DEPARTMENT OF HEALTH & HUMAN SERVICES

OCT 2 4 2005

Food and Drug Administration
Rockville MD 20857

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Re: Docket Nos. 2005P-0008/CP1 and **2005P-0046/CP1**

Dear Mr. Browder, Ms. Beardsley, and Ms. Shepard:

This is a response to citizen petition (petition) 2005P-0008/CP1 filed by Ivax Pharmaceuticals, Inc. (Ivax) on January 12, 2005, and petition 2005P-0046/CP1 filed by Buc & Beardsley, on behalf of Ranbaxy Laboratories Ltd. (Ranbaxy), on February 1, 2005.[1] Both petitions address 180-day exclusivity under section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act or FDCA) (21 U.S.C. 355(j)(5)(B)(iv)) for various strengths of simvastatin.[2] For the reasons that follow, the petitions are denied.

I. ISSUE PRESENTED

Your petitions raise patent listing issues that have implications for 180-day marketing exclusivity for the first generic version of Merck & Co.'s (Merck's) Zocor (simvastatin). This exclusivity period may provide abbreviated new drug application (ANDA) applicants the opportunity to market a generic drug product for 180 days without competition from any other product approved in an ANDA under section 505(j) of the Act. Eligibility for exclusivity depends upon an ANDA applicant filing a so-called "paragraph IV" patent challenge to the patents an innovator

[1] The Food and Drug Administration (FDA) has also reviewed and considered the following comments submitted to Docket No. 2005P-0008 and Docket No. 2005P-0046: Federal Trade Commission (FTC), April 5, 2005; Ivax, April 11, 2005; Ivax, May 6, 2005; Ranbaxy, May 20, 2005; Ivax, May 23, 2005; Teva Pharmaceuticals, USA, June 8, 2005; Ranbaxy, July 1, 2005; and Ivax, July 5, 2005.

[2] Amendments made to section 505(j)(5)(B)(iv) of the FDCA by Title XI (Access to Affordable Pharmaceuticals) of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173) (MMA) amended the provisions related to 180-day exclusivity. The relevant Title XI provisions concerning 180-day exclusivity apply only to drug products for which the first ANDA containing a paragraph IV certification to a listed patent was submitted after December 8, 2003. *See* MMA, Pub. L. No. 108-173, section 1102(b)(1), 117 Stat. 2066, 2460 (2003). Except if otherwise noted, this response refers to the pre-MMA version of the statute.

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drug company has submitted to its new drug application (NDA) for listing as claiming the approved innovator product. The petitions address whether an ANDA applicant's eligibility for this exclusivity survives an NDA holder's request to FDA that the patent be withdrawn from the list of patents that protect the innovator product.

Petitioners' position is that, even if an innovator drug company notifies FDA that its patent should be withdrawn from the list of patents claiming the approved drug product, FDA may not remove the patent from the list and extinguish eligibility for 180-day exclusivity for the first ANDA applicant to have submitted a paragraph IV challenge to the patent. FDA disagrees. We do not interpret the statute to require that an ANDA applicant who has submitted the first paragraph IV certification to a patent always remain eligible for 180-day exclusivity as to that patent even if the NDA holder has asked that the patent be delisted. We believe it is consistent with the language and purposes of the statute generally to delist a patent when the NDA holder requests that we do so and thus to remove the basis for exclusivity as to that patent. FDA's regulations recognize one limited exception to this approach, which is to maintain the listing of such a patent when a paragraph IV patent challenge has resulted in litigation. In that case, the first applicant will remain eligible for exclusivity with respect to a patent the innovator has asked be withdrawn, so that victory in the patent litigation by the ANDA applicant — and a resulting delisting of the patent — would not result in loss of the exclusivity reward. We believe this approach is consistent with the statutory language and policy considerations. The basis for our position is discussed below.

II. FACTUAL BACKGROUND

Merck holds the approved NDA for Zocor (simvastatin) Tablets, 5 milligrams (mg), 10 mg, 20 mg, 40 mg, and 80 mg. Merck submitted to its NDA patents that Merck claimed covered the approved drug or its use (section 505(b)(1) and (c)(2) of the Act). These include U.S. Patent No. 4,444,784 ('784 patent), which was listed at the time the NDA was approved in 1991, and U.S. Patents No. RE 36481 ('481 patent) and RE 36520 ('520 patent), which were submitted to FDA by Merck in 2000 and are at issue in this dispute. FDA published these patents in *Approved Drug Products with Therapeutic Equivalence Ratings* (the Orange Book).

According to Ivax's petition, on December 14, 2000, Ivax submitted ANDA 76-052 for the 5-mg, 10-mg, 20-mg, and 40-mg strengths of simvastatin. Ivax believes its ANDA contained the first paragraph IV certifications pursuant to section 505(j)(2)(A)(vii)(IV) to the '481 and '520 patents with respect to the 5-mg, 10-mg, 20-mg, and 40-mg strengths of simvastatin. Ranbaxy's petition states that Ranbaxy submitted ANDA 76-285 in November 2001 for various strengths of simvastatin, including 80 mg. Ranbaxy believes that it submitted the first paragraph IV certifications to the '481 and '520 patents with respect to the 80-mg strength. The applicants state that they provided notice of the paragraph IV certifications to the NDA holder and patent owner, as required by section 505(j)(2)(B). Merck has not sued any ANDA applicant for infringement as a result of a paragraph IV certification to the '481 or '520 patent.

On October 10, 2003, Merck submitted a letter to FDA requesting that the '481 and the '520 patents be removed from the list of patents claiming Zocor (NDA 19-766) in the Orange Book. On November 3, 2003, the Agency received a letter from a law firm stating that pursuant to the

patent challenge provisions of FDA's regulations at 21 CFR 314.53(f), the '481 and '520 patents should be withdrawn from the Orange Book and briefly describing that the patents do not meet the requirements for listing because they claim metabolites of simvastatin. Consistent with FDA practice, this challenge was forwarded to Merck on November 21, 2003. Merck, by letter of December 19, 2003, confirmed that it had already requested that the '481 and '520 patents be withdrawn from the Orange Book. FDA received another letter from a law firm on June 14, 2004, requesting that the '481 and '520 patents be withdrawn from the Orange Book. In September 2004, in response to Merck's request, FDA removed the '481 and '520 patents from the Orange Book. Ivax's and Ranbaxy's petitions of January and February 2005 challenge the delisting of these patents and loss of associated 180-day exclusivity.

On July 5, 2005, counsel for Ranbaxy requested correction of the patent listings for Zocor through the process described at 21 CFR 314.53(f). Ranbaxy believes the '481 and '520 should be relisted in the Orange Book, and requested that FDA ask Merck to do so. FDA forwarded this request to Merck on September 22, 2005, and has not been asked by Merck to relist the patent.

