the court granted summary judgment to Alcon. *Allergan, Inc. v. Alcon Laboratories, Inc.*, 200 F. Supp. 2d 1219, 1223 (C.D. Cal. 2002) (*Allergan I*). Shortly thereafter, in a June 4, 2002, Order, the court granted summary judgment to Bausch & Lomb, referencing its May 8, 2002, Order granting summary judgment to Alcon.

On March 28, 2003, the Federal Circuit affirmed the decision of the district court. *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322 (Fed. Cir. 2003). On May 22, 2003, the Federal Circuit denied Allergan's petition for rehearing *en banc*.

After the district court decision on the '415 and '741 patents was issued and while the appeal was pending, Allergan listed the '464 patent, which also covered the use of brimonidine for

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Brimonidine Tartrate  
Patent & Exclusivity

neuroprotection. This patent was also the subject of paragraph IV certifications by both Alcon and Bausch & Lomb. Allergan filed patent infringement litigation in the U.S. District Court for the District of Delaware. Alcon and Bausch & Lomb filed a declaratory judgment action in the U.S. District Court for the Central District of California. The Delaware court granted the ANDA applicants' motion to transfer the patent infringement case to California. On March 20, 2003, the California court entered an Order and decision finding that the '464 patent was not infringed under either 35 U.S.C. 271(e)(2) or 271(b) for the same reasons as in *Allergan I. Alcon Labs., Inc. v. Allergan, Inc.*, 02-1192 (C.D. Cal. March 20, 2003) ("*Allergan II*").

II. Eligibility for 180-Day Exclusivity is Based on Each Patent.

Alcon contends that because *Allergan II* was decided on the same principles as *Allergan I*, any exclusivity should have been awarded to Alcon after it won summary judgment in *Allergan I*. Thomasch letter at 2. That argument is contrary to FDA's longstanding position that the first ANDA to submit a paragraph IV certification for each of the patents listed in the Orange Book for a drug product has been, or is, eligible for 180-day exclusivity as to that patent. In responding to a 1999 citizen petition related to approval of ANDAs for the drug product cisplatin, FDA construed the pertinent regulations, 21 C.F.R. § 314.107(c)(1) & (2), and determined that eligibility for 180-day exclusivity would be based on who filed the first paragraph IV certification for each listed patent. Under FDA regulations, a "subsequent" ANDA with a paragraph IV certification relating to the "same patent" as a previous ANDA paragraph IV certification is not eligible for approval until the first ANDA's exclusivity has run. 21 CFR § 314.107(c)(1).

The regulation's reference to the "same patent" as opposed to "any" patent or "all patents related to the same drug" means that eligibility for exclusivity is based upon the particular patent at issue and not the drug product as a whole. As a result, multiple applicants may be eligible for periods of exclusivity for a single drug product. The agency has referred to this approach to determining eligibility for exclusivity as a "patent-by-patent" or "patent-based" analysis. That is, the first applicant with a paragraph IV certification for each listed patent is separately eligible for 180-day exclusivity based on that patent.

The only patent currently relevant to 180-day exclusivity and the timing of brimonidine ANDA approvals is the '464 patent. In a May 21, 2003, letter, FDA informed Alcon, Bausch & Lomb, and Allergan that the May 8, 2002, and June 4, 2002, decisions involving the '415 patent and '741 patent were court decisions of non-infringement for purposes of permitting ANDA approval. The first of these decisions would also have triggered the running of exclusivity under section 505(j)(5)(B)(iv)(II) for the '415 and '741 patents. The 180-day exclusivity period as to those patents has thus expired.

Accordingly, the first ANDA applicant to submit a paragraph IV certification to each of the patents has been eligible for 180-day exclusivity as to that patent, and exclusivity based on the '464 patent is not foreclosed by the earlier decisions on the '415 and '741 patents.

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III. The Facts Involving Exclusivity for Gabapentin Were Significantly Different.

Alcon argues that the facts regarding the patents for brimonidine are the same as those related to the '479 patent for gabapentin, which was at issue in *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003), *Purepac Pharm. Co. v. Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002), and *TorPharm, Inc. v. Thompson*, Civil Action No. 03-0254 (D.D.C. April 25, 2003) (*Purepac* and *TorPharm* have been consolidated on appeal, which is pending in the D.C. Circuit).

A. Background on Gabapentin

*Purepac* and *TorPharm* submitted ANDAs for gabapentin, and the innovator Warner-Lambert sued them both. With respect to one method of use patent (the '479 patent), the Federal Circuit found that *TorPharm* did not infringe the patent because it was not seeking approval for the use claimed in the patent. *Warner-Lambert Co.*, 316 F.3d 1348.

