IVAX

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

Re: 180-Day Exclusivity for ANDA 76-052

CITIZEN PETITION

Introduction

The undersigned, on behalf of IVAX Pharmaceuticals, Inc., (IPI) submits this petition under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) to request that the Food and Drug Administration (FDA) not approve ANDAs for simvastatin tablets, 5 mg, 10 mg, 20 mg, and 40 mg (simvastatin tablets) until IPI's 180-day exclusivity under ANDA No. 76-052 has expired. Under Mova Pharm. Corp. v. Shalala and 21 C.F.R. § 314.107(c), IPI's eligibility for 180-day exclusivity was established when IPI submitted the first substantially complete ANDA for simvastatin tablets containing Paragraph IV certifications to U.S. Patent Nos. RE 36481 and RE 36520 (the '481 and '520 patents). When eligibility for 180-day exclusivity is established, FDA gives effect to it by not delisting patents to which Paragraph IV certifications have been made until eligibility is lost or 180-day exclusivity has expired. FDA has removed the '481 and '520 patents from the Orange Book. Therefore, subsequent applicants will be permitted to omit Paragraph IV certifications from simvastatin ANDAs. Approval of those ANDAs would violate IPI's right to 180-day exclusivity.

A. Action Requested

IPI petitions FDA to:

2005P-0008 CP1

1. Not approve subsequent ANDAs for simvastatin tablets for 180 days from the date of first commercial marketing of simvastatin tablets under IPI's ANDA No. 76-052.

2. Reinstate the '481 and '520 patents in the Orange Book and require subsequent ANDAs for simvastatin tablets to contain certifications to the '481 and '520 patents.

B. Statement of Grounds

1. Statutory and regulatory framework for 180-day exclusivity

a. Patent listing and certification. Applicants for NDAs must submit information on patents that claim the drug or a use of the drug subject to the NDA. FDCA §§ 505(b)(1), (c)(2); 21 C.F.R. § 314.53. Based on this information, FDA lists patents in the Orange Book. FDCA § 505(j)(7)(A)(iii).

Applicants for ANDAs are required to make certifications to any listed patent, or state that a listed patent does not cover a use for which the ANDA applicant is seeking approval. FDCA § 505(j)(2)(A)(vii) and (viii). FDA's regulations specify the criteria for an accurate patent certification. § 314.94(a)(12). Certifications must be made despite disagreement about the accuracy or relevance of the patent information listed in the Orange Book. §§ 314.53(f), 314.94(a)(12)(vii). Patent certifications may be amended at any time, and must be amended if they are no longer accurate. § 314.94(a)(12)(viii).

b. Withdrawal of patents from the Orange Book. The FDCA and FDA's regulations do not specify a procedure for removal of a patent listing from the Orange Book prior to the submission of a Paragraph IV certification. When the right to a 180-day exclusivity period has accrued to an ANDA applicant, however, FDA's regulations prohibit the removal of a patent from the Orange Book for as long as the ANDA applicant remains eligible for 180-day exclusivity, the patent expires, or the 180-day exclusivity period has elapsed. § 314.94(a)(12)(viii)(B). The prohibition against delisting a patent in this circumstance is for the sole purpose of enforcing an ANDA

applicant's right to 180-day exclusivity, and is not based on the accuracy or relevance of the patent information. Therefore, the NDA applicant has no say in the listing of a patent to enforce 180-day exclusivity after an ANDA applicant becomes eligible for it.

c. 180-day exclusivity. Under FDCA § 505(j)(5)(B)(iv),[1] an ANDA that contains a Paragraph IV patent certification and is for a drug for which a previous ANDA has been submitted containing such a certification cannot be made effective for 180 days from the earlier of the first commercial marketing of the drug under the previous ANDA or a court decision of patent invalidity or noninfringement.[2] FDA's regulations implementing the 180-day exclusivity provision were issued in 1994.

d. The mechanics of 180-day exclusivity. To provide 180-day exclusivity to the previous, or first-filed, ANDA, the 1994 regulations incorporated the same mechanism as the statute: subsequent ANDAs that contained Paragraph IV certifications could not be approved for 180 days after a triggering sale or court decision. Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59

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1 This provision of the FDCA was added to the FDCA by the 1984 Hatch-Waxman Amendments. The provision was amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA). Under section 1102(b) of the MMA, the 1984 version of the 180-day exclusivity provision applies to ANDAs that reference a listed drug for which a Paragraph IV certification was made before December 8, 2003, the date of enactment of the MMA. IPI's ANDA for simvastatin tablets included Paragraph IV certifications to the '481 and '520 patents when it was submitted on December 14, 2000. Therefore, all references in this petition are to § 505(j)(5)(B)(iv) as enacted in 1984, prior to the amendments made by the MMA.

2 Although the pre-MMA version of subsection (B)(iv) applies when a Paragraph IV certification was made prior to December 8, 2003, section 1102(b)(3) of the MMA reinstated FDA's original interpretation of the court decision trigger for 180-day exclusivity for Paragraph IV ANDAs for which neither of the triggering events under subsection (B)(iv) occurred before December 8, 2003. For those ANDAs, 180-day exclusivity is triggered by a court of appeals decision, not by a district court decision, in cases where the patent owner has appealed a decision in favor of the ANDA applicant.

Fed. Reg. 50,338, 50,367 (Oct. 3, 1994) (§ 314.107(c)). For this mechanism to work as Congress intended, subsequent ANDAs had to continue to contain Paragraph IV certifications. Patent certifications were required only for patents listed in the Orange Book. Therefore, to support certifications that would make subsequent ANDAs ineligible for approval during the 180-day exclusivity period, patents that were the basis for 180-day exclusivity had to continue to be listed.

Given this mechanism for providing the 180-day exclusivity period, there was an obvious potential for conflict between the right of the applicant for the first-filed ANDA (or first applicant) to 180-day exclusivity and the NDA applicant's usual control of patent listings. FDA described the problem in responding to a comment on proposed § 314.94(a)(12)(viii). That provision authorized an ANDA applicant to amend a patent certification at any time, and required the certification to remain accurate. The comment noted that the rules for changing patent certifications should take into account "a prior IV certificant's exclusivity rights during the remaining lifetime of the patent." 59 Fed. Reg. at 50,348. That is, a subsequent applicant should not be able to amend a Paragraph IV certification in a way that undermined a first applicant's 180-day exclusivity.

In response to the comment, FDA stated:

> [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. To ensure that this 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 § 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.

Id.