Ivax petitions FDA to (1) refuse to approve subsequent ANDAs for simvastatin tablets for 180 days from the date that Ivax first commercially markets simvastatin under ANDA 76-052 and (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. Ranbaxy similarly petitions FDA to (1) refrain from approving any ANDA for simvastatin 80-mg tablets until Ranbaxy's claimed 180-day exclusivity has expired, (2) confirm that Ranbaxy's right to 180-day exclusivity for 80-mg simvastatin has not been affected by the delisting of the '481 and '520 patents, and (3) reinstate those two patents in the Orange Book until Ranbaxy's claimed 180-day exclusivity expires.

The Agency has not yet approved any ANDA referencing Zocor and anticipates that no ANDA will be eligible for final approval until at least June 23, 2006, when the '784 patent and associated pediatric exclusivity expire.

III. LEGAL BACKGROUND: THE HATCH-WAXMAN AMENDMENTS AND FDA REGULATIONS

The Agency has developed its approach to patent delistings and 180-day exclusivity in these circumstances by reference to the relevant provisions of the FDCA, FDA regulations, and related policy considerations.

A. Patent Listings for NDAs

The 1984 Drug Price Competition and Patent Term Restoration Act (the Hatch-Waxman Amendments) amended the Act and established a process for approval of ANDAs for generic versions of approved innovator drug products (section 505(j) of the Act). The timing of approval

of ANDAs will depend in part on patent protections for the approved innovator drug, known as the *listed drug*.[3] Under section 505(b)(1) of the Act (or a similar provision in section 505(c)(2)), an innovator pharmaceutical company must submit to FDA

> 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.

FDA publishes this patent information in the Orange Book.

The Agency believes the statutory provisions governing patent listings assign control over patent submissions to the NDA holder (section 505(b)(1) and (c)(2)). FDA has interpreted the statute to allocate to FDA only a ministerial role in the patent listing process. The Agency has consistently maintained that it has neither the resources nor the expertise to review patents to determine whether they meet the statutory criteria for listing.[4] In lieu of reviewing patents, FDA has established the challenge process described in the regulations at 21 CFR 314.53(f), by which an outside party can convey its doubts about the accuracy of a patent listing to the NDA holder through FDA, and the NDA holder may correct patent listings.[5] The Agency's approach to patent listings has been sustained by the courts against challenges that it accords to the NDA holder too much control over the patent-related timing of ANDA approvals. *Apotex, Inc. v. Thompson*, 347 F.3d 1335 (Fed. Cir. 2003); *aaiPharma Inc. v. Thompson*, 296 F.3d 227 (4th Cir. 2003); *Alphapharm PTY Ltd. v. Thompson*, 330 F. Supp. 2d 1 (D.D.C. 2004).

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[3] In 21 CFR 314.3(b), *listed drug* is defined as

> a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement thereto, as a drug with an effective approval.

[4] Petitioners and others devote considerable ink to the question of whether Merck was justified in delisting the '481 and '520 patents on the grounds that the patents claim metabolites of simvastatin and thus are not among the types of patents permitted to be listed (Ranbaxy petition at 2; Ranbaxy May 20, 2005 comment at 4-5; and Teva June 8, 2005 comment at 2). In keeping with the Agency's role, FDA expresses no opinion as to the merits of these claims.

[5] FDA has taken additional steps to ensure that patents submitted to NDAs for listing in the Orange Book meet the criteria set out in section 505(b)(1) and (c)(2) of the Act. In June 2003, the Agency issued new regulations at 21 CFR 314.53 describing very specifically what types of patents must and must not be submitted to FDA (68 FR 36703, June 18, 2003). These regulations were precipitated in part by publication of the 2002 FTC study, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (2002 FTC Study), describing concerns about patent listings and delays in ANDA approvals.

The statutory provisions applicable to patent listings do not specifically address the delisting of patents, either generally or when 180-day exclusivity is at issue.[6] The Agency's view is that the general rule of deference to the NDA holder's views on the scope and effect of a patent should apply equally to the decision to list a patent and to delist a patent. We note that FDA's regulation states that an NDA holder may, as a result of a patent listing challenge, "amend[] or withdraw[] its patent information" (21 CFR 314.53(f)). FDA further believes that deference to the NDA holder's decision to delist a patent is warranted whether it is the result of a third party challenge via the FDA challenge mechanism or is the result of other factors that may influence patent listing decisions. We have established one narrow exception to such deference, to accommodate statutory exclusivity considerations, and that is described at 21 CFR 314.94(a)(12)(viii).

The Agency does not require an applicant to state the basis for requesting that a patent be delisted. If an NDA holder requests that a patent be delisted, it is reasonable for the Agency to assume that it is because the NDA holder no longer believes the patent meets the standard for listing described in section 505(b)(1) and (c)(2) of the Act and at 21 CFR 314.53. We are aware that some delistings have occurred as a result of settlements with the FTC. *See* FTC comment at 7-8. We also understand that, after publication of FDA's new regulations on patent listings (68 FR 36703-36705), certain NDA holders may have requested that patents be removed from listing because the patents were not of the type permitted to be listed. *See, e.g.,* July 1, 2003, letter from GlaxoSmithKline delisting patents for paroxetine hydrochloride.

B. Generic Drug 180-Day Exclusivity

Patent listings for an approved innovator drug product play a pivotal role in the approval of generic versions of the drug. An applicant seeking approval of an ANDA must submit, among other things, a certification for each patent in the Orange Book that claims the listed drug the ANDA references. Section 505(j)(2)(A)(vii) of the Act provides that an ANDA applicant must submit

> 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 section 505] —
>
> > (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 . . . .

[6] New provisions of the FDCA at section 505(j)(5)(B)(iv) and (j)(5)(D) added by the MMA address the delisting of patents in the context of 180-day exclusivity. The new provisions do not apply to the ANDAs at issue here and provide no persuasive insight into Congress' views on the relationship between patent delisting and 180-day exclusivity under the pre-MMA statutory provisions. Similarly, the Agency interpretation of the pre-MMA statutory language has no bearing on how the Agency would interpret the specific forfeiture provision of the MMA related to patent withdrawal (see section 505(j)(5)(D)(i)(I)(bb)(CC)).

A certification under section 505(j)(2)(A)(vii)(IV) asserts that the patent is invalid, unenforceable, or not infringed (21 CFR 314.94(a)(12)(i)(A)(*4*)). An applicant submitting a paragraph IV certification is required to give notice of the filing of the ANDA to the patent owner and the NDA holder for the listed drug. This notice must include a detailed statement of the factual and legal bases for the ANDA applicant's opinion that the patent is invalid, unenforceable, or will not be infringed (section 505(j)(2)(B), 21 CFR 314.95).[7] If the NDA holder or patent owner sues the ANDA applicant within 45 days of notice, FDA will stay approval of the ANDA for 30 months from that date, unless a court orders otherwise.

