

ORIGINAL

November 19, 2004

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

Re: Citizen Petition re 180-Day Exclusivity for Ipratropium Bromide and
Albuterol Sulfate Inhalation Solution

Dear Sir or Madam:

IVAX Pharmaceuticals, Inc., (IVAX) submits this petition pursuant to 21 C.F.R.
§ 10.35.

A. ACTION REQUESTED

IVAX requests the Commissioner of Food and Drugs to confirm that IVAX is
entitled to 180-day exclusivity with regard to ANDA No. 76-724 if IVAX is the first
applicant to both submit a paragraph IV certification and satisfy the statutory notice
requirement for that certification.¹

B. STATEMENT OF GROUNDS

1. IVAX Was the First Applicant to Challenge the Listed Patent.

There is currently a question regarding eligibility for first applicant status between
two applicants that have submitted ANDAs for ipratropium bromide/albuterol sulfate
inhalation solution that contain paragraph IV certifications – IVAX and Eon Labs, Inc.
(Eon). As between IVAX and Eon, only IVAX may be entitled to 180-day exclusivity
because IVAX provided notice to the NDA holder of its paragraph IV certification prior
to Eon providing notice of its certification.

IVAX believes it was the first applicant to submit an ANDA for ipratropium
bromide/albuterol sulfate inhalation solution, a generic version of Duoneb®. IVAX's
ANDA was received by FDA (accepted for filing) on April 22, 2003. At that time, there
were no patents listed in the Orange Book for Duoneb. During the pendency of IVAX's
ANDA and well after IVAX's submission date, the NDA holder for Duoneb, Dey, L.P.
(Dey) listed a patent in the Orange Book as claiming an approved use for Duoneb. The
patent was listed in the electronic Orange Book database on November 6, 2003. On
December 9, 2003, IVAX submitted a paragraph IV certification via an amendment to its

¹ IVAX does not seek a determination that it is entitled to 180-day exclusivity. It rather seeks
confirmation of the standard that FDA will use to determine whether IVAX is entitled to exclusivity – that
IVAX will be eligible for exclusivity if it is the first applicant to both submit a paragraph IV certification
and satisfy the statutory notice requirement for that certification

2004P.0520

CP1

ANDA and provided notice to Dey on the same day as required by statute. According to Dey, IVAX was the first ANDA applicant to challenge Dey's patent. IVAX's notification was the first such notification Dey received and IVAX was the first ANDA applicant that Dey sued.²

On July 15, 2004, Dey filed a citizen petition requesting that the Commissioner impose a thirty-month stay on IVAX's ANDA (Dey Petition).³ Dey's submitted its petition based in part its conclusion that IVAX is entitled to 180-day exclusivity because IVAX was the first ANDA applicant to contain a paragraph IV certification.⁴

On August 30, 2004, Dey submitted a petition amendment requesting that the Commissioner impose a 30-month stay on Eon (Dey Amendment).⁵ Dey indicated that its petition amendment was based on its revised conclusion that Eon, rather than IVAX, is entitled to 180-day exclusivity. Although Dey received IVAX's paragraph IV notification (and, in fact, sued IVAX) prior to receiving Eon's paragraph IV notification, Dey proposed that Eon should be entitled to 180-day exclusivity because Eon submitted its ANDA prior to Dey's receipt of IVAX's notification.⁶

2. As the First Challenger, IVAX Is Entitled to 180-Day Exclusivity

IVAX is entitled to 180-day exclusivity because IVAX provided notice of its paragraph IV certification, and thereby exposed itself to an infringement suit, prior to Eon. This outcome is mandated in clear terms by the recent amendments to the paragraph IV notice provisions of the Food, Drug, and Cosmetic Act (FDCA).

In the Medicare Prescription Drug, Improvement, and Modernization Act of 2003⁷ (MMA), Congress amended the paragraph IV notice provisions (1) to require ANDA applicants submitting paragraph IV certifications to certify that they will provide notice and (2) *to require that the notice shall be provided by a date certain*. Parallel to these provisions, Congress revised the 180-day exclusivity provisions of the FDCA to make clear that exclusivity should be awarded to the first applicant that both submits a paragraph IV certification *and lawfully maintains the certification* under the new provisions of the statute. Thus, under the amended statute, the paragraph IV certification is not lawfully maintained for purposes of determining eligibility for exclusivity unless and until the actual-notice requirement is met.

