



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

JUN 24 2004

Food and Drug Administration  
Rockville MD 20857

7723 20 JUN 25 7:47

Charles J. Raubicheck, Esq.  
Frommer Lawrence & Haug LLP  
745 Fifth Ave.  
New York, NY 10151

Re: Docket No. 03P-0160/CP1 &amp; RC1

Dear Mr. Raubicheck:

This responds to your citizen petition dated April 15, 2003 (Petition), and your supplemental comments dated May 12, 2003 (Comments), both on behalf of Genpharm Inc. (Genpharm).<sup>1</sup> Your petition requests that the Food and Drug Administration (FDA) refuse to approve the new drug application (NDA) submitted by L. Perrigo Company (Perrigo) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(b)(2)) for loratadine tablets, 10 milligrams (mg) (Perrigo's NDA or 505(b)(2) application).<sup>2</sup> Specifically, you submit that (1) Perrigo's 505(b)(2) application is ineligible for approval, and (2) even if this application were eligible for approval, it could not be approved because of a 30-month stay of approval in effect under section 505(c)(3)(C) of the Act (21 U.S.C. 355(c)(3)(C)).<sup>3</sup> As explained below, we reject the first claim on which your request is premised. As also discussed in this letter, we agree that a 30-month stay of approval on Perrigo's NDA was in effect when your petition was submitted; however, this stay has since been terminated by a court decision. Therefore, your petition is denied.

**I. BACKGROUND**

The key facts underlying your petition and considered in our analysis are set forth as follows. As Perrigo has noted, its 505(b)(2) application seeks approval for loratadine tablets, 10 mg, for over-the-counter (OTC) sale.<sup>4</sup> Perrigo has acknowledged that its application references the listed drug<sup>5</sup> Claritin (loratadine tablets, 10 mg), marketed by

<sup>1</sup> In addition to your petition and comments, we have considered the following comments we received in the petition docket: comments from Perrigo dated April 29, 2003, and June 5, 2003; comments from Novartis dated May 21, 2003; and comments from Heller Ehrman on behalf of Wyeth dated June 20, 2003.

<sup>2</sup> A 505(b)(2) application is an NDA submitted under section 505(b)(1) of the Act for which at least some of the information required for approval comes from studies that were not conducted by or for the applicant and that the applicant does not have a right to reference or use. (See 21 U.S.C. 355(b)(2).)

<sup>3</sup> After your petition was submitted, section 505(c)(3)(C) was amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Pub. L. 108-173) (MMA), enacted on December 8, 2003, which we consider where applicable in this response.

<sup>4</sup> See April 29, 2003, Perrigo comments at 2.

<sup>5</sup> A *listed drug* is defined as:

a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or

03P-0160

PDN1

Schering Corporation (Schering), and has also disclosed that its NDA was submitted at a time when Claritin was available by prescription only.<sup>6</sup> Schering obtained approval to switch Claritin from prescription to OTC status after Perrigo's NDA was under review.

As you are aware, Perrigo provided in its NDA a paragraph IV certification for Patent No. 4,659,716 owned by Schering (the '716 patent).<sup>7</sup> Within 45 days of receiving notice of Perrigo's paragraph IV certification, Schering sued Perrigo on December 2, 2002, alleging infringement of claims 1 and 3 of the '716 patent.<sup>8</sup> In accordance with the Act, this action required FDA to stay approval of Perrigo's NDA for 30 months from the date that Schering received Perrigo's notice unless, in relevant part, the court decided before the expiration of the 30-month period that the patent was invalid or not infringed.<sup>9</sup>

Prior to the time your petition was submitted, and before Schering commenced its litigation challenging Perrigo's NDA on December 2, 2002 (Schering-Perrigo NDA litigation), the United States District Court for the District of New Jersey had decided the invalidity of claims 1 and 3 of the '716 patent in other actions brought by Schering.<sup>10</sup> These other actions involved various applicants, including Perrigo, that had filed abbreviated new drug applications (ANDAs) under section 505(j) of the Act for loratadine tablets, 10 mg. These ANDAs were submitted to FDA before the reference listed drug (RLD),<sup>11</sup> Claritin (loratadine tablets, 10 mg), was switched to OTC status, and

---

suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product.

(21 CFR 314.3(b)).

<sup>6</sup> See April 29, 2003, Perrigo comments at 2.

<sup>7</sup> This certification states that the '716 patent is "invalid or will not be infringed by the manufacture, use, or sale" of the drug described in Perrigo's NDA (21 U.S.C. 355(b)(2)(A)(iv)). (Recent amendments made by the MMA did not alter the above-quoted language.)