The Hatch Waxman Amendments included the provision at section 505(j)(5)(B)(iv), which makes certain ANDA applicants eligible for 180-day exclusivity as a result of these paragraph IV patent challenges. As interpreted by FDA, this provision makes an ANDA applicant eligible for 180-day exclusivity if the applicant is the first to submit a paragraph IV certification to a listed patent.[8] The "exclusivity" for which an applicant becomes eligible is a statutory delay in approval of any ANDA that contains a paragraph IV certification to the listed patent, where such certification was submitted after the first applicant's certification. This 180-day period of marketing exclusivity acts as an incentive and reward to a generic drug manufacturer that exposes itself to the risk of patent litigation by being the first applicant to submit a paragraph IV certification to a patent (section 505(j)(5)(B)(iv)). *See Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1064 (D.C. Cir. 1998); *Mylan Pharm., Inc. v. Henney*, 94 F. Supp. 2d 36, 40 (D.D.C. 2000), *vacated as moot sub nom. Pharmachemie B.V. v. Barr Labs., Inc.*, 276 F.3d 627 (D.C. Cir. 2002). Any 180-day exclusivity thus depends on the existence of a patent to which such certification may be made, and the submission of two or more ANDAs for the listed drug that contain appropriate paragraph IV certifications.

The statutory provision governing 180-day exclusivity, section 505(j)(5)(B)(iv), provides:

> If the application contains a certification described in subclause IV of paragraph [(j)](2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification, the application shall be made effective not earlier than one hundred and eighty days after —
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> > (I) the date the Secretary receives notice from the applicant under the previous application of first commercial marketing of the drug under the previous application, or

[7] An applicant whose ANDA is pending when additional patents are listed must certify to the new patents, unless the additional patents are submitted more than 30 days after they were issued (21 CFR 314.94(a)(12)(vi)).

[8] In determining which applicant submitted the first paragraph IV certification for a listed patent, FDA will consider a number of factors, including whether an ANDA was substantially complete when submitted, whether the paragraph IV certification was submitted in an original ANDA or as part of an amendment, and the date notice was sent to the NDA holder and patent owner. *See Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 888-89 (D.C. Cir. 2004)

> (II) the date of a decision of a court in an action described in clause (ii) holding the patent which is the subject of the certification to be invalid or not infringed, whichever is earlier.

FDA's regulation implementing this provision is at 21 CFR 314.107(c)(1) and (c)(2).[9]

FDA interprets the statute to provide for exclusivity on a patent-by-patent basis.[10] Thus, an ANDA applicant that is first to challenge a particular patent for a particular drug product[11] may enjoy a 180-day period during which it can market its product while approvals of other ANDAs for the same product are held in abeyance. This exclusivity period is triggered either by the ANDA applicant's first commercial marketing of the drug or by a decision of a court finding the patent at issue invalid, unenforceable, or not infringed, whichever occurs earlier (section 505(j)(5)(B)(iv), 21 CFR 314.107(c)(1) and (c)(2)).

The requirements for 180-day exclusivity have changed over the years as the courts have reviewed FDA's implementation of the statute. FDA's original regulations implementing section 505(j)(5)(B)(iv) stated that, to be eligible for 180-day exclusivity, an ANDA applicant was required to submit the first paragraph IV certification to the patent, be sued by the innovator as a result, and win the patent infringement litigation (*See* 21 CFR 314.107(c)(1998)). With the decision in *Mova*, 140 F.3d 1060, an ANDA applicant could become eligible for 180-day exclusivity solely by being first to submit a substantially complete ANDA containing a paragraph IV certification to the patent. An applicant's eligibility for exclusivity is not contingent on successfully defending patent litigation, or even upon being sued as a result of the paragraph IV certification. *Mova*; *Granutec v. Shalala*, 139 F.3d 889, 1998 WL 153410 (4th Cir. 1998) (unpublished opinion); *Purepac Pharm. Co. v. Friedman*, 162 F.3d 1201 (D.C. Cir. 1998). This change in eligibility resulted in many more applicants qualifying for 180-day exclusivity.[12] Currently, the initial question in determining eligibility for 180-day exclusivity is whether the ANDA was the first application to contain a paragraph IV certification to a patent. The Agency then must assess whether, at the time when an applicant's eligibility for exclusivity could delay approval of another ANDA for the drug product, the application appropriately maintains its paragraph IV certification.

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[9] Petitioners note correctly that the drug products referenced in these petitions are subject to section 505(j)(5)(B)(iv) as it appeared prior to passage of the MMA in 2003 (*See* section 1101(b)(2) of the MMA). FDA's response to these citizen petitions addresses withdrawn patents with respect to pre-MMA 180-day exclusivity only.

[10] FDA's interpretation is currently being challenged in *Apotex v FDA*, CA 05-125 (D.D.C. filed Jan. 19, 2005).

[11] Each strength of a drug is a separate drug product potentially eligible for exclusivity. *Apotex v Shalala*, 53 F. Supp. 2d 454 (D D.C. 1999). Therefore, each strength of simvastatin may be subject to its own period of exclusivity.

[12] From 1984 to 1998, only three ANDA applicants qualified for 180-day exclusivity. Since the *Mova* decision, there have been over 110 periods of 180-day exclusivity

IV. RESPONSE TO PETITIONERS' ARGUMENTS

Petitioners' specific concern is that Merck's request to delist the '481 and '520 patents for Zocor will deprive them of exclusivity they believed they earned for their generic simvastatin products by being the first to submit paragraph IV certifications to these patents when they were listed. The basic arguments raised by Ivax and Ranbaxy are that their right to exclusivity became vested with submission of the first paragraph IV certifications to the '481 and '520 patents, and that *Mova* gives FDA no discretion in assessing eligibility for exclusivity. Ranbaxy also raised a number of other points, which are discussed below. We find none of the petitioners' arguments persuasive.

The effect of a withdrawn patent on 180-day exclusivity is not addressed in the statute. This silence in the statute permits FDA to adopt an interpretation that fills the gap, as long as the Agency's approach is consistent with relevant statutory language and with congressional policy goals. *See Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984). Thus, the Agency could address the relationship between patent delisting requests and eligibility for exclusivity in any number of ways:

- FDA could refuse to delist a patent once a paragraph IV certification has been submitted, thus permitting the first challenger to remain eligible for exclusivity;
- the Agency could delist the patent immediately, thus extinguishing any right to exclusivity regardless of the status of any litigation; or
- the Agency could withdraw the patent in some circumstances, but not in others.

Petitioners support the first approach, and contend that once a patent has been listed for an approved drug and paragraph IV certifications to that patent have been submitted, the patent must remain listed and, most importantly, the first applicant to submit a paragraph IV certification to the patent must remain eligible for 180-day exclusivity. They argue that, for purposes of exclusivity, it is irrelevant whether the NDA holder has requested that the patent be delisted or whether any litigation was filed as a result of the first paragraph IV certification. They contend that exclusivity rights vest when the first paragraph IV certification to a listed patent is submitted and, thus, FDA should refuse to withdraw a patent from listing once such a certification is submitted.[13]

We disagree with petitioners' view. The Agency's position is that it is fully consistent with both the relevant statutory language and with applicable policy goals for FDA to delist a patent and remove it as a basis for exclusivity, except when the patent challenge has resulted in litigation.