² Citizen Petition, Docket No. 2004P-0324 (July 15, 2004).

³ *Id.*

⁴ *Id.* at 3.

⁵ Amendment to Citizen Petition, Docket No. 2004P-0324-AMD1 (August 30, 2004).

⁶ *Id.* at 2. IVAX is responding to the first Dey petition in a separate document submitted simultaneously with this petition. With its response to the Dey Petition, IVAX is submitting a copy of this petition as comment on Dey's assertion in its petition amendment that Eon is entitled to 180-day exclusivity.

⁷ Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003).

(a) The MMA Requires that the Applicant Maintain Its Paragraph IV Certification By Providing Notice.

Under the MMA, an ANDA applicant submitting a paragraph IV certification is required to maintain its certification by providing notice to the patent holder by a date certain:

- (i) AGREEMENT TO GIVE NOTICE- An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall include in the application a statement that the applicant will give notice as required by this subparagraph.
- (ii) TIMING OF NOTICE- *An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall give notice* as required under this subparagraph--
 - (I) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or
 - (II) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.⁸

The MMA provides an express enforcement mechanism for these notice requirements by defining 180-day exclusivity as a delay that would apply to an ANDA “submitted by an applicant other than a first applicant,” and by defining a “first applicant” as an applicant that “submits a substantially complete application that contains *and lawfully maintains* a [paragraph IV] certification” on the first day that any applicant submits such a certification. The amended statute provides in relevant part:

- (aa) 180-DAY EXCLUSIVITY PERIOD- The term “180-day exclusivity period” means the 180-day period ending on the day before the date on which an application submitted by an applicant other than a first applicant could become effective under this clause.
- (bb) FIRST APPLICANT- As used in this subsection, the term “first applicant” means an applicant that, on the first day on which a substantially complete application containing a certification described in paragraph (2)(A)(vii)(IV) is submitted for approval of a drug, submits a substantially complete application that contains *and lawfully maintains* a certification described in paragraph (2)(A)(vii)(IV) for the drug.⁹

Thus an applicant cannot qualify as a first applicant until the applicant satisfies the requirement that the paragraph IV certification be lawfully maintained by satisfaction of the notice requirement. Because there is no other duty placed on an ANDA applicant

⁸ FDCA § 505(j)(2)(B)(i), (ii) (emphasis added).

⁹ FDCA § 505(j)(5)(B)(iv)(II)(aa), (bb) (emphasis added).

with regard to a paragraph IV certification, the date of satisfaction of the notice requirement provides the date upon which the applicant has satisfied the requirement that the certification be lawfully maintained.

(b) The Date of Notice Provides the Most Reasonable Basis for Determining Eligibility for Exclusivity.

Although the notice provisions of the MMA apply to the ANDAs filed by Eon and IVAX,¹⁰ the 180-day exclusivity provisions, including the definition of first applicant, do not apply. FDA must thus apply the MMA notice provisions in determining 180-day exclusivity under the pre-MMA exclusivity provisions.

Although the pre-MMA statutory scheme provides no statutory requirement that exclusivity eligibility be determined based on the date of notice, FDA has found implied authority to impose such a requirement. The agency developed this policy based on its view that, where the statute requires that notice be provided by a date certain, first applicant eligibility for 180-day exclusivity logically should be determined based on the satisfaction of the notice requirement.

