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Via Hand Delivery

Dockets Management Branch (HFA-305)
Food and Drug Administration
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CITIZEN PETITION

On behalf of Biovail Corporation, the undersigned submits this petition under 21 C.F.R. § 10.30 and section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDC Act) requesting that the Commissioner of Food and Drugs enforce the patent certification requirements in the FDC Act to curb abuses by the sponsors of Abbreviated New Drug Applications (ANDAs). In addition, FDA should refuse to approve ANDA 75-401, submitted by Andrx Pharmaceuticals, Inc., for a generic version of Biovail's Tiazac® (diltiazem hydrochloride extended-release capsules USP) until the patent certification requirements discussed herein are fully satisfied.

A. Action Requested

1. Biovail requests that the Commissioner of the Food and Drug Administration (FDA) enforce the existing regulation that requires an ANDA applicant that has not yet received final approval, to make a new patent certification under 21 C.F.R. §§ 314.94(a)(12)(i) and 314.94(a)(12)(viii)(C)(1) whenever the patent certification is no longer "accurate" as occurs when a Paragraph IV certification has been made and amendments to the ANDA alter the characteristics of the generic drug. FDA should require all Paragraph IV ANDA filers to include in all ANDA amendments a certification that it will provide to the NDA holder and patent owner (1) a new notice of patent certification or (2) if the amendment does not involve any changes to the chemistry, manufacturing, and controls (CMC) section of the ANDA, a notification to that effect. Requiring a new patent certification whenever the CMC portion of an ANDA is amended will allow a pioneer drug company to ensure that any new patent infringement issues are promptly addressed.
2. Biovail requests that FDA refuse to approve Andrx's ANDA 75-401 until such time as it has ensured that the Andrx ANDA contains an "accurate" patent certification. As discussed below, Biovail believes that Andrx's original patent certification is not "accurate."

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This action is needed to account for changes in the regulatory process for ANDA approvals. The Agency's original regulations were promulgated in final form on October 3, 1994 (59 *Fed. Reg.* 50338), reflecting interpretations and policy decisions that had been in place for some time. As a result of developments since mid-1998, however, those interpretations (and the policy assumptions that supported them) have been superceded. The Agency's patent certification requirements must be more rigorously enforced to ensure that the drug product that is ultimately approved under an ANDA is the same product that has been the subject of the patent certification(s).

B. Statement of Grounds

1. Background

Biovail believes that FDA is well-acquainted with the facts surrounding Andrx's ANDA 75-401 and events since its submission. Following the initial submission of the ANDA in 1998, with a "Paragraph IV" certification, Andrx provided Biovail with a notice of patent certification as required by FDA's regulations. 21 C.F.R. §§ 314.94(a)(12)(i)(A)(4) and 314.95. Throughout this time, FDA's regulations have provided that "an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate." 21 C.F.R. § 314.94(a)(12)(viii)(C)(1).¹ Nonetheless, Andrx has submitted at least a dozen amendments to its ANDA, but has not updated its patent certification.

2. The Regulatory Ground Rules Have Changed Dramatically

The ANDA approval landscape has changed dramatically since FDA first promulgated its regulations implementing The Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act"). In its original final regulations governing patent and exclusivity issues for ANDAs, FDA's "successful defense" requirement ensured that all ANDAs were reviewed on their own merits, and the benefit of the 180-day exclusivity period² went only to a

¹ Since the "certification" and "notice of patent certification" are inextricably tied together in the regulatory scheme, it is reasonable to conclude that any relevant changes in the factual and legal bases presented in the notice of certification cause the certification itself to no longer be accurate. An ANDA amendment that changes the process by which a drug is manufactured may affect patent infringement issues independent of its effect on the approvability of the ANDA.

² FDC Act § 505(j)(5)(B)(iv).

deserving ANDA applicant.³ This regulation, and its effect on determining which ANDA applicant would receive 180-day exclusivity, were successfully challenged in two cases in April 1998.⁴ Following those decisions, FDA changed its interpretation of the statute and put industry on notice of its new position in a guidance document, concluding that the first applicant to submit an ANDA with a Paragraph IV certification will be eligible for 180-day exclusivity even if it is not sued for patent infringement.⁵ FDA then modified its regulations to account for these judicial developments. 63 *Fed. Reg.* 59712 (Nov. 5, 1998). As part of this evolving landscape, FDA has been forced to broaden its definitions of “court”⁶ and “decision”⁷ for purposes of certain statutory triggers.