FDA thus recognized that 180-day exclusivity depended on subsequent ANDAs continuing to include Paragraph IV certifications. FDA also recognized that a first applicant's right to 180-day exclusivity could not be enforced if NDA applicants were permitted to remove patents during the 180-day period because subsequent ANDA applicants could delete Paragraph IV certifications to those patents. To protect the first applicant's right to 180-day exclusivity, FDA revised § 314.94(a)(12)(viii) to prohibit both changing Paragraph IV certifications and removing patents from the Orange Book until FDA determined that no applicant was, or was any longer, entitled to 180-day exclusivity.

The conditions for entitlement to 180-day exclusivity were stated in a different regulation, § 314.107(c), which was cross-referenced in § 314.94(a)(12)(viii)(B). At the time the 1994 final regulations were issued, FDA took the position that eligibility for 180-day exclusivity was conditioned on the ANDA applicant's having "successfully defended against" a Paragraph IV patent infringement lawsuit. 59 Fed. Reg. at 50,367. The restrictions in § 314.94(a)(12)(viii) reflected that position. Thus, Paragraph IV certifications could not be changed "if a patent infringement suit has been filed against another Paragraph IV applicant," and a patent could not be delisted if it "is the subject of a lawsuit under § 314.107(c)." 59 Fed. Reg. at 50,365-66.

As the preamble made clear, the prohibition against patent delistings was simply a component of the statutory mechanism for enforcing eligibility for 180-day exclusivity. Patents had to remain listed so that subsequent ANDAs would be required to certify to them and thus be subject to deferral of approval under subsection (B)(iv). The "subject of a lawsuit" limitation on prohibited patent delistings merely restated FDA's successful defense/lawsuit eligibility condition in § 314.107(c) as issued in 1994. If the eligibility conditions in § 314.107(c) changed, the circumstances in which patents would be

required to remain listed under § 314.94(a)(12)(viii)(B) would necessarily have to change to correspond with the modified eligibility conditions.

e. Eligibility for 180-day exclusivity. To qualify for 180-day exclusivity under FDA's 1994 regulations, an applicant that was first to submit a substantially complete ANDA with a Paragraph IV certification had to have "successfully defended" against a patent infringement lawsuit brought in response to the Paragraph IV certification. 59 Fed. Reg. at 50,367 (§ 314.107(c)). Prior to issuance of the final regulations, eligibility for 180-day exclusivity was conditioned on the ANDA applicant's having been sued for patent infringement, without regard to the success of its defense. See 54 Fed. Reg. 28,872, 28,929. In either case, a first-filed Paragraph IV ANDA did not qualify for 180-day exclusivity unless the patent owner filed an infringement lawsuit.

In January 1997, the successful defense requirement for 180-day exclusivity was invalidated. Mova Pharm. Corp. v. Shalala, 955 F. Supp. 128 (D.D.C. 1997). In April 1998, the court of appeals affirmed the district court. Id., 140 F.3d 1060 (D.C. Cir. 1998) (Mova). In June 1998, FDA issued a guidance for industry[3] stating that it would not enforce § 314.107(c)(1) but would make 180-day exclusivity decisions on a case-by-case basis directly under the statute. The Mova Guidance said the agency would not impose either a successful defense or a lawsuit requirement on 180-day exclusivity. In November 1998, FDA removed the successful defense requirement from § 314.107(c). 63 Fed. Reg. 59,710 (Nov. 5, 1998). Under the regulation as revised, an ANDA applicant was entitled to 180-day exclusivity if it submitted a substantially complete ANDA with a Paragraph IV certification, whether or not it was sued for patent infringement. In December 1998, the Purepac decision upheld the revised regulation's omission of a

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[3] Guidance for Industry: 180-Day Generic Drug Exclusivity (June 1998) (Mova Guidance).

lawsuit requirement for 180-day exclusivity. Purepac Pharm. Co. v. Friedman, 162 F.3d 1201 (D.C. Cir. 1998).[4]

The Mova case, and FDA's response to it, were focused on the conditions of eligibility for 180-day exclusivity, not on the administrative mechanism for preserving a first applicant's eligibility once the conditions were met. Although, in light of Mova, FDA revised § 314.107(c)(1) to eliminate any lawsuit or successful defense eligibility requirement for 180-day exclusivity, the agency did not revise § 314.94(a)(12)(viii) to reflect that change. As a result, § 314.94(a)(12)(viii)(B) continues to describe the prohibition against patent delisting to enforce 180-day exclusivity as relating to a "patent that is the subject of a lawsuit under § 314.107(c)." However, the function of the prohibition is not to prevent the delisting of patents that are in litigation. Its function is to prevent the delisting of patents when a first applicant is eligible for 180-day exclusivity under the criteria stated in § 314.107(c) and a patent must remain listed to enforce that eligibility. Eligibility under § 314.107(c) no longer requires a lawsuit. Therefore, the prohibition against patent delisting under § 314.94(a)(12)(viii) cannot be limited to patents that are the subject of a lawsuit under § 314.107(c).

f. Loss of eligibility for 180-day exclusivity. FDA has identified specific circumstances in which a first-filed ANDA applicant loses eligibility for 180-day exclusivity prior to a triggering event.

(1) The first applicant withdraws its ANDA. See Proposed Triggering Period Regulations, 64 Fed. Reg. 42,873, 42,875 (Aug. 6, 1999) (proposal withdrawn for other reasons, 67 Fed. Reg. 66,593 (Nov. 1, 2002)).

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[4] Section 314.107(c) applies to pre-MMA Paragraph IV ANDAs. Guidance for Industry: Listed Drugs, 30-Month Stays, and Approval of ANDAs and 505(b)(2) Applications Under Hatch-Waxman, as Amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003: Questions and Answers at 11 (Oct. 2004).

(2) The Paragraph IV certification is voluntarily withdrawn or changed. Id.; Mylan Pharm. Inc. v. Henney, 94 F. Supp. 2d 36 (D.D.C. 2000).

(3) The first applicant changes the Paragraph IV certification to a Paragraph III certification after losing a patent infringement lawsuit. 64 Fed. Reg. at 42,875, 42,876 (reinterpreting § 314.94(a)(12)(viii)(A)).

(4) The first applicant does not actively pursue approval of the ANDA. § 314.107(c)(3).

(5) The patent expires. See Letter from J. Woodcock to R. Green, et al. (Aug. 2, 1999)[5] (Dkt. No. 99P-1271) (a Paragraph IV certification must be amended to a Paragraph II certification); 64 Fed. Reg. at 42,877; Dr. Reddy's Lab., Inc. v. Thompson, 302 F. Supp. 2d 340, 350-60 (D.N.J. 2003).