In the meantime, *Purepac* had filed a section viii statement for the '479 gabapentin patent, that is, a statement that a method-of-use patent submitted in connection with an NDA does not claim any use of the drug product for which the applicant is seeking approval, pursuant to 21 U.S.C. § 355(j)(2)(A)(viii); 21 C.F.R. § 314.94(a)(12)(iii). When FDA told *Purepac* that its section viii statement was improper and it would not approve its ANDA, *Purepac* sued FDA (and *TorPharm* intervened) seeking to require FDA to approve its ANDA and not approve an ANDA that contained a paragraph IV certification to that patent. During that litigation, the innovator essentially admitted to FDA that it had violated FDA regulations in submitting the patent for listing that did not claim an approved use.

The district court determined that the patent did not claim an approved use of the drug, and an ANDA applicant could therefore submit a section viii statement as to that patent. *Purepac Pharm. Co.*, 238 F. Supp. 2d 191. In subsequent administrative proceedings, FDA determined that no ANDA applicant was eligible for 180-day exclusivity as to the '479 patent. As the agency described in a January 28, 2003, letter to the ANDA applicants, because the patent owner had informed FDA directly that the '479 patent did not claim an approved use of gabapentin, and because the *Purepac* court had specifically found that an ANDA applicant could submit a section viii statement to the patent, no ANDA applicant could maintain a paragraph IV certification as to the '479 patent and no one would be eligible for 180-day exclusivity as to that patent. See January 28, 2003 letter from Gary Buehler to Apotex Corp. and *Purepac Pharmaceutical Co.* (attached).

*TorPharm* challenged this decision as inconsistent with FDA's treatment of 180-day exclusivity for a patent listed for mirtazapine. In the case of mirtazapine, a district court had found in private patent infringement litigation that the listed patent claimed only unapproved uses of mirtazapine. *Organon, Inc. and Akzo Nobel N.V. v. Teva Pharmaceuticals, Inc.*, C.A. 01-2682 (Dec. 18, 2002 D.N.J.); appeal docketed, CA 03-1218 (Fed. Cir.). Nevertheless, FDA granted the first mirtazapine ANDA applicant to file a paragraph IV certification to that patent 180-day exclusivity. As described in a February 24, 2003 letter to Tim Gilbert, counsel for

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Brimonidine Tartrate  
Patent & Exclusivity

Apotex/TorPharm (attached), FDA's practice under section 505(j)(5)(B)(iv) and 21 C.F.R. § 314.107(c) is to grant 180-day exclusivity to the ANDA applicant that was first to file a valid paragraph IV certification to a listed patent, and for that exclusivity to be triggered, in certain cases, by a court decision in litigation resulting from a paragraph IV certification finding the patent invalid or not infringed. It would be unreasonable, and contrary to FDA regulations and practice, to either remove challenged patents from the Orange Book or require a change from paragraph IV certification to section viii statement for the ANDA applicants on the basis of a district court decision of non-infringement, where that decision was the result of the ANDA applicant's submission of a paragraph IV certification and successful litigation of the patent claim. To do so would vitiate the 180-day exclusivity. Thus, the agency would not rely on a favorable decision obtained by an ANDA applicant in paragraph IV litigation to eliminate that applicant's exclusivity. Gabapentin, however, involved additional circumstances other than the court decision in paragraph IV litigation.

TorPharm sued FDA and Purepac intervened. The district court upheld FDA's decisions contained in the January 28 and February 24, 2003, letters. *TorPharm, Inc. v. Thompson*, Civil Action No. 03-0254 (D.D.C. April 25, 2003). The court explained why a decision in the underlying paragraph IV litigation that the patent did not claim an approved use would not vitiate exclusivity:

If a judicial determination of non-infringement in patent litigation triggered by the use of a paragraph IV certification comes to serve as a basis for the subsequent FDA determination that the patent in question should no longer be listed – and therefore that a paragraph IV certification, and its corresponding promise of exclusivity, is no longer appropriate – the incentive structure created by the Hatch-Waxman Amendments would be turned on its head... It would be cruelly ironic, and perverse, to use an ANDA applicant's success in such an infringement action as the basis for denying exclusivity to that applicant.

*TorPharm*, slip opinion at n. 15. The court noted that the agency's decision to delist the patent in gabapentin was compelled by the court's earlier decision in *Purepac* (which was not paragraph IV litigation) that required FDA to accept Purepac's section viii statement, rather than the result of the *Warner-Lambert* decision in the patent litigation.

B. Comparison of Gabapentin and Brimonidine.

Alcon argues that the gabapentin outcome controls the outcome in brimonidine, and no ANDA applicant is eligible for 180-day exclusivity as to the '464 patent. Alcon cites the court's finding in *Allergan II* that the '464 patent does not claim an approved use for Alphagan. Alcon asserts that the *Allergan II* decision "implicitly recognizes that the '464 Patent, since it does not cover 'an approved or pending use of the new drug' (21 C.F.R. § 314.53(b)), should not have been listed in the Orange Book." Thomasch letter at 8.