<sup>8</sup> See the Complaint in *Schering v. Perrigo Co.*, Civ. Action No. 02CV5718 (D.N.J. Dec. 2, 2002).

<sup>9</sup> See section 505(c)(3)(C)(i) of the Act (21 U.S.C. 355(c)(3)(C)(i)), as in effect on December 2, 2002. Although this provision was subsequently amended by the MMA, these amendments have not changed the facts that a 30-month stay of approval was triggered by Schering's December 2, 2002, litigation against Perrigo, and that this stay would be terminated by a court decision of patent invalidity or noninfringement. See MMA Title XI, section 1101(b)(2)(B)(ii)(II).

<sup>10</sup> See *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 64 U.S.P.Q. 2d 1032 (D.N.J. 2002), and *Schering Corp. v. Perrigo Co.*, Civil Action No. 02-1478 (D.N.J. Aug. 29, 2002). These decisions were subsequently affirmed by the Federal Circuit. See *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373 (Fed. Cir. 2003), and *Schering Corp. v. Perrigo Co.*, 83 Fed. Appx. 319 (Fed. Cir. 2003).

<sup>11</sup> An RLD is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3(b)).

included paragraph IV certifications to the '716 patent.<sup>12</sup>

## II. DISCUSSION

### A. Perrigo's 505(b)(2) Application for OTC Loratadine Tablets, 10 mg, Is Eligible for Approval

In your petition, you maintain that Perrigo's 505(b)(2) application is ineligible for approval because the product described in the application is a duplicate of a listed drug and thus may be approved in an ANDA only (Petition at 2 to 4, Comments at 1). We do not agree with your position.

Your petition references FDA's October 1999 draft guidance for industry entitled *Applications Covered by Section 505(b)(2)* (draft guidance) (Petition at 2 to 3 and 4 to 5). FDA's draft guidance recommends that "section 505(b)(2) applications should not be submitted for duplicates of approved products that are eligible for approval under section 505(j)" of the Act.<sup>13</sup> This statement reflects the Agency's regulation at 21 CFR 314.101(d)(9), which provides that FDA may refuse to file an NDA if "[t]he application is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act." You state that 21 CFR 314.101(d)(9) proves your argument that Perrigo's NDA is invalid (Petition at 5). Your assertion is unwarranted.<sup>14</sup>

First, FDA's regulation at 21 CFR 314.101(d)(9) bars 505(b)(2) applications for products eligible for approval under section 505(j) of the Act only if the product described in a 505(b)(2) application may be approved via section 505(j) at the time of the application's submission. As discussed in section I of this letter, at the time Perrigo's NDA for OTC loratadine tablets, 10 mg, was submitted, the listed drug on which it relied (Claritin) was still restricted to prescription use. Therefore, the product described in Perrigo's application was not eligible for approval under section 505(j) when the application was submitted.<sup>15</sup> Perrigo's NDA was properly submitted as a 505(b)(2) application,

<sup>12</sup> As in the case of 505(b)(2) NDAs, a paragraph IV certification in an ANDA states that the relevant patent "is invalid or will not be infringed by the manufacture, use, or sale" of the drug described in the ANDA (21 U.S.C. 355(j)(2)(A)(vii)(IV)). (The MMA did not alter this statutory language.)

<sup>13</sup> In the draft guidance, the term *duplicate* is used to describe drug products that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity disintegration times and/or dissolution rates. (Glossary at 11).

<sup>14</sup> You also contend that FDA's draft guidance "explicitly prohibits the approval of a duplicate of a previously approved drug under a Section 505(b)(2) NDA." (Comments at 1). However, as earlier noted, relevant provisions of the draft guidance reflect the Agency's regulation at 21 CFR 314.101(d)(9). As subsequently explained, this regulation does not support your contention.

<sup>15</sup> To be approved under section 505(j), an ANDA applicant must establish, among other things, that its proposed drug product has the same labeling and conditions of use as the RLD. See 21 U.S.C.

consistent with 21 CFR 314.101(d)(9). Second, once a 505(b)(2) application has, like Perrigo's, been appropriately submitted, nothing in 21 CFR 314.101(d)(9) addresses, much less requires or permits, denying approval for the application.