(6) The first applicant voluntarily relinquishes its eligibility. See Letter from W. Hubbard to B. Rein, et al. (July 2, 2004) (Dkt. No. 04P-0227), 64 Fed. Reg. at 42,881.

A request by an NDA applicant to remove a patent from the Orange Book after eligibility for 180-exclusivity has been established could not lawfully be, and has never been identified by FDA as, a circumstance in which eligibility is lost by a first applicant.

g. FDA will continue to list patents to enforce 180-day exclusivity without regard to an NDA applicant's request to delist them. Initial eligibility for 180-day exclusivity depends on the NDA sponsor's decision to list a patent in the Orange

[5] A copy of this letter is attached as Attachment A. It is not currently accessible from FDA's website. Copies of two other FDA letters cited in this petition that are not accessible from FDA's website are also attached.

Book, to which a Paragraph IV certification is then made. However, once eligibility is established, FDA's position has consistently been not to remove a patent from the Orange Book list if continued listing is required to support Paragraph IV certifications necessary to enforce 180-day exclusivity, irrespective of the NDA applicant's opinion about the relevance of the patent or its preference as to listing the patent. FDA's position has been stated in several cases in which continued patent listing to support 180-day exclusivity has been the subject of dispute.

In 2002, Purepac sued to require FDA to accept a section (viii) statement in lieu of a Paragraph IV certification to Warner-Lambert's Orange Book listed '479 patent claiming an unapproved use of gabapentin. TorPharm had submitted a Paragraph IV certification to the '479 patent, and therefore would have had priority over a Purepac Paragraph IV certification to the '479 patent. Paragraph IV priority as to Warner-Lambert's '482 patent was unclear. In Purepac Pharm. Co. v. Thompson, 238 F. Supp. 2d 191 (D.D.C. 2002), the court ruled that FDA had to accept Purepac's section (viii) statement, but did not decide whether TorPharm could simultaneously maintain its Paragraph IV certification. In parallel with the Purepac case, the patent infringement litigation went against Warner-Lambert. Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348 (Fed. Cir. 2003). Pfizer (Warner-Lambert's successor) then asked FDA to withdraw the '479 patent. Pfizer had earlier stated to FDA that the '479 patent did not claim an approved use of gabapentin.

TorPharm argued that its Paragraph IV certification to the '479 patent entitled it to 180-day exclusivity. On that view, Pfizer's request to delist the '479 patent should have been denied under § 314.94(a)(12)(viii)(B). However, FDA decided that removal of the '479 patent would not affect 180-day exclusivity, because TorPharm was not eligible for it.[6] FDA pointed to Pfizer's statement that the '479 patent did not claim an approved use

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[6] Letter from G. Buehler to M. Macdonald, et al. (Jan. 28, 2003) (available online at http://www.fda.gov/cder/ogd/75350.479pat.pdf).

of gabapentin, to the district court's ruling that Pfizer had never said otherwise, and to the district court's decision that FDA had to accept Purepac's section (viii) statement. FDA concluded that ANDAs for gabapentin, including TorPharm's, had to contain section (viii) statements and could not contain Paragraph IV certifications. Therefore, TorPharm was not eligible for 180-day exclusivity, and Pfizer's '479 patent could be delisted. FDA's action was upheld in Purepac Pharm. Co. v. Thompson, 354 F.3d 877 (D.C. Cir. 2004).

In two factually similar cases, FDA reached a different conclusion. Organon listed the '099 patent on a method of using mirtazapine. In patent infringement litigation against Paragraph IV ANDA applicants Purepac and Teva, a district court held there was no Paragraph IV infringement because the method claimed by the '099 patent was not an approved use of mirtazapine under Organon's NDA.[7] Organon then asked FDA to remove the '099 patent from the Orange Book. Organon did not affirmatively state that the patent did not claim an approved use of mirtazapine. FDA refused to remove the '099 patent from the Orange Book until Purepac's or Teva's 180-day exclusivity expired.[8]

The second case involved brimonidine tartrate, for which Allergan submitted several patents that claimed a use found by the district court in patent litigation not to be approved in the NDA for Allergan's Alphagan and which, therefore, were not infringed by Alcon's and Bausch & Lomb's Paragraph IV certifications.[9] Allergan did not request removal of the patents from the Orange Book. FDA rejected Alcon's request to convert the Paragraph IV certifications into section (viii) statements.[10] Alcon said the case was

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7 Organon Inc. v. Teva Pharm., Inc., 244 F. Supp. 2d 370 (D.N.J. 2002).

8 See Letter from G. Buehler to T. Gilbert (Feb. 24, 2003) (Attachment B).

9 Allergan, Inc. v. Alcon Laboratories, Inc., 324 F.3d 1322 (Fed. Cir. 2003).

10 Letter from G. Buehler to D. Tomasch (May 28, 2003) (Attachment C).

similar to gabapentin. FDA said it was similar to mirtazapine and would be disposed of the same way. Bausch & Lomb's ANDA was given 180-day exclusivity.

The 180-day exclusivity issues raised by the gabapentin, mirtazapine, and brimonidine cases occurred after FDA changed § 314.107(c) to eliminate the lawsuit/successful defense requirement for 180-day exclusivity in response to the Mova decision. In all three cases, however, the Paragraph IV certifications that created the disagreement did, in fact, lead to patent infringement lawsuits. For this reason, the agency and the drug companies had no reason to consider the continued inclusion of a lawsuit requirement in § 314.94(a)(12)(viii) for patents to remain listed to enforce 180-day exclusivity. Nevertheless, FDA's decisions were not based on the existence of patent infringement lawsuits. The only issue FDA identified as dispositive was whether a first applicant was eligible for 180-day exclusivity based on a Paragraph IV certification to the listed patents whose removal from the Orange Book was at issue.

We are aware of several instances, prior to the removal of Merck's '481 and '520 patents from the Orange Book, in which FDA has delisted patents that supported post-Mova eligibility for 180-day exclusivity based on a Paragraph IV certification that did not result in a lawsuit.[11] These delistings have not been challenged by ANDA applicants. Possible reasons for this include lack of knowledge of first-filed status, failure to understand the relationship between Mova and the lawsuit condition on the delisting prohibition, and the fact that, where other patents remain listed, a particular delisting may have no practical significance.