[13] Petitioners also have advanced the position that FDA may both delist the patents and maintain an applicant's eligibility for exclusivity. This argument is discussed below.

A. Eligibility for Exclusivity Does Not *Vest* With a Patent Challenge

Petitioners assert that submitting the first paragraph IV certification essentially creates a vested exclusivity that withdrawal of the target patent cannot extinguish.[14] That is not our interpretation of the statute. It is not the case that if an ANDA once contained the first paragraph IV certification to a patent, it will forever be eligible for exclusivity as to that patent regardless of changes in circumstances. An applicant's paragraph IV certification to a patent will only serve to delay approval of other ANDAs pursuant to section 505(j)(5)((B)(iv) if, at the time another ANDA is eligible for final approval but for any exclusivity, the application that contained the first paragraph IV certification to the patent still appropriately contains that paragraph IV certification.

An applicant with a pending ANDA is required to maintain accurate patent certifications until its application is approved. FDA's regulations at 21 CFR 314.94(a)(12)(viii) describe when a patent certification must be amended. Thus, there are a number of situations in which an ANDA applicant that was first to file a paragraph IV certification to a listed patent may, as a result of the passage of time or a change in circumstances, be required to amend its certification to something other than the paragraph IV certification upon which exclusivity depends.

An ANDA applicant with a paragraph IV certification must change its certification if the listed patent expires before the ANDA is approved. The correct patent certification in that situation is a paragraph II stating that the patent has expired (section 505(j)(2)(A)(vii)(II), 21 CFR 314.94(a)(12)(i)(A)(*2*)). *Ranbaxy Labs. Ltd. v. FDA*, 307 F. Supp. 2d 15 (D.D.C.), *aff'd*, 2004 WL 886333 (D.C. Cir. 2004); *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272 (D.C. Cir. 2004); *see also Dr. Reddy's Labs., Inc. v. Thompson*, 302 F. Supp. 2d 340, 350-58 (D.N.J. 2003) (conversion of paragraph IV certification to paragraph II certification required when patent expires and can be deemed to have occurred even if no amendment is submitted).

An unsuccessful patent challenge also will require a patent certification change. An ANDA applicant that originally filed a paragraph IV certification and then was unsuccessful in defending a patent infringement suit must change its patent certification to a paragraph III, which states the date the patent expires and signals that the applicant does not seek approval of the ANDA until that date (21 CFR 314.94(a)(12)(viii)(A)). *Mylan Pharm., Inc. v. Henney*, 94 F. Supp. 2d 36 (D.D.C. 2000), *vacated as moot sub nom. Pharmachemie B.V. v. Barr Labs., Inc.*, 276 F.3d 627 (D.C. Cir. 2002). The delisting of a patent will also require an ANDA applicant to amend its certification, with the one exception that is discussed below (21 CFR 314.94(a)(12)(viii)(B)). Finally, a patent certification must also be amended if for any other reason the original certification is no longer accurate (21 CFR 314.94(a)(12)(viii)(C)). Once an applicant amends its certification, the application will no longer be considered to contain the prior certification (21 CFR 314.94(a)(12)(viii)).

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[14] *See, e.g.*, Ivax petition at 15 ("statutory right"), 16 ("entitled"), 23 ("right under subsection (B)(iv)"); Ranbaxy petition at 1 ("rights to 180-day exclusivity"), 2 ("entitled"), 3 ("statutory right"). We do not need to address the distinction made in the submissions between a reward and a right. FTC comment at 9-11. Exclusivity has been recognized as an incentive and reward for challenging a patent, but, as is discussed above, it is not an entitlement that vests with the submission of a paragraph IV certification.

Even if an ANDA originally contained a paragraph IV certification to a patent, once an applicant amends its ANDA to no longer contain a paragraph IV certification, the applicant will lose its eligibility for exclusivity. For example, when an applicant must change its certification to a paragraph II because the patent has expired, the applicant will lose eligibility for 180-day exclusivity. *Dr. Reddy's Labs., Inc. v. Thompson*, 302 F. Supp. 2d 340, 354-55 (D.N.J. 2003). Also, if an ANDA applicant changes its certification for the patent to a paragraph III, it is no longer eligible for exclusivity under section 505(j)(5)(B)(iv) as to that patent. *Mylan Pharm., Inc. v. Henney*, 94 F. Supp. 2d 36, 54 (D.D.C. 2000), *vacated as moot sub nom. Pharmachemie B.V. v. Barr Labs., Inc.*, 276 F.3d 627 (D.C. Cir. 2002).

In each of these situations, the fact that an ANDA applicant may have undertaken some risk and incurred certain costs in challenging a patent is not an adequate basis for maintaining eligibility for exclusivity for which the applicant may once have qualified by being the first to challenge the patent. The court in *Dr. Reddy's Labs* rejected the argument that the statute "requires the award of exclusivity if the ANDA applicant is the first applicant to file a paragraph IV certification on a patent, without more, because at that time the ANDA applicant exposes itself to patent litigation by providing the requisite notice of the certification" (302 F. Supp. 2d at 351). The court found it reasonable for FDA to conclude that eligibility for exclusivity expired with the patent, even though the ANDA sponsor was the first to challenge the patent and had been sued by the NDA holder, thus incurring the cost of litigation (*Id.* at 355).[15] Similarly, the court rejected the argument that failing to grant exclusivity based on expiration of the patent was somehow unfair. The court found that[16]

> the purpose of the exclusivity period is to provide an incentive to challenge patents that block ANDA approval. . . . Once a listed patent expires, there is no longer a need to provide an incentive to challenge it in court. Consistent with this statutory purpose, the FDA construes the statute to award 180-day exclusivity based only upon paragraph IV certifications to unexpired patents. *See* 59 Fed. Reg. 50338, 50348. This construction makes sense in terms of the basic statutory objective of encouraging ANDA applicants to challenge listed patents that prevent final ANDA approval.

This reasoning and conclusion are equally applicable to a withdrawn patent, because a withdrawn patent no longer prevents approval of an ANDA.

It is thus FDA's position that even if an ANDA applicant once qualified for exclusivity because it was the first to submit a paragraph IV challenge to a listed patent, the applicant will lose its eligibility for 180-day exclusivity when its ANDA no longer contains a paragraph IV certification to the patent. As occurs with the expiration of a patent or an unsuccessful patent challenge, eligibility for 180-day exclusivity may be lost if the patent is removed from the Orange Book at the NDA holder's request.

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[15] It is reasonable to assume that the court would be similarly unpersuaded that the cost of designing around a patent would make it "unfair" to deny exclusivity because of a change in the status of the patent. (Ranbaxy petition at 7).

[16] *Dr Reddy's Labs*, 302 F. Supp. 2d at 354.