The result of this turmoil is a regulatory environment for ANDA applicants where the emphasis is now simply on being the first to file an application. There is no longer an incentive to be the first to file the ANDA with the strongest data or the first to file the ANDA with the technology least likely to infringe the pioneer’s patents. This new-found emphasis on timing over quality opens the door for ANDA applicants to “submit first and fix later.”

3. The New Regulatory Environment Warrants Close FDA Scrutiny of Amendments Made During the ANDA Review Process

FDA should be particularly wary of any changes made to the formulation, specifications, or manufacturing procedures of a product while the ANDA is still under review. In the context

³ “If an [ANDA] contains a [Paragraph IV certification] and the application is for a generic copy of the same listed drug for which one or more substantially complete [ANDAs] were previously submitted containing a [Paragraph IV certification] and the applicant submitting the first application has successfully defended against a suit for patent infringement brought within 45 days” of the required patent notice, the first applicant would receive the 180-day exclusivity. 21 C.F.R. § 314.107(c)(1) (1997) (emphasis added) (regulation now superceded).

⁴ *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998); *Granutec, Inc. v. Shalala*, 46 U.S.P.Q.2d 1398, 1998 WL 153410 (4th Cir. (N.C.)) (unpublished disposition).

⁵ FDA, “Guidance for Industry - 180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act” (June 1998). The “no lawsuit required” interpretation was upheld in *Purepac Pharmaceutical Co. v. Friedman*, 162 F.3d 1201 (D.C. Cir. 1998).

⁶ *Mylan Pharmaceuticals, Inc. v. Shalala*, 81 F.Supp.2d 30, 47 (D.D.C. 2000); 65 *Fed. Reg.* 43233 (July 13, 2000) (revising 21 C.F.R. §314.107(e)).

⁷ *Teva Pharmaceuticals, USA, Inc. v. FDA*, 182 F.3d 1003 (D.D.C. 1999).

of considering an ANDA applicant's entitlement to 180-day generic drug exclusivity, FDA has expressed great concern about these types of changes. For example, the Agency has proposed that "if the applicant must conduct a new bioequivalence study to obtain approval of the ANDA, the application will not be considered to be substantially complete and the applicant will not be eligible for exclusivity." 64 *Fed. Reg.* 42873, 42875 (August 6, 1999) (column 2). Similarly, "if the first applicant submits a new paragraph IV certification because, for example, it makes a formulation change requiring a supplement or an amendment to its ANDA, it may no longer be accorded first applicant status." *Id.* (column 3) (emphasis added).⁸

Changes to the formulation, specifications, or manufacturing procedures of a product subject to an ANDA should be particularly suspect after a tentative approval letter has been issued. As FDA describes the significance of a tentative approval letter, an ANDA would have been approved, but for a delay required by existing patent or exclusivity requirements.⁹ As a result, any change in these characteristics should be treated with considerable suspicion. One option for handling these changes would be to consider any such submission following a tentative approval letter to constitute a "major" amendment to the ANDA, thereby discouraging companies from planning a "submit first and fix later" strategy and ensuring the Agency has sufficient time to thoroughly investigate the basis for the change and confirm that it is not due to some underlying fundamental problem with the application. Due to the confidential nature of the drug review process, examples of situations where significant changes are made following the tentative approval decision are not publicly known.¹⁰ Biovail believes FDA is aware of other situations where important changes have been made to ANDAs following tentative approval.

⁸ This comment appears to be in direct response to Andrx's decision to withhold its generic version of Cardizem CD® from the market for nearly one year following final approval. During this time, FDA permitted Andrx to retain its first-filer status for ANDA 74-752 after approval of a supplement to the ANDA that revised the product's specifications and triggered the need for a new Paragraph IV certification. *See Stipulation, Hoechst Marion Roussel v. Andrx Pharm.*, Case No. 96-06121-Civ-Roettger (S.D. Fla.) (signed June 9, 1999) (copy provided as Attachment 1).

⁹ "The only difference between a full approval and a tentative approval is that the final approval of these applications is delayed due to existing patent or exclusivity on the innovator's drug product." Food and Drug Administration. *CDER 2000 Report to the Nation: Improving Public Health Through Human Drugs*. Rockville, Maryland, 2001 (page 13) (document available from FDA at: <http://www.fda.gov/cder/reports/RTN2000/RTN2000.HTM>).