As an example of the last situation, FDA delisted a paroxetine patent in 2003, explaining that "[t]here has been no relevant litigation as to the '927 patent, and therefore the '927 patent is being withdrawn from the Orange Book, and will not serve as a basis

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[11] In addition to ANDA No. 76-052, IPI has at least one ANDA that contained a Paragraph IV certification to a patent over which there was no infringement lawsuit and which was subsequently delisted. IPI is evaluating that ANDA with a view toward filing a petition, similar to this petition, to reinstate the patent.

for exclusivity." Letter from G. Buehler to M. Macdonald (July 30, 2003) (available online at http://www.fda.gov/cder/ogd/shared_exclus_paroxetine.htm). Although the quoted explanation misstates the post-Mova requirements – it is precisely to "serve as a basis for exclusivity" that a nonlitigated patent must remain listed under Mova – there was apparently no objection to the delisting of the '927 patent. There were, however, many paroxetine patents involved in the controversy between the NDA and ANDA applicants and FDA. Because FDA's delisting of the '927 patent would have had little, if any, practical significance, the action would have been unlikely to provoke a challenge.

These uncontested delistings are not evidence of a considered agency practice of routinely delisting nonlitigated patents despite eligibility for 180-day exclusivity. Rather, they result from the erroneous assumption that the prohibition against patent delisting has some purpose other than to implement the eligibility conditions for 180-day exclusivity and can therefore be applied in a manner inconsistent with Mova.

2. Facts relating to IPI's simvastatin ANDA

The listed drug for simvastatin tablets is Zocor, made by Merck & Co., Inc. (Merck). The NDA for Zocor was approved on December 23, 1991. The 1992 Orange Book listed U.S. Patent No. 4444784 (the '784 patent) for Zocor. The 2000 Orange Book listed the '481 and '520 patents. According to the use codes in the Orange Book, all three patents claim methods of treating hyperlipidemia or hypercholesterolemia. Zocor is approved to treat those conditions.

On December 14, 2000, IPI submitted ANDA No. 76-052 for the 5 mg, 10 mg, 20 mg, and 40 mg dosage strengths of simvastatin. The ANDA contained a Paragraph III certification to the '784 patent and Paragraph IV certifications to the '481 and '520 patents. FDA notified IPI on January 29, 2001, that the ANDA was received as substantially complete. IVAX believes the ANDA was the first substantially complete ANDA for the 5 mg – 40 mg strengths of simvastatin tablets with Paragraph IV certifications to the '481 and '520 patents. (Another applicant was the first to submit such an ANDA for the 80 mg strength of simvastatin.)

IPI timely notified Merck of the Paragraph IV certifications. Merck did not sue IPI for patent infringement. In about September 2004, presumably at Merck's request, FDA removed the '481 and '520 patents from the Orange Book. IPI has not amended its ANDA to omit certifications to the '481 and '520 patents. IPI believes the patents are required to be listed due to IPI's continued eligibility for 180-day exclusivity, and that the Paragraph IV certifications remain appropriate and accurate.

Merck's '784 patent expires on December 23, 2005, with a 6-month pediatric extension until June 23, 2006. The '481 and '520 patents expire July 10, 2007, and May 26, 2009, with pediatric extensions until January 10, 2008, and November 26, 2009.

IPI expects to receive tentative approval of its ANDA in due course and to commence marketing of simvastatin tablets on June 23, 2006.

3. 180-day exclusivity for IPI's ANDA No. 76-052

a. Nothing has terminated IPI's statutory right to maintain its eligibility for 180-day exclusivity for generic simvastatin. Section 505(j)(5)(B)(iv) prohibits approval of an ANDA for 180 days from a triggering event if it contains a Paragraph IV certification and is for a drug for which a previous ANDA has been submitted containing a Paragraph IV certification. FDA and the courts have long recognized that subsection (B)(iv) is not a patent listing and certification provision. Patent listing is governed by FDCA § 505(b)(1) and (c)(2); patent certification, by FDCA § 505(j)(2)(A)(vii).

The purpose of subsection (B)(iv) is unrelated to patent listing and certification. Its purpose is to grant 180-day exclusivity to the first-filed Paragraph IV ANDA applicant. Subsection (B)(iv) refers to ANDAs containing Paragraph IV certifications, but it does so not to impose conditions relating to the presence or absence of patent certifications at a specific point in time. It does so to specify the terms of 180-day exclusivity. Exclusivity is awarded to the ANDA of a first applicant that made a

Paragraph IV challenge to a patent on a listed drug, and it applies to ANDAs of other applicants that made later Paragraph IV challenges.

FDA has consistently interpreted subsection (B)(iv) as establishing a statutory benefit of exclusivity for the first applicant, not as specifying the details of making and maintaining Paragraph IV certifications. "[I]n certain circumstances, an ANDA applicant whose ANDA contains a paragraph IV certification is protected from competition from subsequent generic versions of the same drug product for 180 days."[12] In 2003, FDA commented specifically on the fact that delaying approval of subsequent ANDAs containing Paragraph IV certifications is the mechanism for granting 180-day exclusivity, not a technical requirement relating to Paragraph IV certifications and related Orange Book patent listings:

> Although this "exclusivity" provision is commonly characterized as granting 180-day exclusivity to the first applicant . . . , the statute does not provide for that directly. Instead, this end is accomplished by delaying the approval of subsequent ANDAs containing a paragraph IV certification for 180-day days . . .

Letter from G. Buehler to M. Macdonald, et al., Jan. 28, 2003, at 3.

The courts, like FDA, have interpreted subsection (B)(iv) as creating a statutory benefit for the first applicant consisting of 180 days of exclusive generic drug marketing. In 1998, the court in Mova described subsection (B)(iv) as "granting [a first-filed applicant] a 180-day period in which to market his generic drug without competition from other ANDA applicants." Mova, 140 F.3d at 1064. "An ANDA applicant who submits a paragraph IV certification is entitled under certain circumstances to a 180-day period of generic marketing exclusivity during which no other company can market a generic drug. See . . . § 355(j)(5)(B)(iv)." Apotex, Inc. v. FDA, No. 4-5211 (U.S.C.A., D.C. Cir., Dec. 21, 2004).

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12 Mova Guidance at 2. See also Letter to Rein, supra, at 4 (subsection (B)(iv) "has the effect of conferring a specific benefit (marketing exclusivity) on specific private entities (eligible ANDA applicants)").