B. FDA Regulations Permit Delisting and Require Amended Certifications Except When a Patent Is Litigated

FDA regulations state that with one exception, upon the delisting of a patent, an ANDA applicant must amend its certification (21 CFR 314.94(a)(12)(viii)(B)). The Agency's regulations on patent delisting, amended certifications, and 180-day exclusivity, which were promulgated in 1994, provide generally that if a patent is delisted, ANDA applicants who have certified to that patent must amend their certifications. Section 314.94(a)(12)(viii)(B) states:

> 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).

The regulation further describes one exception to this general rule where the paragraph IV certification has resulted in litigation before the request to delist the patent was made. Section 314.94(a)(12)(viii)(B) continues:

> *A patent that is the subject of a lawsuit under §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.* An applicant shall submit an amended certification. Once an amendment or letter for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (a)(12)(i)(A)(4) of this section. (emphasis added)

This regulation recognizes the general requirement that patent certifications be withdrawn when a patent is removed from the list, and describes the one case in which a patent will not be delisted. The reasons for this exception are described in the preambles from the rule-making that implemented the Hatch-Waxman Amendments. In 1989, in the preamble to the proposed rules, the Agency explained that

> [I]f after one or more applicants have made paragraph IV certifications on a patent, that patent has been removed from the list *for any reason other than because that patent has been declared invalid in a lawsuit brought by the patent owner within 45 days of receiving notice under § 314.95* any applicant with a pending application or delayed effective date who has made such a certification should submit an amended patent certification, certifying ... that no relevant patents claim the drug. If other relevant patents claim the

> drug, the applicant should instead submit a request to withdraw the paragraph IV certification. (54 FR 28872 at 28895-28896, July 10, 1989)(emphasis added)

See also id. at 28886. In the preamble to the final rule, the Agency responded to comments on the proposed rule and noted that

> the agency agrees that the protection offered by the 180-day exclusivity should not be undermined by changes from paragraph IV certifications 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 the patent or the applicable exclusivity period, whichever occurs first. (59 FR 50338 at 50348, October 3, 1994)

The Agency's statements express a clear concern that if an ANDA applicant were successful in challenging a patent, withdrawing the patent from the list immediately would destroy any exclusivity benefit by permitting all other ANDAs for the drug product to be approved immediately. As one court has noted "it would be cruelly ironic, and quite perverse, to use an ANDA applicant's *success* in such an infringement action as the basis for *denying* exclusivity to that applicant" (*Torpharm, Inc. v. Thompson*, 260 F.2d 69, 83 n. 15 (D.D.C. 2003) (emphasis in original), *aff'd sub nom. Purepac Pharm. Co. v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004)). To appropriately maintain the statutory reward, FDA's regulation at 21 CFR 314.94(a)(12)(viii) permits the Agency to maintain the patent listing when there is litigation, against the possibility that the ANDA applicant will prevail and the patent will be found invalid or not infringed.[17]

In contrast, under the same regulation, if the patent was not the subject of litigation as a result of a paragraph IV challenge, it will be removed from the Orange Book at the request of the NDA holder and ANDA applicants must amend their certifications accordingly. This approach removes the patent as a barrier to ANDA approval, and no applicant can maintain a paragraph IV certification that would render it eligible for 180-day exclusivity as to that patent.

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[17] We note that 21 CFR 314.94(a)(12)(viii)(B) states that a patent "that is the subject of a lawsuit under § 314.107(c) shall not be removed from the list" for a certain period. The regulation at 21 CFR 314.107(c) was amended after *Mova* to remove reference to the "successful defense" requirement (63 FR 59710, November 5, 1998). The Agency interprets the reference to "lawsuit under § 314.107(c)" to be a lawsuit as a result of the first applicant's paragraph IV certification, as described in 21 CFR 314.107(c) before it was amended ("and the applicant submitting the first application has successfully defended against a suit for patent infringement brought within 45 days of the patent owner's receipt of notice"), rather than a lawsuit arising from any ANDA applicant's paragraph IV certification to the patent. Because no lawsuit was filed against any ANDA applicant submitting a paragraph IV certification to the '481 or '520 patent, the Agency's interpretation of this portion of the regulation is not at issue here.

C. FDA's Regulation Appropriately Fills a Gap in the Statute

The Agency has rejected the position that it must maintain a patent listing even when no suit has been filed as a result of the first patent challenge.[18] Instead, to maintain the appropriate balance between competition and incentive, the Agency has determined that in making delisting decisions, it is appropriate to consider whether a paragraph IV certification resulted in patent infringement litigation.

The regulation at 21 CFR 314.94(a)(12)(viii)(B) was issued when FDA maintained a "successful defense" requirement for exclusivity, that is, before the decision in *Mova*. FDA amended some of its regulations, including 21 CFR 314.107(c), as a result of the *Mova* decision to remove the provisions describing the successful defense requirement (63 FR 59710, November 5, 1998). The Agency did not address the effect of the *Mova* decision on the delisting regulation at 21 CFR 314.94(a)(12)(viii)(B). The regulation retained the litigation element for determining whether a patent could be delisted and thus no longer serve as a basis for paragraph IV certification and resulting 180-day exclusivity.

Since the *Mova* decision, with its fundamental change in the relative ease with which an ANDA applicant may qualify for 180-day exclusivity (i.e., by submitting the first patent challenge versus by submitting the first patent challenge *and* successfully defending resulting patent litigation), the Agency has considered whether maintaining the litigation element in making patent delisting determinations is consistent with the Act, or whether the Agency is required to maintain — or to delist — a patent in response to a delisting request from the NDA holder, without regard to any additional factors. Even though successful defense of a patent infringement lawsuit is not a factor in eligibility for exclusivity, the Agency believes it is reasonable to interpret the patent listing and 180-day exclusivity provisions of the Act to permit the Agency to leave a patent listed only when a lawsuit has been filed as a result of a paragraph IV certification.

D. FDA's Regulation Survives *Mova*

Petitioners argue that the *Mova* decision requires that the first applicant to challenge a patent must always receive exclusivity, and because a listed patent is a prerequisite to exclusivity, the Agency may not consider the status of any litigation in deciding whether to maintain a patent listing. FDA agrees with petitioners that, following *Mova*, an ANDA applicant may be eligible for 180-day exclusivity as a result of submitting the first paragraph IV certification to a particular patent in an ANDA, even if that applicant is not sued as a result. However, FDA does not agree that the first applicant is entitled to exclusivity regardless of subsequent events. FDA also does not agree with petitioners' view of the relationship between eligibility for 180-day exclusivity

[18] The Agency likewise has not adopted an interpretation of the statute that would permit a patent to be immediately withdrawn upon the NDA holder's request and any eligibility for exclusivity extinguished, regardless of the status of any litigation. We note, moreover, that none of the comments to the dockets propose that approach. However, although such an interpretation could result in undermining the benefit to the ANDA applicant who successfully litigates an invalidity or non-infringement claim that results in a patent delisting, always delisting a patent immediately when requested by the NDA holder to do so would recognize the NDA holder's statutory role in determining which patents must and must not be listed with the Agency.

and the effect of withdrawal of a patent on continued eligibility for exclusivity. Petitioners reason that they are entitled to 180-day exclusivity on the grounds that *Mova* prohibited FDA from making 180-day exclusivity turn on litigation and that FDA's regulation is unlawful because FDA's regulation governing withdrawn patents refers to litigation. We disagree with petitioners' analysis.

