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BY FEDERAL EXPRESS

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20857

Re: Docket No. 2004P-0520/CP1: Comments on Ivax Pharmaceuticals'  
Citizen Petition re 180-Day Exclusivity for Ipratropium Bromide and Albuterol  
Sulfate Inhalation Solution

Ladies/Gentlemen:

Dey, L.P. ("Dey"), holder of New Drug Application ("NDA") 20-950 for DuoNeb<sup>®</sup> (ipratropium bromide and albuterol sulfate inhalation solution), indicated for treatment of bronchospasm associated with chronic obstructive pulmonary disease, submits the following comments in opposition to the above-referenced citizen petition filed by Ivax Pharmaceuticals, Inc. ("Ivax").

Ivax's petition seeks a confirmation from the Food and Drug Administration ("FDA") that Ivax is entitled to a period of 180-day generic market exclusivity as the first applicant to file an Abbreviated New Drug Application ("ANDA") for a generic version of DuoNeb<sup>®</sup> containing a paragraph IV certification of invalidity or non-infringement against U.S. Patent No. 6,632,842 B2 ("the '842 patent") owned by Dey.<sup>1</sup> For the reasons set forth below, Ivax's petition should be denied.

**1. Eon Labs is the First Paragraph IV Filer**

Ivax bases its petition on the proposition that it was the first ANDA applicant to both file a paragraph IV certification against the '842 patent and send notice of its certification to Dey, the patent owner and NDA holder. (Ivax Petition at 2).

<sup>1</sup> While Ivax couches its petition in the subjunctive (Ivax is entitled to 180-day exclusivity if it is the first paragraph IV filer), it is clear from the petition as a whole that Ivax is seeking a ruling from FDA that it is eligible for exclusivity. Whether or not FDA issues a ruling on the first-filer issue or merely confirms the standards it will apply to this issue, the principles set forth in these by Dey comments should govern.

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However, Ivax glosses over the undisputed fact that Eon Labs Inc. ("Eon") was the first ANDA applicant to file a paragraph IV certification against the '842 patent. Eon's ANDA containing a paragraph IV certification was received (i.e., accepted for filing) by FDA on November 28, 2003 (see letter from FDA to Eon dated January 5, 2004, attached as Exhibit 1 to these comments). This was **12 days prior to December 9, 2003**, the date Ivax amended its ANDA to include a Paragraph IV certification (Ivax Petition at 1-2). Thus, **Eon is plainly the first paragraph IV filer**, or "first challenger" as Ivax's petition calls it.<sup>2</sup>

## 2. Eon Complied with the MMA Notice Statute

That Ivax sent notice of its paragraph IV certification to Dey before Eon did does not deprive Eon of its first-to-file status, and concomitant eligibility for 180-day exclusivity, **because Eon fully complied with the notice requirement** of the Medicare Prescription Drug Improvement and Modernization Act of 2003 ("MMA"). This requirement, embodied in 21 U.S.C. § 355(j)(2)(B)(ii)(I), provides:

"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."

Eon fulfilled this statutory mandate by sending a letter to Dey providing notice of its paragraph IV certification on January 20, 2004 (copy of notice letter attached as Exhibit 2 hereto), which was within 20 days of the date of FDA's letter of January , 004 informing Eon that its ANDA containing a paragraph IV certification had been received (accepted for filing) by the agency.

The MMA notice statute affords a time lag between the date an ANDA applicant files a paragraph IV certification and the date the applicant is required to send notice of the certification to the patent owner and NDA holder, to allow FDA sufficient time to review the ANDA for substantial completeness before receiving it for substantive review. In this respect, the MMA notice statute is consistent with (i) FDA regulation 21 C.F.R. § 314.101(b)(1), which provides a period of time for

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<sup>2</sup> See also Dey's related Citizen Petition 2004P-0324/CP1, AMD 1 dated August 30, 2004 (docketed September 2, 2004), and AMD 2 dated December 3, 2004 (docketed December 6, 2004). We note further that Eon has filed comments on Ivax's position, dated December 17, 2004, supporting Eon's position as first-filer based on the same analysis advanced herein.

the agency to review an ANDA to ascertain that the application is sufficiently complete to permit a substantive review, and (ii) FDA regulation 21 C.F.R. § 314.95(b), providing that the applicant shall send notice of its paragraph IV certification when it receives written acknowledgment from FDA that its ANDA has been received for review.