After an NDA, including one described by section 505(b)(2) of the Act, has been appropriately submitted and is under review, FDA may refuse to approve the application only if one or more specific conditions warranting refusal apply.<sup>16</sup> These conditions are enumerated in the Act and the Agency's regulations.<sup>17</sup> Significantly, they do not include situations where, as in this case, a product that is the subject of a pending 505(b)(2) application becomes eligible for approval under section 505(j) *after* the application's submission. Your assertion that approval of Perrigo's NDA is "flatly prohibit[ed]" because of this factual circumstance (Comments at 1) is therefore unfounded.

In addition to the restrictions on our authority, we decline to deny Perrigo's NDA on the grounds you request because doing so would inappropriately discourage use of the 505(b)(2) approval pathway. As we have recently emphasized,<sup>18</sup> section 505(b)(2) provides a distinct and important regulatory option for qualifying applicants who would

---

355(j)(2)(A)(i) and (v). (The MMA did not amend these statutory provisions.) Because the labeling and conditions of use differ for a product that is restricted to prescription use versus one that is available OTC, at the time Perrigo's NDA was submitted, the company could have submitted an ANDA for loratadine tablets, 10 mg, only if it sought to have this product approved for prescription, rather than OTC, use.

<sup>16</sup> See 21 U.S.C. 355(c)(1)(A) and 21 CFR 314.105(a). (The MMA did not affect these provisions.)

<sup>17</sup> See 21 U.S.C. 355(d) and 21 CFR 314.125. (The MMA did not change these provisions.) As articulated in the Act (section 505(d)), the conditions that would warrant denying an NDA approval are as follows:

- (1) the investigations, reports of which are required to be submitted...pursuant to [section 505(b)], 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;
- (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;
- (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;
- (4) upon the basis of the information submitted...as part of the application, or upon the basis of any other information before [FDA] with respect to such drug, [FDA] 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 [FDA] as part of the application and any other information before [FDA] 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
- (6) the application failed to contain the patent information required by [section 505(b)]; or
- (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular....

FDA's regulation at 21 CFR 314.125 reiterates and expands upon these conditions.

<sup>18</sup> See our October 14, 2003, consolidated response to the citizen petitions numbered 2001P-0323 (submitted by Morgan, Lewis & Bockius, LLP, on behalf of Pfizer Inc. and Pharmacia Corporation); 2002P-0447/CP1 (submitted by Morgan, Lewis & Bockius, LLP, on behalf of Pfizer Inc.); 2003P-0408/CP1 (submitted by Lord, Bissell & Brook LLP on behalf of TorPharm); and 2003P-0176 (submitted by the Biotechnology Industry Organization (BIO)).

not be eligible to submit applications under section 505(j) of the Act, or who would be deterred by the duplicative work required to seek approval under section 505(b)(1)'s full NDA provisions.<sup>19</sup> Those who might otherwise seek to avail themselves of the approval pathway provided by section 505(b)(2) would be unnecessarily discouraged from doing so if an application under this section could ultimately be refused because of an event that, like the one here, does not impugn the fundamental safety or effectiveness of the drug under review, is beyond the applicant's control, and occurs after the application's preparation and submission.

Consistent with the discussion above, and as comments on your petition have observed, FDA has previously approved another 505(b)(2) application for an OTC loratadine product in circumstances identical to those pertinent here.<sup>20</sup> Like Perrigo, Wyeth Consumer Healthcare (Wyeth) submitted a 505(b)(2) application for an OTC version of loratadine (in Wyeth's case, orally disintegrating loratadine tablets, 10 mg). The listed drug relied upon by Wyeth was Schering's Claritin Redi-Tabs (orally disintegrating loratadine tablets, 10 mg), which, at the time of Wyeth's submission, were still restricted to prescription use. Claritin Redi-Tabs were switched from prescription to OTC status while Wyeth's NDA was under review. Because it was appropriately submitted and met the requirements for approval, Wyeth's NDA was subsequently approved, notwithstanding the switch in Claritin Redi-Tabs' status. By hewing to our earlier precedent in this response, we affirm the legal and policy positions that are discussed in this letter and exemplified by Wyeth's approval.

Finally, you contend that permitting Perrigo to maintain its 505(b)(2) application would be inequitable, because doing so would allow the company to potentially obtain approval more quickly than other applicants that had filed ANDAs for loratadine tablets, 10 mg, before Perrigo and that were subject to the 180-day period of generic marketing exclusivity held by the first such applicant under section 505(j)(5)(B)(iv) of the Act (180-day exclusivity) (Petition at 7).<sup>21</sup> We do not accept this contention. First, any of the other ANDA applicants mentioned in your petition could have invoked the 505(b)(2) pathway prior to Claritin's switch to OTC status, as Perrigo did; therefore, Perrigo's use of this pathway is not unfair. Moreover, the period of 180-day exclusivity delaying the approval of generic loratadine tablets, 10 mg, by ANDA applicants that were not first applicants (including your client, Genpharm) has expired, thus mooted your concerns about circumvention of this exclusivity.