In other words, the purpose of subsection (B)(iv) is to grant – although indirectly – a right of 180-day exclusivity to an ANDA applicant that meets the eligibility requirements. The status of 180-day exclusivity as an enforceable statutory right is not diminished by the fact that it is conditional. In the Mova case, the district court ordered FDA to enforce Mova's right to exclusivity before either triggering event had occurred, i.e., before Mova was entitled to use the 180-day exclusivity period for which it was eligible. See Mova, 140 F.3 at 1065-66. The right a first applicant has under subsection (B)(iv) includes the right to maintain its eligibility for exclusivity, so that it can benefit from the exclusivity if the conditions specified in subsection (B)(iv) occur, i.e., the first applicant markets under the ANDA or there is a court decision of invalidity or noninfringement.

IPI's ANDA No. 76-052 was the first-filed Paragraph IV ANDA for simvastatin 5 mg-40 mg tablets. It was therefore eligible for 180-day exclusivity under § 314.107(c) beginning in the year 2000. Nothing has occurred since that time to cause ANDA No. 76-052 to lose its eligibility for 180-day exclusivity. IPI therefore has a statutory right that the ANDA remain eligible for 180-day exclusivity until exclusivity ends.

b. Delisting Merck's '481 and '520 patents revives FDA's pre-Mova regulation. Under § 314.94(a)(12)(viii)(B), a patent "that is the subject of a lawsuit under § 314.107(c)" cannot be removed from the Orange Book until FDA determines that no ANDA is eligible for 180-day exclusivity, that the patent has expired, or that the period of 180-day exclusivity has been used. At the time the '481 and '520 patents were removed from the Orange Book, IPI was eligible for 180-day exclusivity, neither patent had expired, and the 180-day exclusivity period had not been used.

It necessarily follows that FDA permitted removal of the Merck patents from the Orange Book because the patents were not "the subject of a lawsuit under § 314.107(c)." However, after 1998, the absence of an infringement lawsuit became completely irrelevant to the prohibition on delisting patents. The only reason the prohibition was included in § 314.94(a)(12)(viii) was to enforce eligibility for 180-day exclusivity under

§ 314.107(c). Prior to Mova and FDA's 1998 regulation, eligibility depended on whether a patent was the "subject of a lawsuit." After 1998, eligibility did not depend on whether a patent was the "subject of a lawsuit."

In permitting Merck's patents to be removed from the Orange Book, FDA appears to have overlooked the fact that the "lawsuit" condition for requiring a patent to remain listed under § 314.94(a)(12)(viii)(B) is the identical successful defense/lawsuit condition that, respectively, the Mova court invalidated, and FDA decided not to impose, in 1998. This is clear from the preamble to the 1994 final rule, which explained that the prohibition against delisting patents that were the "subject of a lawsuit" was included to protect eligibility for 180-day exclusivity, not because there was some attribute peculiar to litigated patents that made it uniquely improper to remove them, as opposed to non-litigated patents, from the Orange Book. It is also clear from the cross reference to "a lawsuit under § 314.107(c)," because § 314.107(c) contains eligibility criteria for 180-day exclusivity, not standards for the listing and delisting of patents. The only lawsuit § 314.107(c) has ever referred to was the lawsuit that FDA once regarded as a condition of eligibility for 180-day exclusivity.

Ten years of controversies and lawsuits over 180-day exclusivity may have obscured the relationship between the prohibition against patent delisting in § 314.94(a)(12)(viii) and the eligibility conditions for 180-day exclusivity in § 314.107(c). Nevertheless, the prohibition's only purpose was, and is, to preserve the first applicant's eligibility for 180-day exclusivity. Since 1998, there has been no "lawsuit" condition on eligibility for 180-day exclusivity. Accordingly, notwithstanding the wording of § 314.94(a)(12)(viii), FDA's removal of the '481 and '520 patents from the Orange Book was unlawful. IPI established eligibility of ANDA No. 76-052 for 180-day exclusivity in 2000 by meeting all post-Mova conditions stated in current § 314.107(c). IPI is entitled to remain eligible for 180-day exclusivity until it has an

opportunity to use it. If FDA's mechanism for giving effect to 180-day exclusivity[13] requires patents to remain listed in the Orange Book to support Paragraph IV certifications, then FDA must reinstate and continue to list the '481 and '520 patents for as long as IPI is eligible for 180-day exclusivity for ANDA No. 76-052. Failure to do so would violate Mova and § 314.107(c) as amended in 1998.

c. Section 314.53 is irrelevant to listing the '481 and '520 patents. Listing patents under FDCA §§ 505(b)(1) and 505(c)(2) and § 314.53 advises potential ANDA applicants of patents that may be asserted against them, and it allows ANDA applicants to challenge patents under FDCA § 505(j)(2)(A)(vii). After an ANDA applicant establishes eligibility for 180-day exclusivity by making a Paragraph IV certification, patent listing also becomes the means for requiring subsequent ANDAs to maintain Paragraph IV certifications, and thus continue to fit the 180-day deferral language in subsection (B)(iv). Once a patent is listed for this purpose, it can no longer be removed from the Orange Book under the patent listing standards of the statute and § 314.53, but must remain listed for the duration of a first applicant's eligibility for 180-day exclusivity. Indeed, FDA has recognized that listing a patent to enforce exclusivity is required when the patent has been specifically shown not to qualify for listing: "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 [Paragraph IV ANDA] might seek to certify that there is no relevant patent and seek an immediately effective approval. To ensure that this does not occur, the agency has required that a patent remain on the list after being declared invalid or unenforceable until the end of the 180-day exclusivity period." 59 Fed. Reg. at 50,348.

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13 Alternative interpretations of subsection (B)(iv) would not require continued patent listing. The conditions "if the [subsequent] application contains," and that the previous ANDA be one "containing," a Paragraph IV certification could be construed to apply to the time of initial ANDA submission, and ANDAs submitted at a later time, after patent delisting but before 180-day exclusivity expires, could be "deemed" to contain Paragraph IV certifications.

The lawsuit example from the preamble to FDA's 1994 regulations fit FDA's successful defense interpretation of 180-day exclusivity, but the agency was illustrating a broader principle: It is unlawful to allow eligibility for 180-day exclusivity to be undermined by delisting patents that support the Paragraph IV certifications that create 180-day exclusivity, irrespective of whether a patent meets the Orange Book listing standards of § 314.53. In this context, § 314.53 is irrelevant. For the prohibition against patent delisting to apply after Mova, all that matters is whether a first applicant has made a Paragraph IV certification to a patent and is eligible for 180-day exclusivity based on that certification.