The decision in *Mova* did not prohibit FDA from considering litigation in the context of patent withdrawal. The *Mova* court held that FDA's then-prevailing "win first" successful defense approach to awarding exclusivity was inconsistent with the plain statutory language because it effectively wrote the commercial marketing trigger out of existence; however, because the statutory language was ambiguous or silent, the court explicitly would have permitted FDA to adopt a "wait and see" approach to granting exclusivity (140 F.3d at 1069). Under "wait and see," if a first applicant did not trigger exclusivity with commercial marketing first, FDA would not approve a subsequent application until the end of the first applicant's litigation, when the applicant either won its litigation and thus retained exclusivity, or lost its patent litigation and lost its exclusivity (*Id*). The *Mova* court expressly did not address the question of exclusivity when the first applicant to submit a paragraph IV certification to a patent is not sued (*Id.* at 1070-1071 ("We begin by setting aside the problems of the first applicant who is never sued or who loses his lawsuit")). The *Mova* court noted that "Congress may have intended to reward the first ANDA applicant for his enterprise whether or not he is later sued ... " (*Id.* at 1071 n.11).

In regulating directly from the statute, post-*Mova*, the Agency determined that an ANDA applicant could become eligible for exclusivity under section 505(j)(5)(B)(iv) by submitting the first paragraph IV certification to the patent; eligibility did not require that the applicant be sued as a result. The FDA's approach was upheld as consistent with the statutory language in *Purepac Pharmaceutical Co. v. Friedman* 162 F.3d 1201 (D.C.Cir. 1998), but the court did not find that such an outcome was required by the statute. Moreover, even if the Act were construed to require that an applicant become eligible for 180-day exclusivity solely by virtue of submitting the first paragraph IV certification to the patent, nothing in the cases cited by petitioners supports the proposition that once eligible for 180-day exclusivity, an applicant must remain eligible even if the patent is withdrawn or that the Agency cannot consider whether the paragraph IV certification resulted in litigation in determining whether to maintain a patent listing in the face of the NDA holder's request to delist.

E. FDA Appropriately Considered the Effects of Maintaining or Delisting a Patent

Among the factors the Agency has considered in interpreting the regulation at 21 CFR 314.94(a)(12)(viii)(B) post-*Mova* are the effects on generic drug approvals of maintaining or removing a listed patent when an NDA holder requests that the patent be delisted. These effects may be substantial and thus are an important factor in considering how to implement the regulation appropriately.

Listed patents are barriers to approval of generic drugs. If a patent remains listed, any applicant submitting an ANDA for the drug product after the NDA holder requests delisting must nonetheless comply with the patent certification requirements of section 505(j)(2). These

include analysis of whether the sponsor wishes to challenge the patent as invalid or not infringed, submission of the patent certification to FDA, notification of the NDA holder and patent owner if the certification submitted is a paragraph IV, including a description of the basis for the patent challenge, and the defense of any patent litigation that may result. All of these steps would need to be undertaken if the patent remains listed, even though the NDA holder has represented (by requesting the delisting) that the patent does not meet the listing criteria under section 505(b)(1) or (c)(2) and 21 CFR 314.53.

We note that to avoid the regulatory hurdles imposed by patent listings, many ANDA applicants have used the procedure described in 21 CFR 314.53(f) to request that a patent be removed from the Orange Book. See, for example, *Apotex v. Thompson*, 347 F.3d 1335 (Fed.Cir. 2003) (delisting of patents for paroxetine hydrochloride) and the correspondence in this matter described above in section II of this response seeking delisting of the '481 and '520 simvastatin patents. However, the positions taken by petitioners could render this patent challenge process largely ineffective. Because of the value under section 505(j)(5)(B)(iv) of being first to challenge a patent, often very little time passes between the submission to FDA of a patent for an approved drug and the submission of ANDAs containing paragraph IV certifications to the patent. *See Guidance for Industry 180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day* (July 2003) at 4. If, as petitioners assert, once an ANDA applicant has submitted the first paragraph IV certification to a patent, the patent cannot be removed from the list for any reason, there could be little, if any, time for meaningful use of the patent challenge process.

In contrast, if an NDA holder requests that a patent be delisted and the patent is removed from the list, ANDAs for the drug product will not be required to contain a certification to that patent. There will be no delay of any ANDA approval for the drug product arising from a 30-month stay, nor will approval of any ANDA be delayed by the time required to give effect to an applicant's 180-day exclusivity as to that patent. It is FDA's experience that not only may approval of subsequent ANDAs be delayed during the 180-day period of exclusivity, approval of any ANDA for the listed drug may be delayed substantially if the applicant eligible for 180-day exclusivity is unable to obtain approval for its ANDA or fails to begin marketing of an approved drug, or if there is no court decision that triggers exclusivity under section 505(j)(5)(B)(iv)(II). For these reasons, delisting a patent at the NDA holder's request is likely to speed approval of generic drugs.

We note two additional arguments made by Ranbaxy that relate to the balance between incentives and competition. First, Ranbaxy asserts that if FDA interprets its regulation and the statute to permit an NDA holder to withdraw a patent and extinguish exclusivity, the Agency will be giving the NDA holder the power to decide whether 180-day exclusivity will be awarded (Ranbaxy petition at 8).[19] Although the withdrawal of a patent would have such effect when the NDA holder has not litigated the claims made in the paragraph IV certification, we do not believe that FDA's approach would result in NDA holders abusing the patent withdrawal process. We note that the statute gives an NDA holder no discretion to list or delist a patent: if the patent falls within the scope of listable patents described in section 505(b)(1) and (c)(2) and

[19] We note that the statute already gives complete control (if no discretion) to the NDA holder for listing a patent, which inherently gives NDA holders control over the possibility of 180-day exclusivity.

21 CFR 314.53, the patent must be listed; if it falls outside that scope, it must not be listed. In addition, an NDA holder that delists a patent removes that patent as a barrier to ANDA approval, in that it will no longer give rise to patent certification obligations, 30-month stays, or delays in approval of multiple ANDAs as a result of 180-day exclusivity. Notwithstanding Ranbaxy's fears, it seems unlikely that an NDA holder would withdraw an otherwise listable patent merely to deprive an ANDA applicant of eligibility for exclusivity, where such act would expose the NDA holder to the risk of earlier and more extensive competition from multiple generic products.