¹⁰ One rare public example can be found in *Andrx Pharm., v. Biovail Corp. Int'l.*, Case No. 01-6194-Civ-Dimitrouleas (S.D. Fla.) (complaint filed February 9, 2001). *See* Plaintiff Andrx Pharmaceutical, Inc.'s Notice of Filing of Declaration of Diane Servello (dated April 9, 2001) (relevant pages provided as Attachment 2). Although cited for a different purpose, "Exhibit A" to this pleading is a fax from FDA to Andrx dated February 2, 2001, preliminarily agreeing with Andrx's change to the dissolution testing parameters of its ANDA 75-401. This change was

4. Amendments Can Affect the Accuracy of Patent Certifications

FDA's regulations provide that "an applicant shall amend a submitted [patent] certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate." 21 C.F.R. § 314.94(a)(12)(viii)(C)(1). Amendments to a pending ANDA can mean that the proposed drug product has changed in important respects from the product described in the original ANDA, and these changes may have significant patent infringement implications. Since such changes may affect the course of the patent infringement litigation, prompt disclosure is essential to resolving any question about the accuracy of the patent certification and the factual/legal justifications presented in the notice of certification. The fact that an original ANDA contained a Paragraph IV certification and, after amendment, the appropriate certification is still a Paragraph IV certification is inadequate to conclude that the certification is still "accurate." As discussed in more detail below, under 35 U.S.C. § 271(e)(2), the jurisdiction of a court to adjudicate a potential patent infringement is critically dependent upon the identity and characteristics of the drug product that is the subject of the ANDA. Any amendment of the CMC section of the ANDA redefines the product that is covered by the application and, at the very least, requires a fresh assessment of whether infringement has arisen.

Biovail is well aware of FDA's unwillingness to involve itself in evaluating substantive patent matters because of the Agency's professed lack of expertise in this area.¹¹ This Petition does not request or require that FDA venture into these turbulent waters. However, FDA must implement the patent certification procedures in a way that affords a pioneer drug company the opportunity to protect its intellectual property prior to the approval of an ANDA. This process is part of the carefully balanced compromise between maintaining patent protection and simplifying the generic drug approval process reached in Hatch-Waxman Act. FDA's current "hands off" approach to patent matters is an abdication of the Agency's responsibility to ensure that ANDAs are in compliance with 21 C.F.R. § 314.94(a)(12)(viii)(C)(1) prior to approval.

When an ANDA is submitted originally and the applicant seeks approval before the expiration of any patents listed in the *Orange Book*, the applicant must make a certification "that such patent [on the innovator drug product] is invalid or will not be infringed by the

apparently submitted in an amendment dated December 13, 2000. Tentative approval of this ANDA was granted on September 29, 2000 (a copy of this letter is provided as Attachment 3 and is available on FDA's web site at: <http://www.fda.gov/cder/approval/index.htm>).

¹¹ FDA reports that it "does not have the expertise or the desire to become involved in issues concerning patent law and sufficiency of notice." 59 *Fed. Reg.* at 50350 (FDA response to comment 60).

manufacture, use, or sale of the new drug for which the [ANDA] is submitted.¹² The product that ultimately will be approved under the ANDA will reflect any modifications made through amendments to the ANDA prior to approval. This product may differ in important respects from the product that was originally described in the ANDA.

The courts have held that the patent infringement inquiry “‘is properly grounded in the ANDA application and the extensive materials typically submitted in its support.’ Therefore, it is proper for the court to consider the ANDA itself, materials submitted by the ANDA applicant in support of the ANDA, and any other relevant evidence submitted by the applicant or patent holder.”¹³ Indeed, “the question of infringement must focus on what the ANDA applicant will likely market if its application is approved . . .”¹⁴ In a case closely related to the subject of this Citizen Petition, the U.S. Court of Appeals for the Federal Circuit found that:

The obligation to inform the parties, and the trial court, as to any material amendment to the ANDA continues throughout the litigation that is artificially provoked under Paragraph IV. Andrx’s failure to disclose the amendments it filed to the ANDA after the close of discovery constitutes a violation of that obligation.¹⁵

Biovail is not asking FDA to consider substantive patent issues as part of its ANDA review. Rather, the point is that the product an ANDA applicant expects to have approved (following numerous amendments and other changes) may not be the product described in its original ANDA and that was the subject of a patent certification given many months (if not years) earlier. In that case, the applicant’s patent certification would no longer be “accurate” because the notification provided in connection with this certification would no longer be

¹² FDC Act § 505(j)(2)(A)(vii)(IV) (emphasis added); 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

¹³ *Bayer v. Elan Pharmaceutical Research Corp.*, 212 F.3d 1241, 1248 - 49 (Fed.Cir. 2000) (internal citation omitted).

