DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 76-203

APR 6 2004

Three Rivers Pharmaceuticals, LLC
Attention: Donald J. Kerrish
312 Commerce Park Drive
Cranberry Township, PA 16066

Dear Sir:

This is in reference to your abbreviated new drug application submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Ribavirin Capsules, 200 mg. Specifically, this letter addresses the matter of 180-day exclusivity under section 505(j)(5)(B)(iv) of the Act for abbreviated new drug applications (ANDAs) referencing Rebetol®, manufactured by Schering Plough (Schering).

As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book), multiple patents are listed for this drug product. The patent numbers and expiration dates of the patents listed in the Orange Book for NDA 20-903 are:

U.S. Patent No. 5,767,097	expiration (with pediatric exclusivity)	July 23, 2016
U.S. Patent No. 5,914,128	"	June 22, 2018
U.S. Patent No. 6,051,252	"	June 22, 2018
U.S. Patent No. 6,063,772	"	July 23, 2016
U.S. Patent No. 6,172,046	"	March 21, 2018
U.S. Patent No. 6,335,032	"	June 22, 2018
U.S. Patent No. 6,337,090	"	June 22, 2018
U.S. Patent No. 6,177,074	"	May 1, 2017
U.S. Patent No. 6,461,605	"	May 1, 2017
U.S. Patent No. 6,472,373	"	March 21, 2018
U.S. Patent No. 6,524,570	"	May 1, 2017[1]

(Note: Patents will be referred to in this letter by the last three digits of the patent number.)

[1] Please note that there are two drug products approved in NDA 20-903. One product (001) is Rebetol as labeled for co-packaging as Rebetron® with Intron-A® (interferon alfa-2b, recombinant) Injection, a biological product licensed under the Public Health Service Act. Product 002 is Rebetol as a stand-alone ribavirin capsule product, marketed for use with (but not co-packaged with) Intron-A or PEG-Intron (peginterferon alfa-2b, recombinant) Injection. The Orange Book currently has the 11 patents identified above listed under product 001 for NDA 20-903, and only seven of those patents listed under product 002. After reviewing the documentation for the submission of the listed patents by Schering, FDA believes that Schering intended to have all 11 patents listed for NDA 20-903, without distinguishing between products 001 and 002. This conclusion was confirmed in a March 16, 2004 letter from Schering. Applicants with ANDAs referencing Rebetol as a stand-alone product have acknowledged all 11 patents in their applications. FDA considers all 11 listed patents relevant to its 180-day exclusivity analysis.

We have reviewed the submissions, including original applications and amendments, for the ANDAs referencing Rebetol as a stand-alone product, and have determined that different applicants were the first to submit paragraph IV certifications for these patents. Three Rivers was the first to submit a paragraph IV certification as to the '032 patent, the '090 patent, the '605 patent, and the '373 patent. Another ANDA applicant was the first to submit a paragraph IV certification as to other listed patents.

As you may be aware, in a limited number of cases, FDA has addressed the situation in which different ANDA applicants were first to submit patent challenges as to different listed patents. FDA has adopted the "shared exclusivity" approach to address eligibility for 180-day exclusivity in these circumstances.[2]

The facts related to Ribavirin ANDAs present many of the same issues as were addressed by FDA in its first application of the shared exclusivity approach to approval of ANDAs for omeprazole delayed-release capsules in November 2001. As explained below, the same general principles apply to the Ribavirin ANDAs.

Background

The statutory provision governing 180-day exclusivity in this case reads:

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

Section 505(j)(5)(B)(iv).[3]

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[2] The "shared exclusivity" approach described and applied in this letter to ribavirin ANDAs was also applied to approvals of ANDAs for paroxetine. FDA's application of the "shared exclusivity" approach to the paroxetine ANDAs was successfully challenged in *TorPharm, Inc. v. FDA*, CA. No. 03-02401(D.D.C.). FDA is appealing the district court's Final Order of January 8, 2004, and will continue to apply the shared exclusivity approach to ANDA approvals during the pendency of that appeal, or until further developments warrant the suspension of that approach.

