DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

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

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

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

I. Background

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

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

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

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

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

II. Statutory and Regulatory Provisions

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

> If the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection continuing [sic] such a certification, the application shall be made effective not earlier than one hundred and eighty days after-
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> > (I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
> >
> > (II) the date of a decision of a court in action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed,
>
> whichever is earlier.

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

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

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

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

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

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

The regulations further provide

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

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

III. Discussion

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

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

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

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

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

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

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

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

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

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

IV. Conclusion

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

Sincerely,

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