IPI does not know why FDA removed the '481 and '520 patents from the Orange Book. Perhaps Merck decided that, despite its decision to list the patents four years ago, the patents do not qualify under § 314.53. Whatever the reasons, however, they are irrelevant. Under Mova and revised § 314.107(c), the patents cannot be delisted so long as ANDA No. 76-052 meets the eligibility conditions for 180-day exclusivity.

d. FDA precedents prohibit delisting the '481 and '520 patents. The court in Organon, Inc. v. Teva Pharmaceuticals, Inc., 244 F. Supp. 2d 370 (D.N.J. 2002), held that Organon's '099 patent on a use of mirtazapine was not infringed by Teva's Paragraph IV certification because the patent did not qualify for listing in the Orange Book. Organon asked FDA to delist the '099 patent one month after the court decision. FDA refused to delist the '099 patent at that time. The agency explained:

> 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.

Letter to Gilbert, supra, at 3.

In Allergan, Inc. v. Alcon Laboratories, Inc., 200 F. Supp. 2d 1219 (C.D. Cal. 2002), the court issued a decision similar to that in the Organon case, holding that

Paragraph IV certifications did not infringe Allergan's '415 and '791 patents on an unapproved use of brimonidine tartrate. Allergan did not request delisting, but Alcon argued that the patents could not be used to support 180-day exclusivity for the first applicant, Bausch & Lomb, because the patents did not qualify for listing. FDA stated:

> 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.

Letter to Tomasch, supra, at 4.

The FDA decisions in the mirtazapine and brimonidine matters are precedent for requiring patents to remain listed to support eligibility for 180-day exclusivity notwithstanding an NDA applicant's delisting request and notwithstanding that the patents demonstrably do not qualify to be listed in the Orange Book under the FDCA and § 314.53. They are also precedent for not delisting patents over which there has not been patent litigation. FDA's stated reasons for not removing the Organon and Allergan patents from the Orange Book related only to the need to preserve 180-day exclusivity. Although there was infringement litigation over the Organon and Allergan patents, the patent lawsuits figured in the agency's analysis only because TorPharm and Alcon, applicants for ANDAs for gabapentin and brimonidine, made arguments about the effect of specific holdings in the court decisions on the listing status of various patents.

For example, TorPharm was an applicant for a gabapentin ANDA, and was the first applicant with respect to Pfizer's '479 patent. TorPharm argued that FDA's decision

to delist Pfizer's '479 patent was inconsistent with its later refusal to delist Organon's '099 patent. But the circumstances leading to the delisting of the '479 patent were unique. FDA had been ordered by a court to accept Purepac's section (viii) statement to the '479 patent. The resulting availability of section (viii) precluded Paragraph IV certifications to the '479 patent from other ANDA applicants, thereby nullifying any ANDA applicant's eligibility for 180-day exclusivity. Because the '479 patent could no longer support eligibility for 180-day exclusivity, FDA granted Pfizer's delisting request.[14]

Alcon was an applicant for a brimonidine ANDA. It was a subsequent applicant with respect to Allergan's patents, and argued that FDA's failure to delist those patents was inconsistent with its earlier decision to delist the Pfizer '479 patent.

TorPharm and Alcon's arguments raised the issue of the effect of the court decisions in the patent infringement litigation on the listing of the mirtazapine and brimonidine patents. FDA's analysis explained why the court decisions did not justify delisting the mirtazapine and brimonidine patents, and distinguished the decision to delist the '479 gabapentin patent. Although there were infringement lawsuits over the gabapentin, mirtazapine, and brimonidine patents, none of the parties involved in the subsequent petition controversies suggested that the infringement lawsuits were, per se, a condition of continued patent listing to support 180-day exclusivity.

Merck's '481 and '520 patents listed for simvastatin have the same status as the Organon and Allergan patents. The Organon and Allergan patents were the subject of Paragraph IV certifications, and FDA refused to delist them for the duration of the first

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[14] Under FDA's patent-by-patent exclusivity approach, 180-day exclusivity was awarded to Purepac based upon the FDA's determination that Purepac was the first applicant with respect to the '482 gabapentin patent. By comparison, there are no other listed patents for simvastatin that were the subject of paragraph IV certifications, and thus no other basis for awarding exclusivity for being the first applicant to file a paragraph IV certification with a substantially complete ANDA.

applicants' eligibility for 180-day exclusivity. Under Mova and current § 314.107(c), that eligibility was established by the submission of the Paragraph IV certifications, not by the patent infringement lawsuits brought by Organon and Allergan. Similarly, here, IPI's eligibility for 180-day exclusivity was established when it submitted Paragraph IV certifications to the '481 and '520 patents. The fact that Merck did not sue IPI for patent infringement had no effect on IPI's eligibility. Moreover, none of the circumstances that could have caused IPI to lose eligibility has occurred. Accordingly, FDA is required to enforce IPI's eligibility for exclusivity until 180 days from a triggering event or until IPI loses its eligibility for one of the reasons explained in section 1.f., above.

Insofar as FDA's removal of the '481 and '520 patents from the Orange Book compromises exclusivity for ANDA No. 76-052, the agency's action violated IPI's rights under Mova and § 314.107(c). Therefore, FDA must retract its decision to delist the Merck patents. Even if it does not, the agency must, in its own words, consider the '481 and '520 patents "deemed to be relevant," 59 Fed. Reg. at 50,348, for purposes of enforcing IPI's eligibility for 180-day exclusivity by requiring subsequent ANDAs to contain certifications to the '481 and '520 patents.

e. The regulation prohibits delisting the '481 and '520 patents. FDA cannot lawfully enforce an interpretation of § 314.94(a)(12)(viii)(B) at variance with the FDCA as interpreted in Mova. Conversely, that provision, construed in context with § 314.107(c), prohibits the delisting of the '481 and '520 patents. As FDA has acknowledged, "removal of the successful defense requirement has resulted in a fragmented regulatory framework, forcing the agency to modify not only the regulatory language in certain parts, but also, as in this case, its interpretation of language that is to remain." Proposed Triggering Period for 180-Day Exclusivity, 64 Fed. Reg. 42,873, 42,876 (Aug. 6, 1999). The reference to "this case" was to § 314.94(a)(12)(viii)(A). FDA reinterpreted language in that provision as having a substantive rather than a "housekeeping" effect in the application of 180-day exclusivity by FDA after the court's

decision in Mova (and without regard to the subsequently withdrawn triggering period proposal).