Ivax had to send notice when it did in order to comply with a further requirement of the MMA notice statute, namely, that an ANDA applicant who amends its application to include a paragraph IV certification must send notice to the patent owner and NDA holder "at the time at which the applicant submits the amendment." 21 U.S.C. § 355(j)(2)(B)(ii)(II) (emphasis supplied). Ivax had initially filed its ANDA in April 2003, but did not make a paragraph IV certification against the '842 patent until it amended its application on December 9, 2003. This notice requirement for ANDA amendments containing paragraph IV certifications is consistent with FDA regulation 21 C.F.R. § 314.95(d), which provides that notice be sent "at the same time" as the paragraph IV certification in an ANDA amendment is filed.

**3. The Difference in Timing of the Respective Notice Requirements Is Grounded in Law, and in Sound Policy**

The notice requirement applicable to ANDA amendments containing paragraph IV certifications is different from the notice requirement for such certifications in originally-filed ANDAs, in that an original applicant must wait to send notice until it is informed that its ANDA has been received by FDA, while an amending applicant must send notice when it files its amendment. This difference, however, is justified by valid legal and policy factors.

Under the Hatch-Waxman Amendments, even as amended by the MMA, a paragraph IV certification must inform the patent owner and NDA holder that an ANDA containing data from bioavailability or bioequivalence studies and a Paragraph IV certification against the pertinent listed patent "has been submitted" to FDA. 21 U.S.C. § 355(j)(2)(B)(iv)(II). As FDA long ago observed in the preamble to its proposed ANDA regulations, an applicant can only properly make this representation to comply with this statutory provision after the agency has reviewed the application and concludes that the ANDA is sufficiently "complete" for substantive review, with facially adequate bioavailability or bioequivalence data.<sup>3</sup>

Further, the difference in timing reflects statutory Congress' and FDA's sound policy judgment that notice be sent as soon as reasonably practicable. When an ANDA applicant amends its ANDA to include a paragraph IV certification, the applicant is obviously in a position to send notice at that time. On the other hand,

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<sup>3</sup> 54 Fed. Reg. 28872, 28887 (July 10, 1989).

an original ANDA applicant making a paragraph IV certification does not know at the time of submitting its application whether FDA will receive the application for substantive review. If the agency does not, notice to the patent owner and NDA holder will be premature, and maybe even superfluous. As FDA has pointed out:

“[r]eceipt of the notice by the patent owner or its representative or the approved application holder triggers the 45-day clock within which a patent owner or application holder must bring suit if it wishes to challenge an applicant’s certification of patent invalidity or noninfringement. The statute and legislative history of Title I [of Hatch-Waxman] demonstrate that Congress did not intend incomplete application submissions to trigger legal action by a patent owner or approved application holder.”<sup>4</sup>

**4. Ivax’s “Lawfully Maintains” Argument is Meritless**

Eon is the first paragraph IV filer against the ‘842 patent not only in fact, but also under the MMA definition of “first applicant for 180-day exclusivity purposes. This provision, 21 U.S.C. § 355(j)(5)(B)(iv)(II)(bb), defines a “first applicant” as

“...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.

FDA’s letter of January 5, 2004 (Exhibit 1 hereto) conclusively demonstrates that Eon is the first applicant to submit a paragraph IV certification against Dey’s ‘842 patent. That Eon has lawfully maintained this certification is evidenced by the facts that Eon has not withdrawn or amended this certification, and that its ANDA is pending before FDA.