[3] The referenced provision governing paragraph IV certifications at section 505(j)(2)(a)(vii)(IV) states 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 referred to in clause (i) or which claims a use for such listed drug for which the

FDA's regulations at 21 C.F.R. § 314.107(c)(1) & (2) address the beginning of 180-day exclusivity as follows:

> 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 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
> (ii) The date of a decision of the court holding the relevant patent invalid, unenforceable, or not infringed.
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> The "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.

In the last five years, the agency has, on several occasions, been required to construe the statute and apply its regulations in such multiple patent situations. In 1999, FDA first considered whether multiple ANDA applicants each may be eligible for 180-day exclusivity because each applicant was the first to file a paragraph IV certification to a different patent for the listed drug. In responding to a 1999 citizen petition relating to approval of ANDAs for the drug product cisplatin, FDA construed the statute and the pertinent regulations, and determined that eligibility for 180-day exclusivity would be based on who filed the first paragraph IV certification for each listed patent. The plain terms of the statute appear to require separate 180-day periods for each patent claiming the listed drug. The statute does so by containing references to "each" patent rather than to "all" patents listed for a particular drug in the relevant exclusivity provision itself and the provision it cross-references. 21 U.S.C. § 355(j)(2)(A)(vii). Under FDA regulations, a "subsequent" ANDA with a paragraph IV certification relating to the "same patent" as a previous ANDA paragraph IV certification is not eligible for approval until the first ANDA's exclusivity has run. 21 C.F.R. § 314.107(c)(1).

In FDA's view, the regulation's reference to the "same patent" as opposed to "any" patent or "all patents related to the same drug" means that eligibility for exclusivity is based upon the

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applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c)...

(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.

particular patent at issue and not the drug product as a whole. As a result, multiple applicants may be eligible for periods of exclusivity for a single drug product, because they each may have filed the first paragraph IV challenge to different patents. The agency has referred to this approach to determine eligibility for exclusivity as a "patent-by-patent" or "patent-based" analysis. That is, the first applicant with a paragraph IV certification for each listed patent is separately eligible for 180-day exclusivity based on that patent.[4]

Exclusivity Standoff

The agency has recognized, however, that if eligibility for exclusivity is patent-based, without regard to the facts and circumstances of specific applications, the agency could be prevented from approving ANDAs referencing a particular drug product by multiple conflicting exclusivities, which is inconsistent with the purpose and operation of the statute. This issue is discussed in some detail in the preamble to the proposed rule addressing changes to the ANDA approval regulations. 64 Fed. Reg. 42873, 42875-6 (August 6, 1999); *withdrawn* 67 Fed. Reg. 66593 (Nov. 1, 2002).

The situation with omeprazole ANDAs referencing Prilosec illustrated how untenable the patent-based multiple exclusivity approach could be in certain situations, when there are multiple patents listed for the listed drug and different first applicants for these patents. Under the patent-by-patent approach described in the cisplatin petition response, different ANDA applicants would have been eligible for exclusivity with respect to different patents listed for the reference listed drug. Absent a regulatory solution, these different exclusivity periods would have blocked approval of omeprazole ANDAs indefinitely.

An exclusivity stand-off whereby each ANDA applicant's approval is delayed indefinitely would be so at odds with both the narrow purpose of the 180-day exclusivity provision and the broader purposes of 1984 Drug Price Competition and Patent Term Restoration Act (the Hatch-Waxman Amendments) as to be absurd. Court decisions, including *Mova Pharmaceutical Corp., v. Shalala*, 140 F.3d 1060, 1074 (D.C.Cir. 1998), observe that the 180-day exclusivity period is intended as a reward to the ANDA applicant who challenges a listed patent. Such a challenge may make it possible for generic drugs to be approved before the expiration date of the challenged patent. The exclusivity stand-off would prevent the ANDA applicants who are eligible for the exclusivity from benefiting in any meaningful way from the exclusivity, and