The agency's pre-MMA policy grew out of the agency's experience with ANDA applicants that failed to heed the express statutory mandate that, where a paragraph IV certification is submitted in an ANDA amendment, the applicant provide the notice on the date that the amendment is submitted.¹¹ The courts have agreed with FDA's approach because (1) the statute provided a mandate that the notice be provided by a date certain, (2) the statute provided no express enforcement mechanism for the notice requirement, and (3) FDA fashioned a reasonable enforcement mechanism by determining eligibility for exclusivity based on the date of compliance with the notice

¹⁰ On the date of enactment of the MMA, each ANDA was pending and neither applicant had satisfied the MMA notice requirement. Each applicant filed its paragraph IV certification after August 18, 2003. Thus the MMA notice provisions were applicable. MMA § 1101(c) provides in relevant part as follows:

(1) IN GENERAL- Except as provided in paragraphs (2) and (3), the amendments made by subsections (a) and (b) apply to any proceeding under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) that is pending on or after the date of the enactment of this Act regardless of the date on which the proceeding was commenced or is commenced.

(2) NOTICE OF OPINION THAT PATENT IS INVALID OR WILL NOT BE INFRINGED- The amendments made by subsections (a)(1) and (b)(1) apply with respect to any certification under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) submitted on or after August 18, 2003, in an application filed under subsection (b) or (j) of that section or in an amendment or supplement to an application filed under subsection (b) or (j) of that section.

¹¹ Letter to Apotex Corp. and Purepac Pharmaceutical Co. from Gary Buehler, FDA Office of Generic Drugs (Jan. 28, 2003).

requirement.¹² The alternative enforcement mechanism suggested under the pre-MMA statute, nullification of the paragraph IV certification, was rejected by FDA and properly considered “draconian” by one district court.¹³

The pre-MMA approach, permitting enforcement of statutory timeframes for notice through eligibility for 180-day exclusivity, remains a reasonable approach and provides the most a reasonable basis for enforcing the new MMA notice provisions.

(c) The MMA Notice Provisions Require the Same Enforcement Mechanism for Both ANDA Amendments and Original ANDAs.

Under the pre-MMA notice provisions, FDA’s enforcement mechanism was limited to paragraph IV certifications submitted in amended ANDAs. The agency did not interpret the statute to provide such an enforcement mechanism in the case of paragraph IV certifications submitted in original ANDAs because, under the pre-MMA statute, the notice requirement for an original ANDA was significantly different. In announcing its pre-MMA policy, the agency noted that the statutory notice provisions regarding ANDA amendments expressly required that the applicant provide notice on a date certain: “[I]f an application is amended to include a [paragraph IV certification], the notice required by clause (ii) *shall be given when the amended application is submitted.*”¹⁴ The pre-MMA provision governing submission of a paragraph IV certification in an original ANDA, however, unlike the new MMA notice provision, did not require a date certain for notice and did not even include an express mandate that notice be given. The statute rather provided that “an applicant who makes a [paragraph IV certification] shall include in the application *a statement that the applicant will give the notice . . .*”¹⁵

Under the MMA, Congress eliminated this distinction between original ANDAs and ANDA amendments, providing that for each submission the applicant not only shall provide a statement that the applicant will give notice¹⁶ but also “*shall give notice* as required under this subparagraph.”¹⁷ Although the MMA notice provisions provide differing timelines for an original application and for an amendment, the provisions provide an express mandate for notice by a date certain for both.

Consistent with these parallel requirements, Congress provided an enforcement mechanism under the MMA that is applicable to both forms of submission. That enforcement mechanism, like FDA’s pre-MMA enforcement mechanism, is based on the criteria for eligibility for 180-day exclusivity. In the MMA, eligibility for first applicant

¹² *Purepac v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004), *aff’g TorPharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 79-81 (D.D.C. 2003).

¹³ *TorPharm, Inc. v. Thompson*, 260 F. Supp. 2d at 81.

¹⁴ FDCA § 505(j)(2)(B)(ii) as in effect prior December 8, 2003 (emphasis added).

¹⁵ *Id.* § 505(j)(2)(B)(i) as in effect prior December 8, 2003 (emphasis added).

¹⁶ FDCA § 505(j)(2)(B)(i).

¹⁷ *Id.* § 505(j)(2)(B)(ii) (emphasis added).

status is determined based on the date of both submission of a paragraph IV certification and lawful maintenance of that certification through compliance with the notice requirement.

