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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

3103 '03 JUN 23 A9:34

Re: Docket No. 03P-0160 – Wyeth's Comments in Response to Genpharm's Petition for Rejection of Perrigo's Section 505(b)(2) NDA For Loratadine Tablets

Dear Sir or Madam:

Wyeth respectfully submits these comments in response to the above-referenced Citizen Petition, filed on behalf of Genpharm Inc., in which Genpharm requests that FDA refuse to approve the 505(b)(2) NDA submitted by L. Perrigo Company ("Perrigo") for a loratadine tablets 10 mg drug product. These comments also respond to Genpharm's reply comments dated May 12, 2003, and to Novartis Consumer Healthcare's comments dated May 21, 2003. As discussed herein, Genpharm's petition should be denied to the extent it requests that FDA determine that Perrigo's 505(b)(2) NDA is completely ineligible for approval due to the fact that the Reference Listed Drug, Claritin® tablets, has been converted to OTC status.

I. Perrigo's 505(b)(2) NDA May Eventually Be Approved Notwithstanding the OTC Switch of the Reference Listed Drug

Perrigo, like Wyeth, pursued approval of an OTC loratadine product through the 505(b)(2) NDA process by filing its NDA prior to FDA approval of Schering's voluntary OTC switch of Claritin. This approach was completely proper because Claritin, the Reference Listed Drug ("RLD"), was not, at the time of Perrigo's NDA filing, approved for OTC sale, and accordingly it was not possible for Perrigo or any other applicant to obtain OTC approval through an Abbreviated New Drug Application (ANDA). *See* 21 C.F.R. § 314.94 (requiring "sameness" of ANDA product and RLD); 21 C.F.R. § 314.54(a) (allowing 505(b)(2) NDA for modifications to RLDs); Draft Guidance for Industry: *Applications Covered by Section 505(b)(2)* at 6 (October, 1999) (same).

The fact that the difference which required Perrigo to submit its application in the form of a 505(b)(2) NDA – i.e., OTC use of a prescription product – was eliminated by Schering's voluntary switch of Claritin to OTC status after the filing, but prior to the approval, of Perrigo's NDA, does not preclude FDA from eventually approving Perrigo's properly filed NDA.

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First, the relevant statute, regulations, and FDA's Draft Guidance governing 505(b)(2) NDAs are specifically directed only at the eligibility criteria for the *submission* of such applications, and do not address approvability criteria. *See* 21 U.S.C. § 355(b)(2), 21 C.F.R. § 314.54, *Procedure For Submission Of An Application Requiring Investigations For Approval Of A New Indication For, Or Other Change From, A Listed Drug* ("Any person seeking approval of a drug product that represents a modification of a listed drug...may...submit a 505(b)(2) application.") (emphasis added). It is beyond dispute that Perrigo's NDA qualified for submission under section 505(b)(2) at the time it was submitted.

Second, the statute and regulations set forth specific, and limited, criteria by which FDA is authorized to refuse to approve an NDA, including a 505(b)(2) NDA. *See* 21 U.S.C. §§ 355(c), (d); 21 C.F.R. §§ 314.105, 314.125. These provisions do not permit FDA to refuse to approve a product for which a 505(b)(2) was properly submitted but for which an applicant subsequently could have submitted an ANDA. Specifically, the statute and regulations require FDA to approve an NDA submitted under section 505(b) (including a 505(b)(2) NDA) unless one of the enumerated reasons for refusing such approval applies. 21 U.S.C. § 355(c)(1)(A) ("the Secretary shall...approve the application if he finds that none of the grounds for denying approval specified in subsection (d) applies."); 21 C.F.R. § 314.105(a) (FDA "will approve an application ... if none of the reasons in § 314.125 for refusing to approve the application apply.") (emphases added). Thus, FDA may only refuse to approve Perrigo's 505(b)(2) NDA if FDA finds that one of the following applies:

> **(1)** the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;
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> **(2)** the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions;
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> **(3)** the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity;
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> **(4)** upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or
>
> **(5)** evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or
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> **(6)** the application failed to contain the patent information prescribed by subsection (b) of this section; or

> (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular.

21 U.S.C. § 355(d). Because none of these statutory non-approval grounds relate to the scenario at issue here – a 505(b)(2) for a product that subsequently becomes eligible for approval under an ANDA – Genpharm's assertion that Perrigo's 505(b)(2) NDA is ineligible for approval due to the Claritin OTC switch must be rejected.[1]

Moreover, although Genpharm argues that approval of Perrigo's 505(b)(2) NDA would reward Perrigo for allegedly "gaming" the Hatch-Waxman scheme in order to jump ahead of pending ANDAs for competing loratadine products, Petition at 5-7, adopting Genpharm's erroneous interpretation could have the much more troubling effect of removing any incentive to seek innovative changes to existing drugs through the 505(b)(2) NDA process. This is because when the sponsor of an RLD learns of a pending 505(b)(2) NDA through the Paragraph IV Notification procedure, the sponsor/patent holder could sue the 505(b)(2) applicant, thereby imposing an automatic 30-month approval stay on the 505(b)(2) NDA. During that period, the RLD sponsor could seek to obtain approval of the change proposed in the 505(b)(2) application for the RLD itself. After such change was approved for the RLD, the 505(b)(2) applicant would have to file an ANDA, but would then itself be at risk of having its approval delayed by 180 days if another ANDA sponsor filed a Paragraph IV ANDA before the 505(b)(2) applicant re-filed its application as an ANDA.