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[4] Congress recently amended section 505(j) of the Act to change the patent-based approach to a product-based approach for 180-day exclusivity. See The Access to Affordable Pharmaceuticals provisions of the Medicare Prescription Drug, Improvement, and Modernization Act, Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003). Under these new provisions, only the first applicant to file a paragraph IV certification to any listed patent will be eligible for 180-day exclusivity; however, there may be multiple first applicants when more than one applicant files an ANDA with a paragraph IV certification to the same patent on the same "first" day. Section 1102(a)(1). To protect the incentive structure that Congress intended in the Hatch-Waxman Amendments, the new legislation also includes incentives for applicants to challenge as many patents as early as possible and certain forfeiture provisions to ensure that a first applicant's eligibility for 180-day exclusivity will not unreasonably delay the approval of subsequent ANDAs. Section 1102(a)(2). These 2003 amendments do not apply to the ribavirin ANDAs at issue here because the first ANDA referencing Rebetol that contained a paragraph IV certification was submitted before December 8, 2003. Section 1102(b)(1). The references to relevant statutory provisions throughout this document are references to the provisions as they apply to the specific ANDAs under consideration, that is to the 1984 Hatch-Waxman provisions, not to the amendments made in 2003.

could substantially and indefinitely delay the availability of lower cost drugs for consumers. In that case, the eligible first ANDA applicants would be hamstrung by the very provision intended to provide them a benefit, and competition would be stifled by the very provision intended to encourage it. The only beneficiary of this interpretation would be the innovator who – despite the expiration of 30-month stays on ANDA approval – would see an indefinite extension of its monopoly market in a manner inconsistent with the intent of the Hatch-Waxman Amendments.

Regulatory Solution

To avoid results that cannot be reconciled with the purposes of the 180-day exclusivity provision in particular and the Hatch-Waxman Amendments in general, the agency has sought an approach to 180-day exclusivity that both hews as closely as possible to statutory language and is consistent with the goals of the legislation. It seems clear that, in 1984, Congress did not anticipate, and therefore did not address, this factual situation in drafting the 180-day exclusivity provisions of the Act, and FDA certainly did not contemplate it in promulgating in 1994 the regulations now in effect. As noted in the cisplatin petition response, these regulations were adopted when the agency interpreted the statute to require that an ANDA applicant be sued and win its patent litigation to qualify for exclusivity. The chances of two applicants, each of whom was first for a different patent, winning their patent litigation was extremely low.[5]

The text of the 1984 amendments to the Act does not address the situation in which two ANDA applicants' eligibility for exclusivity will create a standoff in approvals, and the legislative history is similarly unilluminating. Accordingly, the agency has the discretion to construe the statute reasonably to further the purposes of the statute. Alternatively, even if the statutory language could be interpreted to result in an exclusivity standoff, such an interpretation would be inconsistent with the purpose of the statute, inconsistent with agency policy, and the agency should reject it for producing an absurd result.

Once the interpretation resulting in the exclusivity standoff is rejected, the choice appears to be between rewarding all applicants who submitted a first paragraph IV ANDA by giving them all the shared chance to market during the exclusivity period, or rewarding the very first applicant to challenge any listed patent by giving that applicant the entire exclusivity period to itself.

Under the usual application of the 180-day exclusivity provision, the agency would approve the ANDA eligible for exclusivity whenever it was ready for approval, and the exclusivity would begin to run, independent of the approval, with the commercial marketing of that drug product or with a court decision on the patent, whichever was first. However, when two or more applicants have exclusivity as to different patents that effectively blocks one another, the approval of the eligible ANDAs (and thus the possibility of the commercial marketing trigger coming into play) cannot occur without some resolution of the stand-off. The agency reviewed two approaches to resolving the question of which ANDA(s) may be approved - and when – in cases where different applicants are first to submit paragraph IV certifications to different patents.