¹⁴ *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed.Cir. 1997).

¹⁵ *Biovail Corp. Int’l, v. Andrx Pharm.*, 239 F.3d 1297, 1304 (Fed.Cir. 2001). “It is an abuse of the judicial role for Andrx to ask us to review on appeal what should have been made known, and adequately explored, at trial.” Despite this admonition, the court curiously went ahead and reviewed 11 previously-undisclosed ANDA amendments *de novo* and concluded, with no discussion, that “the amendments do not show reversible error” in the district court’s original judgment of non-infringement. The fact that infringement was not found does not excuse Andrx for failing to update its patent certification.

relevant to the product the applicant intends to market. A new certification must be required before the ANDA can be approved.

This problem can be remedied by the granting the requested action, with little additional work on FDA's part. FDA should require all Paragraph IV ANDA filers to include in all ANDA amendments a certification that it will provide to the NDA holder and patent owner (1) a new notice of patent certification or (2) a notification that the amendment does not involve any changes to the CMC section of the ANDA. This process will not involve FDA in any substantive patent disputes. Rather, the Agency's only responsibility would be to ensure that the ANDA applicant has provided an appropriate notification for each amendment to the ANDA. FDA already performs this documentation function for patent certifications made for the original ANDA submission, and it is consistent with the Agency's "ministerial" role in patent listing matters.¹⁶ The notice concerning subsequent amendments to the ANDA would provide the innovator company with the opportunity to seek a judicial determination of whether the changes to the ANDA are such that the drug "for which the applicant is seeking approval" would infringe the listed patent(s).

5. Mandatory Reissuance of Paragraph IV Certifications for All CMC Amendments Will Not Create New Abuses

The purpose of this petition is not to create extra-statutory obstacles to the approval of generic drug products. Rather, it is to ensure that the statutory provisions of the Hatch-Waxman amendments to the FDC Act are faithfully followed. The CMC section of virtually every ANDA is amended to some extent during the FDA approval process. In theory, this could mean that the statutory 30 month delay would run not from the date of the initial notification, but from the date of the notification that accompanied submission of the last CMC amendment. This would effectively extend the 30 month stay in a manner not intended by Congress. Fortunately, Congress had the foresight to include a provision which prevents that outcome. Section 505(j)(5)(B)(iii) of the FDC Act provides that the court which is adjudicating an alleged infringement under 35 U.S.C. § 271(e)(2) which gives rise to the 30 month delay of FDA approval when such action is timely commenced may order that the delay of FDA approval be "shorter or longer ... because either party to the action failed to reasonably cooperate in expediting the action...."

If an amendment to the CMC section of a pending ANDA alters the nature and/or manner by which an alleged infringement arises and/or makes proof of infringement more complicated

¹⁶ "FDA has . . . reiterat[ed] . . . that its role in listing patents is 'purely ministerial' and that it 'does not have the expertise nor the resources to resolve complex patent coverage issues.'" *Mylan Pharmaceuticals, Inc., v. Thompson*, 139 F.Supp.2d 1, 11 (D.D.C. 2001) (internal citations omitted).

or difficult to prove, the plaintiff would be entitled to either of two remedies. It can point to the delays created by the amendment and seek to have the original 30 month delay appropriately extended, or it could initiate a new suit within 45 days of receiving the new notification and, thereby, trigger a new 30 month delay. If the plaintiff were to seek to delay FDA approval by either of these means in a situation where the CMC amendment had absolutely no impact on the infringement issues that were in dispute, such actions would easily constitute failure to reasonably cooperate in expediting the action and an extension of the 30 month delay would not be granted or the new 30 month period that would arise by statutory action if a new suit were timely filed could be appropriately shortened.

One last possible scenario bears mention. A patent holder might choose to not file an infringement suit when initially notified and gamble that a subsequent notification triggered by an amendment to the CMC section of the ANDA would be required prior to approval. Again, we would expect that the court would have not difficulty appropriately adjusting the 30 month period that would arise if a reasonable basis existed for the infringement action to be initiated at the time of the initial (or any earlier) notification. In other words, if the amendment, *per se*, did not create a new potential for infringement, the failure to have brought the infringement action sooner would be a clear failure by the patent holder to reasonably cooperate in expediting the action and the court would order whatever curtailment or elimination of the 30 month delay it deemed appropriate.