Similarly, here, the modified interpretation of § 314.94(a)(12)(viii)(B) required by Mova precludes removal from the Orange Book of a patent that is the basis for 180-day exclusivity under § 314.107(c), irrespective of whether the patent is the "subject of a lawsuit under § 314.107(c)." This interpretation gives effect to the intent underlying the 1994 version of the regulation, which was, and remains, to continue the listing of patents when necessary to enforce eligibility for 180-day exclusivity. The interpretation recognizes that the reference in § 314.94(a)(12)(viii)(B) to a "patent that is the subject of a lawsuit under § 314.107(c)" was not meant to limit the patents to which the language applied. Rather, it was intended to describe the circumstances specified in § 314.107(c), as it was worded in 1994, in which a Paragraph IV applicant was eligible for 180-day exclusivity. Now that § 314.107(c) has been changed to state different circumstances of eligibility, § 314.94(a)(12)(viii)(B) applies to those different circumstances.

Just as statutes must be construed as a "harmonious whole," FTC v. Mandel Bros., Inc., 359 U.S. 385, 389 (1959), so, too, must regulations. It is therefore not necessary for FDA to amend § 314.94(a)(12)(viii)(B) to make explicit that a patent may not be delisted when eligibility for 180-day exclusivity has been established under § 314.107(c) as amended after Mova. The sole purpose of the provision is to preserve eligibility for 180-day exclusivity that is established under § 314.107(c), which is expressly cross-referenced. The two provisions can be harmonized only by interpreting § 314.94(a)(12)(viii)(B) as implicitly omitting the lawsuit requirement that was explicitly removed from § 314.107(c) after Mova.

f. Conclusion. Under subsection (B)(iv) and § 314.107(c), IPI established a right to maintain its eligibility for 180-day exclusivity by filing ANDA No. 70-052 with Paragraph IV certifications to the '481 and '520 patents. This right was in force at the time FDA delisted the '481 and '520 patents. Therefore, FDA's delisting of the '481 and '520 patents was unlawful. The decision should be revoked and the patents

reinstated in the Orange Book. Even if the patents are not physically reinstated, FDA cannot lawfully approve other ANDAs for simvastatin tablets until 180 days from a triggering event. To do so would violate IPI's right under subsection (B)(iv) as interpreted in Mova and implemented in revised § 314.107(c).

C. Environmental Impact

The relief requested in this petition would result in relisting two patents and in refusal to approve ANDAs for simvastatin tablets for a period of time. Granting the petition would have no effect on the environment. Therefore, no environmental assessment is required. 21 C.F.R. § 25.31(a).

D. Economic Impact

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

E. Certification

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

Respectfully submitted,

Monte R. Browder
Intellectual Property Counsel
IVAX Pharmaceuticals, Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

99P-1271

AUG - 2 1999

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Re: Docket No. 99P-1271/PSA1 and PSA2

Dear Mr. Green, Mr. Sklar, and Ms. Beardsley:

This letter responds to your petitions for stay of action (PSAs) filed on behalf of American Pharmaceutical Partners, Inc. (APP) and Pharmachemie B.V. (Pharmachemie). The APP petition (PSA1), filed on May 6, 1999, requests the Agency to stay final approval of any abbreviated new drug application (ANDA) referencing the listed drug Platinol-AQ (cisplatin injection),[1] other than APP's ANDA, until 180 days after APP first commercially markets its drug product or a court decision finds the relevant patent invalid, unenforceable, or not infringed. The Pharmachemie petition (PSA2), filed on June 9, 1999, requests the Agency to stay final approval of any ANDA referencing Platinol-AQ, other than that of Pharmachemie, until 180 days after Pharmachemie first commercially markets its drug product or a court decision finds the relevant patent invalid, unenforceable, or not infringed.

The Agency has considered the petitions, a submission dated June 18, 1999, filed on behalf of APP, a submission dated July 16, 1999, filed on behalf of Pharmachemie, a submission dated June 17, 1999, and the relevant law. For the reasons explained below, the APP petition is granted and the Pharmachemie petition is denied.

I. Background

When the Platinol-AQ new drug application (NDA) was approved in 1988, information on U.S. Patent Number (No.) 4,310,515 (the '515 patent) was published in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*). On May 26, 1995, Pharmachemie filed its ANDA for cisplatin injection. This ANDA contained a paragraph IV certification to the '515 patent, claiming that the patent is invalid, unenforceable, or not infringed.[2] Other applicants subsequently filed ANDAs containing paragraph IV certifications to the '515 patent. BMS did

[1] Sponsored by Bristol-Myers Squibb (BMS).

[2] See section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act (the Act).

99P-1271

PDN 1

Attachment A

not file a patent infringement lawsuit against Pharmachemie. The '515 patent expired on January 12, 1999, without Pharmachemie marketing its product and without a court decision finding the patent invalid, unenforceable, or not infringed.

In October 1996, BMS submitted newly issued U.S. Patent No. 5,562,925 (the '925 patent) to the Food and Drug Administration (FDA) as protecting Platinol-AQ, and FDA published the patent information in the *Orange Book*. APP filed a paragraph IV certification to the '925 patent as part of an amendment to its application. Pharmachemie subsequently filed a paragraph IV certification to the '925 patent, as did other ANDA applicants. The patent owner and NDA holder filed suit against a number of the ANDA applicants, including APP and Pharmachemie.[3] Because of the pending litigation, FDA was not able to approve any ANDA for cisplatin until 30 months elapsed from the date BMS received notice of the paragraph IV certification.[4] The 30-month period for APP expired on June 17, 1999; the 30-month period for Pharmachemie will expire on August 4, 1999.

II. Statutory and Regulatory Provisions

The 180-day generic drug exclusivity was created as part of the 1984 Drug Price Competition and Patent Term Restoration Act (Pub. L. 98-417) (the Hatch-Waxman Amendments). Section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)) provides that

> 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 [sic] 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 action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed,
>
> whichever is earlier.

FDA's regulations implementing this provision are found at 21 CFR 314.107(c). These regulations provide

> If an abbreviated new drug application contains a certification that a relevant patent is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted containing a certification **that the same patent**

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[3] That litigation apparently has been consolidated into one proceeding.

[4] See section 505(j)(5)(B)(iii) of the Act.

> **was invalid, unenforceable, or would not be infringed,** approval of the subsequent abbreviated new drug application will be made effective no sooner than 180 days from whichever of the following dates is earlier:
>
> (i) The date the applicant submitting the first application first commences commercial marketing of its drug product; or
>
> (ii) The date of a decision of the court holding the relevant patent invalid, unenforceable, or ~~not infringed~~.

21 CFR 314.107(c)(1)(emphasis added).[5]

The regulations further provide

> [T]he "applicant submitting the first application" is the applicant that submits an application that is both substantially complete and contains a certification that the patent was invalid, unenforceable, or not infringed prior to the submission of any other application for the same listed drug that is both substantially complete and contains the same certification.