[5] In the years from 1984 to 1998, only three ANDA applicants qualified for 180-day exclusivity. Since the *Mova* decision in 1999, over 80 ANDAs have received 180 days of exclusivity.

FDA determined that when approval of an ANDA eligible for exclusivity is blocked by another applicant's eligibility for exclusivity, the applicants that are eligible for the 180-day period of generic drug exclusivity may share the same exclusivity period. An approach that shares the exclusivity among all of the first ANDA applicants ("shared exclusivity") would reward the first applicants to submit a paragraph IV certification with respect to any listed patent, and is therefore consistent with the most natural reading of the statutory text, which refers to the paragraph IV certification for the patent. The general approach to shared exclusivity is as follows:

When different applicants have submitted first paragraph IV ANDAs for different listed patents, FDA will approve the ANDAs that are first for any listed patent as soon as they are otherwise eligible for approval. That is, if it is only another applicant's eligibility for 180-day exclusivity as to a different patent that would block approval for an applicant that is itself eligible for 180 days of exclusivity, FDA will approve the ANDA. Exclusivity for all the ANDAs eligible for exclusivity at that time will be shared, and it will be triggered by the earlier of either first commercial marketing of any first applicant or a court decision on any one of the patents that qualified any applicant for exclusivity.[6] During that "shared" exclusivity period, FDA may approve any ANDA eligible for exclusivity, but no other ANDAs.

Obviously, this approach may deprive any one applicant of the chance to be the sole competitor to the NDA holder. But the exclusivity is already structured in such a way that eligibility for exclusivity does not guarantee 180 days as the sole marketed generic drug (i.e., the court decision trigger could start exclusivity before an ANDA is approved, or uncertainty over the patent could result in no marketing of an approved product until an affirmance in the Federal Circuit of a district court win). A shared exclusivity approach will limit the number of ANDAs approved during the exclusivity period to the number of "first" applicants. Moreover, it may give each first applicant some part of the benefit from removing the multiple patents as barriers to approval, when any one of those patents could have delayed approval of ANDAs. There is also a clear benefit to consumers if FDA were to approve more than one ANDA: with multiple ANDAs approved and eligible for exclusivity, it is more likely that the exclusivity period will be triggered more quickly and at least one of the generic drugs will reach the market during the exclusivity period. Past experience has shown that first generics who are the sole applicants eligible for exclusivity often find it in their interest not to begin the exclusivity period.

FDA rejected a "one first applicant" approach, which would give all the exclusivity to the very first ANDA applicant to submit a patent challenge to any patent listed for the innovator drug.[7] FDA would approve only the ANDA of the applicant who submitted the first paragraph IV certification for any patent, regardless of the patent for which it was submitted. That applicant's

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[6] FDA has been asked to clarify which court decisions on which patents may begin the running of "shared" exclusivity. FDA intends that exclusivity could be triggered by a court decision on any of the patents that qualify an ANDA applicant for exclusivity as of the time of the application of the shared exclusivity: that is, at the time an applicant eligible for 180-day exclusivity is ready for final approval except for another applicant's eligibility for 180-day exclusivity as to another patent.

[7] The court in *TorPharm, Inc. v. FDA* reasoned that the statute grants 'one first applicant' exclusivity in marketing the new generic drug. *See supra* n.2. FDA disagrees with the court's reading of Section 505(j)(5)(B)(iv) and has appealed the decision.

exclusivity would then begin to run with first marketing or a court decision on the patent that is the subject of the first certification. During the exclusivity period the agency would approve no other ANDA for the listed drug. When the exclusivity expired, all subsequent applicants would be eligible for approval if they otherwise met the approval requirements.