As explained above, a court decision in private patent litigation finding that a listed patent does not claim an approved use for the listed drug *does not* render the first ANDA applicant to file a

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Brimonidine Tartrate  
Patent & Exclusivity

paragraph IV certification as to that patent ineligible for exclusivity. The facts involved in the mirtazapine case resemble those involved for brimonidine in that there was a decision in the paragraph IV litigation that the patent did not claim an approved use. Thus, the reasoning underlying the agency's treatment of the mirtazapine patent applies as well to the concerns Alcon has raised regarding the '464 patent for brimonidine.

The circumstances surrounding the gabapentin patent were different in that there had been an admission by the patent holder to FDA that the '479 patent does not claim an approved use, and a district court decision in a case brought against FDA in which the court expressly found that a section viii statement is the correct submission for the listed patent. Neither the *Purepac* court's narrow decision based on unique factual circumstances involving gabapentin, nor FDA's decision regarding exclusivity as to the '479 gabapentin patent required a change in established FDA practice regarding 180-day exclusivity. As the *TorPharm* court held in distinguishing the gabapentin and mirtazapine, "[w]hatever similarities may exist . . . , one crucial difference remains: in the [mirtazapine] case, there was no court decision requiring the FDA to accept a section viii statement with respect to the patent in question." 2003 WL 1957490 at 14.

Alcon further asserts that, in light of *Purepac* and *Warner-Lambert*, Alcon and Bausch & Lomb should have been permitted to submit section viii statements to the '464 patent. Bausch & Lomb should not be permitted to benefit from an improperly submitted paragraph IV certification. Thus, the paragraph IV certifications should be deemed to be section viii statements and no exclusivity should attach.

FDA understands that Alcon and Bausch & Lomb may well have believed that the '464, '415, and '741 patents should not have been listed in the Orange Book. However, the patents were submitted to the agency accompanied by the declaration required by 21 CFR §314.53, and the patents remain in the Orange Book. As the agency has stated repeatedly, an ANDA applicant may not submit a section viii statement unless it "carves out" its labeling to correspond to a listed method of use patent. If the ANDA proposes to duplicate the innovator's label, it must certify to the listed use patents. The district court's narrow decision in *Purepac* on the specific facts in the gabapentin case has not changed the agency's practice. Thus, whatever their views on the propriety of the listing of the brimonidine use patents, including the '464 patent, Alcon and Bausch & Lomb were required to submit paragraph IV certifications, rather than section viii statements.

Furthermore, as FDA stated in the mirtazapine case, it would be unreasonable to either remove challenged patents from the Orange Book or require a change from paragraph IV certification to section viii statement for the ANDA applicants on the basis of a district court decision of non-infringement, where that decision was the result of the ANDA applicant's submission of a paragraph IV certification and successful litigation of the patent claim. Unlike gabapentin, there has been no court decision requiring FDA to accept section viii statements for one or more of the brimonidine patents.

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Moreover, both applicants submitted paragraph IV certifications and there is no reason to retroactively deem them otherwise. Whether or not the applicants believe they would file paragraph IV certifications today, based on the current state of the law, is simply irrelevant. Therefore, the courts' decisions in the underlying paragraph IV litigation that the '415, '741 and '464 patents do not claim approved uses of brimonidine do not eliminate exclusivity on those patents.

IV. The Date of FDA Receipt of the Hard-Copy of the Paragraph IV Certification Governs Exclusivity.

Finally, your letter briefly raised the question of whether the date of a facsimile submission from Alcon would serve for calculating when Alcon submitted its paragraph IV certification to the '464 patent. FDA has reviewed its regulations and practices, and has determined that it relies only on the date stamped copy of a paragraph IV certification submitted to the addresses described in 21 CFR § 314.440. Items submitted through the addresses listed in the regulation are date stamped upon submission. FDA relies on the date stamped document submitted to these addresses for determining when a paragraph IV certification was submitted. The regulation does not provide for submission by facsimile. Facsimile copies have not been and are not used by the Office of Generic Drugs for determining receipt dates for patent certifications. Therefore, the date stamp on Alcon's paragraph IV certification submitted in hard copy to the address in 21 CFR § 314.440 will control for purposes of determining eligibility for 180-day exclusivity.

Sincerely,



Gary Buchler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Enclosures:

1. January 28, 2003 Letter to Apotex & Purepac
2. February 24, 2003 Letter to Gilbert

cc: Elizabeth Dickinson, Associate Chief Counsel for Drugs  
Thomas Scarlett, Counsel for Bausch & Lomb