Indeed, that is essentially what happened with respect to loratadine. Until Wyeth notified Schering of its filing of a 505(b)(2) NDA for an OTC loratadine product, Schering had steadfastly refused to switch Claritin to OTC status. Shortly after it learned of Wyeth's plans, however, Schering sought the OTC switch of Claritin. Fortunately, FDA's lawful and eminently correct approval of Wyeth's 505(b)(2) NDA, even though it occurred after the approval of the Claritin switch, avoided giving an undeserved head start to ANDA applicants who made no innovative effort to bring about the change to the RLD. Under Genpharm's approach, Wyeth's and Perrigo's investment and efforts to bring to market previously unavailable OTC loratadine products would have been severely compromised, to the detriment of the consuming public. FDA should not adopt the Genpharm approach because to do so would not only be contrary to law, but would also be bad public policy.

Novartis Consumer Healthcare, Inc. ("NCH") filed comments on May 21, 2003 supporting Genpharm's interpretation that FDA may, and should, refuse to approve Perrigo's 505(b)(2) NDA because of the changed circumstances arising from Schering's Rx→OTC switch of Claritin. NCH, like Genpharm, makes the fatal error of failing to acknowledge the dispositive statutory approval criteria discussed above. NCH also

[1] The implementing regulations reiterate and clarify these non-approval criteria, and like the statute itself, do not preclude approval of Perrigo's 505(b)(2) NDA on the grounds asserted by Genpharm. The governing regulation, 21 C.F.R. § 314.125, is set forth in relevant part as an addendum to these comments.

attempts to paint an "extreme" example of a 505(b)(2) NDA being filed a day before the approval of a change in the reference listed drug that would thereafter allow filing of an ANDA for the changed version of the RLD. NCH Comments at 3. However, this example is inapposite because, as shown above, the 505(b)(2) submission criteria differ from the NDA approval criteria, and FDA is not at liberty to alter the governing statutory and regulatory approval criteria merely because, in one unusual hypothetical circumstance, an interested party characterizes the application of the unambiguous legal requirements as "extreme."

Finally, Genpharm argues in its May 12 reply comments that FDA's approval of Wyeth's Alavert 505(b)(2) NDA is distinguishable from the Perrigo 505(b)(2) NDA because Alavert is an orally disintegrating tablet whereas Perrigo's product is intended to be swallowed. Specifically, Genpharm argues that Wyeth's 505(b)(2) was appropriately approved because, Genpharm surmises, "Wyeth evidently submitted additional studies to FDA demonstrating that its orally disintegrating tablet is safe and effective, thereby warranting 505(b)(2) approval." Genpharm reply comments at 2. Genpharm is misinformed. Alavert is an orally disintegrating tablet, as is the reference listed drug – Claritin Redi-Tabs – upon which Wyeth's 505(b)(2) NDA relied, in part, for approval. Thus, FDA's lawful and correct bases for approval of Alavert® are equally applicable to Perrigo's 505(b)(2) NDA, and Genpharm's asserted point of differentiation is simply inapposite.

CONCLUSION

For the foregoing reasons, Genpharm's petition should be denied.

Respectfully submitted,

James N. Czaban
Counsel for Wyeth

cc: Geoffrey M. Levitt, Vice President & Chief Regulatory Counsel, Wyeth Pharmaceuticals
Kathy A. Gleason, Assistant General Counsel, Wyeth; Senior Vice President, Wyeth Consumer Healthcare

21 C.F.R. § 314.125 Refusal to Approve an Application

(a) The Food and Drug Administration will refuse to approve the application...if: (3) FDA finds that any of the reasons given in paragraph (b) of this section apply.

(b) FDA may refuse to approve an application for any of the following reasons:

(1) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability.

(2) The investigations required under section 505(b) of the act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(3) The results of the tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.

(4) There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(5) There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in § 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

(6) The proposed labeling is false or misleading in any particular.

(7) The application contains an untrue statement of a material fact.

(8) The drug product's proposed labeling does not comply with the requirements for labels and labeling in part 201.

(9) The application does not contain bioavailability or bioequivalence data required under part 320 of this chapter.

(10) A reason given in a letter refusing to file the application under § 314.101(d), if the deficiency is not corrected.

(11) The drug will be manufactured or processed in whole or in part in an establishment that is not registered and not exempt from registration under section 510 of the act and part 207.

(12) The applicant does not permit a properly authorized officer or employee of the Department of Health and Human Services an adequate opportunity to inspect the facilities, controls, and any records relevant to the application.

(13) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211.

(14) The application does not contain an explanation of the omission of a report of any investigation of the drug product sponsored by the applicant, or an explanation of the omission of other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source.

(15) A nonclinical laboratory study that is described in the application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(16) Any clinical investigation involving human subjects described in the application, subject to the institutional review board regulations in part 58 of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

(17) The applicant or contract research organization that conducted a bioavailability or bioequivalence study described in § 320.38 or § 320.63 of this chapter that is contained in the application refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer or employee of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

(18) For a new drug, the application failed to contain the patent information required by section 505(b)(1) of the act.