Although the MMA definition of first applicant does not apply to the ANDAs filed by IVAX and Eon, the MMA notice provisions do apply, and they no longer permit a notice enforcement mechanism that would apply to ANDA amendments but not to original ANDAs. The statute now expressly mandates that notice be given within a specified timeframe for both original applications and for amendments, using precisely the same wording for each type of submission. The fact that the timeframe is different for original applications (20 days after FDA acknowledgment of receipt of the ANDA) than for amendments (day of submission of amendment) provides no basis for enforcement of one requirement without enforcement of the other. There is nothing in the statute or legislative history to support the view that Congress was less concerned over timeliness of notices in original applications than over timeliness of notices in amendments. In fact, the new statute demonstrates the opposite intent. Congress rewrote the notice provisions to provide an express mandate for original applications that notice be provided within a statutory timeframe, using the same language as used in the notice requirement for ANDA amendments. The new provisions are a clear and direct statement that Congress' concern that notice be provided by a date certain in the case of an original ANDA was equal to its concern that notice be provided by a date certain in an ANDA amendment.

FDA must thus enforce the notice provisions of the MMA in the same manner for both original ANDA submissions and for ANDA amendments.¹⁸ Differing enforcement mechanisms would be arbitrary, capricious, and contrary to the clear intent of Congress that ANDA applicants provide notice in a timely manner for both original applications and amendments.

(d) Other Provisions of the MMA Support a Consistent Interpretation of the Exclusivity Eligibility Requirement.

A consistent interpretation of the first applicant eligibility requirement, based on date of notice for both original and amended or supplemental ANDAs, is required not only by the parallel wording of the notice provisions, but also by the broader structure and purposes of the MMA amendments.

¹⁸ This means that two ANDA applicants submitting original ANDAs containing paragraph IV certifications on the same day will not share first-filer status if one satisfies the notice requirement prior to the other. Because an applicant's ability to provide notice will depend on the issuance by FDA of a notification that its application has been received for filing, FDA should ensure that agency notifications of receipt for filing are issued at the end of the same period of time for each ANDA, or at least for each ANDA that does not present an unusual issue requiring additional time for the initial review. Thus, where two ANDAs are submitted on the same day, FDA would issue its notification of receipt for filing on the same day in the absence of an unusual issue involving one of the ANDAs.

One of the key purposes of the MMA amendments to the FDCA was to eliminate 30-month stays in the approval of an ANDA based on the listing of a patent during the agency's review of the ANDA. An inconsistent interpretation of the MMA notice requirements would undermine the purposes of the MMA restrictions on 30-month stays. Should the agency determine first applicant status for an original ANDA based on date of submission of the paragraph IV certification but determine first applicant status for an ANDA amendment based on date of notice, applicants that submit later ANDAs will enjoy an unfair advantage over applicants that have submitted ANDAs months earlier and whose applications may be well along in the review process.

This means that an applicant filing a later ANDA with a paragraph IV certification would always have an advantage over an applicant filing the same certification in a pending ANDA because first applicant status of the applicant filing the original ANDA would be determined based on the date of submission of the certification rather than on the date of satisfaction of the notice requirement. Moreover, the applicant submitting the new ANDA would be deemed a first applicant even if it later failed to comply with the statutory requirement that notice be provided within 20 days of FDA's acknowledgment of receipt of the ANDA.

This outcome would be not only unfair, but would also be directly contrary to Congress' clear intent to protect pending ANDAs from delays in approval based on patent listings during the review of the ANDA that might result in 30-month stays.¹⁹ The legislative history reveals that FDA, FTC, and Congress were all concerned over this problem. The FTC conducted a study and provided recommendations related to delays in generic drug approval resulting from the patent listing process²⁰ that played a central role in passage of the MMA.²¹ The FTC Report, cited in the legislative history, makes clear

¹⁹ FDCA § 505(j)(5)(B)(iii)(I), as amended by the MMA, provides as follows:

If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in paragraph (2)(B) is received, an action is brought for infringement of the patent that is the subject of the certification *and for which information was submitted to the Secretary under subsection (b)(1) or (c)(2) before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted*

(Emphasis added.) Dey argues in its original citizen petition that this provision permits 30-month stay based on the submission of patent information *after* the submission of the ANDA if the NDA holder did not submit any other patent information prior to the submission of the ANDA. Citizen Petition, Docket No. 2004P-0324 (July 15, 2004). As discussed more fully in comments filed on this date by IVAX in response to the Dey petition, Dey's proposed interpretation is contrary to the plain meaning of the statute and contrary as well to the congressional intent expressed in the legislative history of the statute.