The one first applicant approach would reward the first applicant to begin to clear the path to ANDA approvals by challenging a listed patent. However, the agency believes that this approach would be less consistent with the statutory language than the shared exclusivity option, because this approach would be based upon a challenge to only one listed patent (the one for which the earliest paragraph IV certification was submitted). As noted above, the statute appears to apply exclusivity specifically with respect to an ANDA containing a paragraph IV certification for a patent for which a previous paragraph IV certification has been received for the same patent. Also, although promptness in challenging patents listed early in the Orange Book is important, it is certainly not adequate to remove the barriers to approval posed by later listed patents. Finally, by vesting the power to begin the exclusivity and the marketing of the drug in the hands of only one applicant, this approach would hold the potential for delays in the approval of generic drugs because there may be no court decision on this particular patent and the sole first applicant might not begin commercial marketing of its drug product. As a result, the 180-day exclusivity period would not begin to run, and the availability of multiple generic drugs could be substantially delayed.

Thus, the agency has adopted the shared exclusivity approach as more consistent with the statutory language before the recent amendments, and with the intent of both the 180-day exclusivity provision and the Hatch-Waxman Amendments. FDA has now applied this approach on several occasions.

Shared 180-Day Exclusivity and Ribavirin Capsules

Shared exclusivity applies to Ribavirin Capsule ANDAs because different applicants are eligible for 180-day exclusivity as to different listed patents.

The agency has determined that Three Rivers' ANDA was the first substantially complete ANDA to contain a paragraph IV certification as to the '032 patent, the '090 patent, the '605 patent, and the '373 patent. Another applicant was the first to submit paragraph IV certifications as to other listed patents. No one is eligible for 180-day exclusivity as to some patents. Currently, no ANDA applicant has a paragraph IV certification to the '074 patent; therefore, no applicant is eligible for 180-day exclusivity as to that patent. Only one applicant has a paragraph IV certification to the '570 patent; other applicants have submitted section viii statements. In the absence of a subsequently submitted paragraph IV certification to the '570 patent, the applicant is not eligible for 180-day exclusivity as to that patent under Section 505(j)(5)(B)(iv).

Finally, exclusivity as to the '097 and '772 patents was triggered by the entry of final judgment for TEVA on August 11, 2003, following the July 14, 2003 district court decision in the consolidated case *ICN v. Geneva et al.*, 272 F. Supp. 2d 1028 (C.D. Cal.), finding the patents not infringed by any of the ANDA applicants. Under the approach first applied in the ranitidine case, a decision of invalidity or non-infringement in any patent infringement litigation regarding

the patent can trigger the running of exclusivity. See *Granutec v. Shalala*, 139 F. 3d 889 (4th Cir 1998). The August 11, 2003, entry of judgment in the TEVA case, therefore, was a court decision triggering the running of exclusivity for the '097 and '772 patents. The exclusivity as to these patents has run and, as a result, the applicant who was first to submit a paragraph IV certification for these patents is no longer to be considered for shared exclusivity on that basis.

Therefore, FDA has determined that it will approve your ANDA, and the ANDA of any other applicant also eligible for 180-day exclusivity, as soon as they are otherwise eligible for approval (i.e., all patents with a paragraph III certification have expired, no 30-month stay, ANDA meets other 505(j) approval requirements, etc.). Approval of an ANDA will not trigger the beginning of exclusivity. Exclusivity will begin to run with 1) the first commercial marketing of the drug product by any sponsor eligible for 180-day exclusivity, or 2) a court decision on any of the patents as to which any applicant qualified for the 180-day exclusivity, whichever comes first. During the 180-day exclusivity period only those applicants eligible for exclusivity may be approved. Once the 180 days of exclusivity expires, FDA may approve any other ANDAs for Ribavirin Capsules that are otherwise eligible for approval.

Please note that a letter containing substantially the same information is being sent to any other ANDA applicant eligible to share the 180-day exclusivity for Ribavirin Capsules. If you have any questions regarding this letter, please contact Ms. Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 301-827-5845.

Sincerely,

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

cc: Daniel E. Troy, OCC