An "application" includes supplements and amendments to the application or abbreviated application. 21 CFR 314.3(b)

III. Discussion

The issue presented to FDA by the APP and Pharmachemie petitions is whether multiple ANDA applicants each can be eligible for 180-day exclusivity because each applicant was the first to file a paragraph IV certification as to a different patent for the listed drug. This is a question of first impression for FDA. It is arising now because the changes in the law wrought by the *Mova* decision have made it much easier for ANDA applicants to become eligible for exclusivity. *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998). Prior to the *Mova* decision, an applicant would only be eligible for 180-day exclusivity if it was the first to file an ANDA with a paragraph IV certification, was sued by the innovator, and prevailed in that litigation. Because the *Mova* case determined that a key aspect of FDA's requirements was inconsistent with the statute, FDA has withdrawn the challenged regulation, and has been regulating directly from the statute on 180-day exclusivity issues not addressed by the current regulations. Currently, an ANDA applicant who files the first paragraph IV certification for a listed patent is eligible for exclusivity even if that applicant is not sued for patent infringement. *Purepac v. Friedman*, 162 F.3d 1201 (D.C. Cir. 1998).

Prior to the *Mova* decision, the question of multiple applicants being eligible for exclusivity for the same product never arose, no doubt because it would have required that multiple "first" applicants successfully defend litigation on two or more different patents. Now, with the changes in the law making an applicant eligible for exclusivity merely by being the first to file a paragraph IV certification for a patent, it is no surprise that this issue has arisen. Although FDA is planning to propose new regulations to address 180-day exclusivity in light of the *Mova* decision, and expects to address the question of multiple 180-day exclusivity periods for a drug product in that context,

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[5] The text cited is 21 CFR 314.107(c)(1) as amended by the Interim Rule published in November, 1998. 63 Fed. Reg. 59710 (Nov. 5, 1998).

until such new regulations are final, FDA's determinations are governed by the existing regulations and the relevant provisions of the statute.

Under FDA's current regulations, APP is eligible for 180 days of exclusivity because it was the first ANDA applicant to file a paragraph IV certification for the '925 patent. As to APP's certification for the '925 patent, all other ANDA applicants are subsequent applicants, as described in 21 CFR 314.107(c)(1). The regulations direct that the inquiry is whether one or more substantially complete ANDAs were submitted that contained a certification that the same patent was invalid, not enforceable, or would not be infringed. Therefore, under the current regulations, eligibility for exclusivity is to be determined on a patent-by-patent basis.

Pharmachemie suggests that the only relevant assessment is which applicant was the first to file an ANDA containing a paragraph IV certification to any patent. The Agency agrees that the ambiguous text of section 505(j)(5)(B)(iv) of the Act could be read to provide exclusivity only to the first applicant to file a paragraph IV certification for any patent for the listed drug, and that multiple periods of exclusivity could be difficult to administer. Nonetheless, the current regulations do not support exclusivity only for the first applicant to provide a paragraph IV certification to any patent, nor is that outcome required by the statute. As with other issues arising as a result of *Mova*, FDA is relying on existing regulations to the extent they are relevant. New regulations promulgated pursuant to notice and comment rulemaking may ultimately adopt different interpretations of the statute from those currently expressed in the regulations.

Pharmachemie's argument that its paragraph IV certification to the '925 patent should "relate back" to its position as first in line for the '515 patent is likewise unpersuasive. In the case cited as an example,[6] Genpharm's subsequent paragraph IV certification that related back to an initial certification was a paragraph IV certification that related back to an initial first paragraph IV certification to the same patent. In the case of cisplatin injection, the issue is first paragraph IV certifications as to different patents.

Pharmachemie is correct in its assertion that its position as first applicant to file a paragraph IV certification to the '515 patent made it eligible for exclusivity. But that eligibility was only with respect to the '515 patent. Because exclusivity cannot extend beyond the expiration of a patent, Pharmachemie lost its eligibility for exclusivity when the '515 patent expired before either of the events described in section 505(j)(5)(B)(iv)(I) and (II) occurred. 21 CFR 314.94(a)(12)(viii). Under 21 CFR 314.94(a)(12)(viii)(C), Pharmachemie — and all other ANDA applicants for cisplatin injection — should amend their applications to provide a paragraph II certification stating that the '515 patent has expired.

Based on this analysis FDA has approved APP's ANDA 74-735 and determined that it is eligible for 180 days of exclusivity. Pursuant to section 505(j)(5)(B)(iv)(I) and (II) of the Act, this exclusivity will begin when APP begins to market its cisplatin injection product or with a court decision finding the '925 patent invalid, unenforceable, or not infringed.

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[6] *Granutec v. Shalala*, 1998 U.S. App. LEXIS 6685, Nos. 97-18973, 97-1874 (4th Cir. Apr. 3, 1998).

IV. Conclusion

APP's request that the Agency stay final approval of any ANDA referencing the listed drug Platinol-AQ (cisplatin injection), other than APP's ANDA, until 180 days after the earlier of the first commercial marketing of APP's drug product or a court finding that the '925 patent is invalid, unenforceable, or not infringed, is granted. Pharmachemie's request that the Agency stay final approval of any ANDA referencing Platinol-AQ, other than that of Pharmachemie, until 180 days after the earlier of the first commercial marketing of Pharmachemie's drug product or a court finding that the relevant patent is invalid, unenforceable, or not infringed, is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

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

Attachment B

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.[1]

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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[1] 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.

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
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DEPARTMENT OF HEALTH & HUMAN SERVICES

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MAY 28 2003

Daniel J. Tomasch, Esq.
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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*.

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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.

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 mirtazipine. *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 mirtazipine 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

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.

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> 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.

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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

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 mirtazipine 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.

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 Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosures:
1. January 28, 2003 Letter to Apotex & Purepac
2. February 24, 20003 Letter to Gilbert

cc: Elizabeth Dickinson, Associate Chief Counsel for Drugs
Thomas Scarlett, Counsel for Bausch & Lomb

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 28 2003

Daniel J. Tomasch, Esq.
Orrick, Herrington & Sutcliffe LLP
666 Fifth Ave.
New York, NY 10103

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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 Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosures:
1. January 28, 2003 Letter to Apotex & Purepac
2. February 24, 20003 Letter to Gilbert

cc: Elizabeth Dickinson, Associate Chief Counsel for Drugs
Thomas Scarlett, Counsel for Bausch & Lomb