Ranbaxy also argues that if exclusivity does not continue to apply to all challenged patents that an NDA holder seeks to delist, NDA holders will have an incentive to use the litigation element as a "bargaining chip" and to enter into anticompetitive agreements with generic drug companies, a practice that has drawn FTC scrutiny (Ranbaxy petition at 8). In reality, the Agency's position advances FTC's competitive goals. FTC's April 14, 2005, comment to the dockets for these petitions expressly states that to prevent delays in the availability of generic drugs, it is important that the NDA holder have the ability to delist a patent, either as a result of its own decision that the patent is incorrectly listed or as a result of an FTC or court order (FTC comment at 8-9).

F. FDA's Approach Maintains Reasonable Incentives for ANDA Applicants

The 180-day exclusivity period is intended to provide an incentive and reward to encourage prompt challenges to patents that act as barriers to ANDA approvals. When an NDA holder requests that a patent be withdrawn from the list of patents protecting an approved drug and FDA removes the patent, that patent no longer acts as a barrier to ANDA approval, and it also may no longer serve as a basis for 180-day exclusivity. In contrast, when the patent remains listed to protect an applicant's exclusivity, it continues to act as a barrier to approval of generic drugs. The question for the Agency in interpreting and applying 21 CFR 314.94(a)(12)(viii)(B), then, is whether the benefit derived from continuing to provide an exclusivity incentive as to a patent justifies the delay in generic drug approvals arising from maintaining the patent listing in the face of a NDA holder's request to delist.

FDA has determined that as a general rule, the benefit derived from maintaining exclusivity does not justify the delay in generic drug approvals that would arise from leaving a patent listed when the NDA holder has requested that the patent be withdrawn. Termination of exclusivity in these circumstances would not appear to undermine the effectiveness of exclusivity as an incentive to challenge patents. An ANDA applicant that challenges a patent with a paragraph IV certification already does so with the knowledge that if the patent expires or the challenge is unsuccessful, it will forfeit eligibility for exclusivity. Moreover, because patent delistings are relatively uncommon, the possibility that a challenged patent might someday be removed from the Orange Book would not appear to cast enough doubt on the value of being first to discourage prompt paragraph IV certifications. Delays — possibly substantial — in the approval of generic drugs to maintain exclusivity when a patent is withdrawn thus seem unwarranted.

In contrast, delays in approval of generic drugs do not seem a high price to pay to maintain exclusivity as an incentive to challenge and litigate the validity or non-infringement of a listed patent. For example, if an ANDA applicant eligible for 180-day exclusivity knew that its

successful challenge to the validity of a listed patent could lead to the patent being removed from the Orange Book upon a finding of invalidity — and the concomitant loss of exclusivity — the incentive to challenge patent validity would be seriously weakened. This outcome would be inconsistent with the incentive scheme established in the Hatch-Waxman Amendments.

Ranbaxy argues that the principles justifying retaining the listing of a patent when it is the subject of a lawsuit are "equally applicable" when the paragraph IV certification causes the NDA holder to change its mind about the appropriateness of the patent listing (Ranbaxy petition at 3, 7). FDA disagrees. The narrow exception applicable when the patent has been the subject of a lawsuit serves to continue to provide an incentive to the first applicant to pursue its patent litigation by assuring the applicant that the exclusivity reward will not be extinguished if the patent is removed from the Orange Book as a result of success in that litigation. In contrast, should a paragraph IV certification prompt a delisting, the threat of litigation has been defused and the need for any continuing exclusivity incentive has been obviated. Nor is it at all clear why the patents in this case were delisted; FDA does not inquire into the reasons, and it would be entirely impractical to have a delisting decision depend upon an ANDA applicant's characterization of why the delisting was sought.[20]

Therefore, the Agency interprets 21 CFR 314.94(a)(12)(viii) to mean that if a paragraph IV certification to a patent has not resulted in litigation, FDA will remove a patent from the Orange Book at the NDA holder's request and require all pending ANDA applicants to withdraw their certifications to that patent. FDA may approve ANDAs for the drug product with reference only to the remaining listed patents and the corresponding certifications (section 505(j)(5)(B), 21 CFR 314.107). Only if the listed patent has been the subject of a paragraph IV certification that resulted in a lawsuit will FDA not remove that patent until (1) the first ANDA applicant loses the lawsuit and changes its certification to a paragraph III (thus disqualifying it from exclusivity), (2) the patent expires, or (3) the exclusivity has been triggered either by commercial marketing or by a court decision finding the patent invalid or not infringed and the 180-day period has run. The Agency believes that this approach is both a reasonable interpretation of the statute and maintains an appropriate balance between preserving incentives and removing barriers to ANDA approvals.

Finally, if the regulation at 21 CFR 314.94(a)(12)(viii)(B) were considered to have been so closely linked to the Agency's successful defense requirement articulated in 21 CFR 314.107(c)(1998) that the delisting regulation did not survive the amendment to 21 CFR 314.107(c) to remove the successful defense provision, then the Agency would be required to regulate directly from the FDCA in determining how to address the relationship between patent delistings and eligibility for 180-day exclusivity. As the discussion in this response indicates, the statute does not directly address this issue and the Agency believes that the most appropriate response to this statutory gap is to delist a patent when requested to do so by the NDA holder except when there has been litigation as a result of a paragraph IV certification to that patent.

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[20] We do note that because the Ivax and Ranbaxy ANDAs for simvastatin were submitted in late 2000 and 2001, and Merck did not seek to delist the '481 and '520 patents until late 2003, it seems unlikely on its face that the notices of the paragraph IV certifications provided to Merck as required under section 505(j)(2)(B) prompted Merck's request to delist the patents.

G. Petitioners' Proposed Approaches

Petitioners offer two alternatives for addressing 180-day exclusivity when an NDA holder has sought to have a patent delisted and there are paragraph IV certifications to those patents, but no resulting litigation (Ranbaxy May 20, 2005, comment at 3). First, petitioners suggest that FDA remove the patent from the list, but maintain the applicant's eligibility for exclusivity by refusing to approve any other ANDA for the drug product until 180 days after the eligible applicant begins to market its product. Second, Ranbaxy suggests that FDA maintain the patent listing only until the exclusivity expires. Neither of these alternatives is acceptable.

As described above, 180-day exclusivity depends upon both a listed patent as to which an applicant may submit a certification and the submission of two or more ANDAs containing paragraph IV certifications to the patent (section 505(j)(5)(B)(iv)). The statute at section 505(j)(2)(A)(vii) provides that an ANDA must contain

> 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 ... 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 [section 505(b) or (c)].* (emphasis added)

If a patent is not listed for the referenced drug, an ANDA may not contain a paragraph IV certification to the patent. *Alphapharm PTY Ltd. v. Thompson*, 330 F. Supp. 2d 1 (D.D.C. 2004). This is true whether an applicant never submits the patent to FDA, or has submitted and later withdraws the patent. Further, if there can be no paragraph IV certifications to a patent, there is no basis under section 505(j)(5)(B)(iv), or elsewhere in the statute, for delaying subsequent approvals to protect 180-day exclusivity. Thus, the Agency may not both delist the '481 and '520 patents and delay approval of other ANDAs for the drug product because of 180-day exclusivity.