²⁰ *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (2002) (FTC Report) (Tab 1).

²¹ See *Hearing Before the Senate Judiciary Comm. on the Senate and House Versions of the "Greater Access to Affordable Pharmaceuticals Act,"* 108th Cong. (2003) (remarks of Senator Hatch) ("The one and only 30-month stay for all patents filed when the ANDA was submitted was also a centerpiece of the Federal Trade Commission report issued last summer."); *id.*, (testimony of Dan Troy, Chief Counsel, FDA) ("Both the Senate and the House bills amend Hatch-Waxman to allow only one 30-

that the recommendation that 30-month stays be eliminated for patents listed during the review of an ANDA was based in part on the concern that such stays might delay the ANDA approval significantly beyond the normal review period. The Report states:

One 30-month period historically has approximated the time necessary for FDA review and approval of the generic's ANDA. Thus, it does not appear that the 30-month stay provision, as applied once to each ANDA for patents listed in the Orange Book prior to the ANDA's filing date, has a significant potential to delay generic entry beyond the time already necessary for FDA approval of the generic's ANDA²²

An interpretation of the statute that would determine eligibility for exclusivity for original ANDAs differently than for pending ANDAs, based on date of submission of the certification for the former and date of notice for the latter, would undermine this important statutory objective and potentially pose an unfair paradox in the case of IVAX's ANDA. IVAX developed a generic alternative to DuoNeb[®] ipratropium bromide/albuterol sulfate inhalation solution prior to any other generic drug company. IVAX submitted its ANDA on April 18, 2003. The DuoNeb[®] patent was not issued until October 16, 2003, and Dey (the NDA holder) has taken the position in a citizen petition that Eon's ANDA was submitted after the listing of the patent.²³ Thus an inconsistent interpretation of the first applicant eligibility requirement for 180-day exclusivity would not only award Eon 180-day exclusivity on the eve of completion of FDA's review of the IVAX ANDA, but would also block approval of IVAX's ANDA *during the 30-month stay* resulting from a patent lawsuit filed against Eon should the agency grant Dey's petition.

This outcome would be directly contrary to Congress' intent in passing the MMA to protect an ANDA from a 30-month stay on a later-listed patent that might delay approval beyond the normal review cycle. It would essentially impose a 30-month stay on IVAX's ANDA, based on a later-listed patent, that would delay approval of the ANDA beyond the normal review cycle – an outcome that would be clearly and extraordinarily unfair, and that would not withstand judicial review.

C. ENVIRONMENTAL IMPACT

As provided in 21 C.F.R. § 15.30 neither an environmental assessment nor an environmental impact statement is required.

month stay per drug product, per ANDA for patents listed in the Orange Book prior to the generic company filing its ANDA. The FTC Study recommended this exact change.”).

²² FTC Report at iv.

²³ Dey Amendment, *supra* n.1. In the petition amendment, Dey argues that Eon is subject to a 30-month stay because, according to Dey, Eon submitted its ANDA subsequent to the listing of the patent. Dey Amendment at 3.

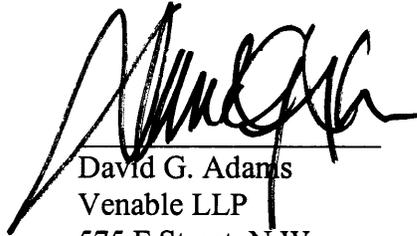
D. CERTIFICATION

As provided in 21 C.F.R. § 10.30(b) economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

E. ECONOMIC IMPACT

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

Respectfully submitted,

A handwritten signature in black ink, appearing to read "David G. Adams", is written over a horizontal line.

David G. Adams
Venable LLP
575 F Street, N.W.
Washington, D.C. 20004-1601
(202) 344-8014

Counsel for IVAX