---

<sup>19</sup> Full NDAs are those that, like 505(b)(2) applications, are submitted under section 505(b)(1) of the Act but, unlike 505(b)(2) applications, contain full reports of investigations of safety and effectiveness, all of which were conducted by or for the applicant or for which the applicant has a right of reference.

<sup>20</sup> See comments submitted by Heller Ehrman on behalf of Wyeth dated June 20, 2003, at 3 and 4, and comments submitted by Perrigo dated April 29, 2003, at 3.

<sup>21</sup> Section 505(j)(5)(B)(iv) of the Act applies to the loratadine ANDAs referenced in and submitted before the date of your petition as that section was worded prior to the MMA's enactment. Although the MMA amends section 505(j)(5)(B)(iv) with respect to certain ANDAs, its amendments do not affect these loratadine ANDAs, which were submitted before the MMA's enactment on December 8, 2003, and for which 180-day exclusivity was triggered prior to this date. See MMA Title XI, section 1102(b).

In sum, for the reasons stated above, we do not agree with your assertion that Perrigo's NDA is ineligible for approval under section 505(b)(2) of the Act.

**B. The 30-Month Stay of Approval on Perrigo's NDA Has Been Terminated**

As explained in section I of this letter, the initiation of Schering's lawsuit against Perrigo on December 2, 2002 (alleging that Perrigo's NDA infringed claims 1 and 3 of Schering's '716 patent) created a 30-month stay of approval on Perrigo's NDA. Comments on your petition maintained that this 30-month stay had been terminated prior to the petition's submission by court decisions declaring claims 1 and 3 of the '716 patent invalid in earlier litigation challenging ANDAs for generic loratadine tablets, 10 mg (discussed in footnote 10 and accompanying text).<sup>22</sup> Although these decisions concerned the same patent at issue in the Schering-Perrigo NDA litigation, they could not truncate the 30-month stay imposed by this litigation.

While court decisions of patent invalidity or noninfringement in particular actions have been applied to trigger 180-day exclusivity for parties outside those actions, such exclusivity is governed by statutory and regulatory provisions distinct from those that terminate 30-month stays for 505(b)(2) applications like Perrigo's. Neither FDA nor the courts have found that a judicial decision holding a patent invalid, not infringed, or unenforceable truncates the 30-month stay of approval on a 505(b)(2) application, or an ANDA, in an unrelated action. We agree, then, with your position that the 30-month stay of approval on Perrigo's NDA was in effect at the time your petition was submitted (Petition at 7).

Since your petition's submission, however, the United States District Court for the District of New Jersey has decided the invalidity of claims 1 and 3 of the '716 patent in the Schering-Perrigo NDA litigation.<sup>23</sup> As provided by section 505(c)(3)(C)(i) of the Act, this decision has terminated the 30-month stay of approval on Perrigo's 505(b)(2) application.<sup>24</sup> Accordingly, Perrigo's NDA may be approved when it is otherwise ready for approval.

---

<sup>22</sup> See comments submitted by Perrigo dated April 29, 2003, at 5 to 6.

<sup>23</sup> See the Order and Opinion (unpublished), both in *Schering v. Perrigo Co.*, Civil Action Nos. 02-5718 and 02-6087 (D.N.J. October 31, 2003).

<sup>24</sup> Section 505(c)(3)(C)(i) of the Act, as in effect at the time of the court order and opinion in footnote 23, above, stated that a 30-month stay would be terminated "if before the expiration of [the 30-month] period the court decides that [the] patent [at issue] is invalid or not infringed...." As discussed previously in footnote 9, this section was subsequently amended by the MMA, but the amendments did not disturb the termination of the 30-month stay of approval on Perrigo's NDA by the court actions in footnote 23.

### III. CONCLUSION

For the reasons set forth in this letter, approval of Perrigo's NDA (if and when otherwise warranted) would not be prohibited under section 505(b)(2) of the Act or by a 30-month stay of approval. Therefore, your request that we refuse to approve this NDA is denied.

Sincerely,

A handwritten signature in black ink, appearing to read "Galson", written in a cursive style.

Steven K. Galson, M.D., M.P.H.  
Acting Director  
Center for Drug Evaluation and Research