Likewise, the Agency does not believe that leaving all "delisted" patents as to which an applicant has submitted a paragraph IV certification in the Orange Book only until the exclusivity expires is an acceptable way to reconcile delisting and exclusivity. When there is no patent infringement litigation that will result in a triggering court decision under section 505(j)(5)(B)(iv)(II) and the ANDA applicant does not trigger exclusivity with marketing (e.g., because the applicant cannot obtain approval of its ANDA, another patent blocks approval of the ANDA, or the applicant declines to market its product for other reasons), the patent may have to remain in the Orange Book for many years until the exclusivity expires, all the while acting as a barrier to ANDA approvals.

H. The Agency's Treatment of Other Patent Delisting Requests

FDA has been consistent in its treatment of patent delistings under the regulations. For example, the Agency has delisted patents for Paxil (paroxetine hydrochloride), Serzone (nefazadone), Zyprexa (olanzapine), and Detrol (tolterodine) on the grounds that, although paragraph IV

certifications had been submitted to the patents, those certifications did not result in litigation.[21] GlaxoSmithKline (Glaxo), by letter of July 1, 2003, requested that FDA delist U.S. Patents No. 6,063,927, No. 6,080,759, and No. 6,172,233 for Paxil (paroxetine hydrochloride), as a result of FDA's new regulations describing permissible patent listings. FDA informed Glaxo by letter of July 18, 2003, that it would delist the patents as provided in 21 CFR 314.94(a)(12)(viii)(B). As FDA explained in a July 30, 2003, letter to Apotex regarding 180-day exclusivity for paroxetine hydrochloride, the Agency delisted one of the patents pursuant to 21 CFR 314.94(a)(12)(viii)(B) because there had been no relevant litigation, but retained the listing of two other patents because there was litigation (Letter at 7). FDA later delisted these two patents when exclusivity expired.

Bristol-Myers Squibb likewise requested the delisting of U.S. Patent No. 5,256,664 for Serzone (nefazedone) on April 4, 2003.[22] In July of 2003, counsel for two ANDA applicants requested that FDA delist the patent because the NDA holder had not sued any ANDA applicant for infringement of that patent. FDA withdrew the patent from the Orange Book and notified the ANDA applicants seeking approval for nefazadone drug products accordingly on July 31, 2003.

Lilly requested by letter of May 21, 2002, that FDA delist eight patents from the Orange Book listings for Zyprexa Tablets (olanzapine) and Zyprexa Zydis (olanzapine) Orally Disintegrating Tablets. These patents were removed from the Orange Book because no ANDA applicant who had submitted a paragraph IV certification to any of these patents was sued. In September 2004, Pfizer requested that FDA remove U.S. Patent No. 5,559,269 for the listing for Detrol and Detrol LA (tolterodine). Consistent with the approach described in 21 CFR 314.94(a)(12)(viii)(B), the Agency delisted these patents.

Ivax cites the Agency's treatment of patents for mirtazapine and brimonidine as precedent for maintaining a patent listing to preserve exclusivity. In both of these instances, referred to in the Ivax petition at 9-11, FDA continued to list a withdrawn patent in the Orange Book because that patent had been the subject of litigation, as per the regulation. In the February 24, 2003, letter to Tim Gilbert and the May 28, 2003, letter to Daniel J. Tomasch submitted as attachments B and C respectively, to the Ivax petition, FDA made clear that "[i]t 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 a paragraph IV certification and successful litigation of the patent claim. To do so would vitiate the 180-day exclusivity" (*See* attachment C to Ivax petition at 4). This statement is consistent with the regulation at 21 CFR 314.94(a)(12)(viii)(B). These attachments expressly

[21] Since the issues raised in these petitions were first brought to the Agency's attention in correspondence from counsel for Ranbaxy in October 2004, FDA has received a request from the NDA holder to delist U.S. Patents No. 5,863,559 and No. 6,368,627 for Imitrex (sumatriptan succinate). In light of the questions raised in the petitions, and to avoid any further disputes over eligibility for exclusivity arising from delisting and relisting patents, FDA — after determining that it will have no immediate effect on the timing of ANDA approvals — has refrained from delisting these patents until the issues raised in these petitions are resolved.

[22] The other drug products for which Bristol-Myers Squibb sought to have patents delisted (Buspar, Platinol, Lyophilized Cytoxan, and Taxol) no longer had unapproved ANDAs that had been eligible for exclusivity

contradict Ivax's assertion, Ivax petition at 11, that "FDA's decisions were not based on the existence of patent infringement lawsuits."

The third example cited by Ivax was a patent for gabapentin that was at issue in *Purepac Pharm Co. v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004). As Ivax notes, the dispute over the '479 patent involved unique circumstances (Ivax Petition at 20). In that case, FDA had withdrawn, at the request of the NDA holder, a patent that had been the subject of paragraph IV induced litigation. However, the court had determined that FDA could not require certifications to the '479 patent and had ordered the Agency to accept a so-called "section viii" statement under section 505(j)(2)(A)(viii) instead (354 F.3d at 885). Because of the availability of section viii statements to the '479 patent, FDA concluded that no ANDA applicant could maintain a paragraph IV certification to the patent, and thus there could be no 180-day exclusivity under section 505(j)(5)(B)(iv) (*Id.* at 886-888). FDA's treatment of the '479 patent is fully consistent with the Agency's interpretation of 21 CFR 314.94(a)(12)(viii)(B) — that the Agency will not delist a patent at the NDA holder's request when there are paragraph IV certifications to the patent and resulting litigation — because, in the case of the '479 patent, there could no longer be any paragraph IV certifications. Finally, the court was untroubled by FDA's delisting of the '479 gabapentin patent and the loss of any related exclusivity, thus supporting the Agency's position that exclusivity does not vest with the initial submission of the first paragraph IV certification to the patent, but can be lost as a result of subsequent changes in the status of the patent (*See id.* at 888).

V. CONCLUSION

The Agency's treatment of patent delistings described in 21 CFR 314. 94(a)(12)(viii)(B) reconciles the statutory provisions governing patent listings and 180-day exclusivity, and is consistent with the policy considerations underlying the Hatch-Waxman Amendments. This approach requires appropriate ministerial deference to an NDA holder's request that a patent be delisted. At the same time, it recognizes one exception to patent delisting to give effect to the 180-day exclusivity benefit when a paragraph IV certification results in litigation, and the litigation results in the NDA holder requesting withdrawal of the patent. By adopting this approach, FDA has maintained a reasonable balance between allowing NDA applicants to correct patent listings and protecting the incentive for ANDA applicants to challenge listed patents.

Consistent with this conclusion, the Agency will not relist the '481 and '520 patents for Zocor, no applicant will be eligible for 180-day exclusivity as to these patents, and FDA will approve ANDAs for all strengths of simvastatin when they are otherwise eligible for approval under section 505(j) of the Act. The citizen petitions are denied.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Director
Center for Drug Evaluation and Research