Ivax’s argument that the words “lawfully maintains” relate to compliance with the MMA notice letter statute (Ivax Petition at 3-4) is an utter fabrication, unsupported by the language of either the MMA “first applicant” definition or the MMA notice statute. Not surprisingly, Ivax cites no authority for this self-serving contention, which is obviously a contrived effort to undermine Eon’s first-filer status. Even assuming, *arguendo*, that Ivax’s contention were accepted, Eon is the “first applicant,” because Eon is the first paragraph IV filer in fact and has lawfully

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<sup>4</sup> 54 Fed. Reg. at 28887.

maintained that status by satisfying the MMA notice statute (see p. 2, *infra*), without withdrawing or amending its Paragraph IV certification.

**5. Ivax's Remaining Arguments Are Misplaced**

- (i) Ivax's contention that the date of notice rather than the date of filing a paragraph IV certification provides a more reasonable basis for determining eligibility for exclusivity (Ivax petition at 4-5) flies in the face of the plain language of the 180-day exclusivity provision of Hatch-Waxman, 21 U.S.C. § 355(j)(5)(B)(iv).

While Ivax is correct that the pre-MMA version of Section 355(j)(5)(B)(iv) applies here in that both Ivax's and Eon's ANDAs were filed before the MMA enactment date (see MMA, Section 1102(b)(1), Ivax petition at 4), the plain language of that version of Section 355(j)(5)(B)(iv) make it absolutely clear that the "previous application" containing a paragraph IV certification (the ANDA of the first paragraph IV filer) is entitled to 180-day exclusivity. The 180-day exclusivity statute makes no mention of notice whatsoever in terms of qualification for exclusivity.

Nor does *Purepac Pharmaceutical Co. v. Thompson, et al.*, 354 F.3d 877 (D.C. Cir. 2004) (Ivax petition at 5, n. 12) aid Ivax here. That case stands for the principle that exclusivity is perfected by sending a notice letter in compliance with Hatch-Waxman, which Eon has done. Furthermore, that case only involved an ANDA amendment containing a Paragraph IV certification, whereas here Eon's ANDA is an originally-filed ANDA with a paragraph IV certification, which both pre- and post-MMA is governed by a different notice time frame (see pp. 2-4, *supra*). In any event, *Purepac v. Thompson* certainly did not substitute first notice for first filing as the statutory standard for eligibility for 180-day exclusivity.<sup>5</sup>

- (ii) Ivax's argument that the MMA notice provisions require the same "enforcement mechanism" for original ANDAs and ANDA amendments (Ivax petition at 5-6) is beside the point. Eon has satisfied the MMA notice requirement for the paragraph IV certification in its original ANDA, so there is no disparity of enforcement (indeed, there is nothing to enforce).

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<sup>5</sup> As the D.C. Circuit in its opinion stated: "Nothing in the statute says that applicants earn exclusivity by simultaneously filing and providing notice. In fact, the simultaneity requirement and the provisions regarding exclusivity appear in different sections of the statute. The simultaneity requirement appears in FDCA section 505(j)(2), which lays out the required elements of an ANDA. The exclusivity provisions are in FDCA section 505(j)(5), which addresses FDA approval of ANDAs." 354 F.3d at 889 (emphasis supplied).

- (iii) Finally, Ivax's argument that an inconsistent standard of determining first applicant status based on date of filing for original ANDAs but date of notice for amendments is being applied (Ivax petition at 6-7) is once again a red herring. There is only one 180-day exclusivity standard – first-to-file a paragraph IV certification – and Eon has met that standard here.

### **Conclusion**

Ivax's petition, at bottom, is a belated, unsupportable effort to rectify its tardiness in promptly amending its ANDA for a generic version of DuoNeb<sup>®</sup> to include a paragraph IV certification against the '842 patent once the patent was listed. Ivax waited too long to do so. Eon beat Ivax to the punch. Ivax's petition must be denied.

Sincerely,

DEY, L.P.



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