Automatic updating of Paragraph IV certifications for all CMC amendments ensures that the courts are entertaining only those actions under 35 U.S.C. § 271(e) that relate to products ANDA applicants intend to market. The court has ample authority in dealing with new actions filed in response to these amendment-triggered certifications to put an end to the current ability of ANDA filers to hide behind CMC amendments to gain approval of a drug product that may be more likely to be found to be infringing than the drug product described in the original ANDA, without exposing the infringing product to litigation under 35 U.S.C. § 271(e)(2). The court also has ample authority to thwart any attempt by patent owners to utilize the additional notifications to improperly extend the default 30 month delay that arises from the timely filing of an infringement suit after receipt of a patent notification. Where the amendment does alter the basis for infringement, appropriate extensions of the 30 month period would be ordered.

6. The Product for Which Andrx is Now Seeking Approval is Not the Product for Which It Made Its Patent Certification

This petition seeks two separate actions. The discussion above explains the need for a policy by which CMC amendments to ANDAs automatically trigger the need for a new Paragraph IV patent certification. The request that a new certification be provided by Andrx with regard to NDA 75-401 is necessary because automatic notification of amendments does not fully prevent abuse of the system. For sure, CMC amendments have the potential to disrupt both FDA's substantive review of an application and resolution of any relevant patent infringement

issues. Less obviously, subtle process changes may also alter product performance in a manner that creates infringement, even if it does not affect bioequivalence.

Andrx has conceded that the product it now wishes to market differs from the product it provided to Biovail at the start of the patent infringement suit triggered by Andrx's original patent certification. As part of correspondence from Andrx to FDA that was released under the Freedom of Information Act (FOIA),¹⁷ Andrx discussed how it "has learned that Taztia is extremely sensitive to even small changes in the extended-release coating step, such as drying time, spray rate, and atomization pressure." This "sensitivity" apparently caused certain batches of Andrx's product to fail long-term stability testing at the 3-month station (attributed to a "high dissolution rate at the 4-hour time point"). As a result, Andrx plans to "tighten the drying time specifications, as well as the spray rate and atomization pressure parameters . . ."

In light of the stability failure, this product clearly could not serve as a basis for approving the ANDA. Nevertheless, Andrx supplied this deficient product to Biovail as representative of the product that Andrx intended to market and which it alleged did not infringe any of Biovail's patents:

The ANDA specifies a drying time for coated extended-release pellets of not more than [redacted] hours. The pellets in the batch used for Andrx's 360 mg biostudies were dried for [redacted] hours. The batches provided to Biovail, by contrast, were dried for [redacted] hours.

The patent infringement allegations at issue turn on subtle aspects of the product's behavior after ingestion. Manufacturing changes involving parameters as to which dissolution is extremely sensitive will obviously affect product performance after ingestion.

Based on information in the public domain, it is apparent that Andrx's ANDA has been amended at least 12 times since the application was originally submitted: the 11 ANDA amendments noted by the Federal Circuit¹⁸ and at least one additional amendment.¹⁹ In light of

¹⁷ Letter from Andrx Pharmaceuticals, Inc. to FDA (dated October 5, 2001). All references to this correspondence are to footnote 1. This footnote is excerpted from the letter and is enclosed as Attachment 4. Other than being presented on a single page, the text (including redactions) is exactly as it was received in the FOIA response.

¹⁸ *Biovail Corp. Int'l*, 239 F.3d at 1304.

¹⁹ ANDA amendment dated December 13, 2000, proposing a change to the dissolution testing parameters. See "Exhibit A" to Plaintiff Andrx Pharmaceutical, Inc.'s Notice of Filing of

the Court of Appeals' decision and additional information that Biovail has provided to FDA,²⁰ the product that Andrx intends to market is not the same as the product for which it made its original patent certification. Therefore, Andrx's ANDA can not be approved until a new, "accurate" patent certification has been submitted to reflect the changes that have been made to the generic product for which Andrx is seeking approval.

7. Conclusion

For the reasons presented above, Biovail requests that the Commissioner adopt the patent certification requirements described in Part A of this Citizen Petition. Furthermore, the Commissioner is requested to confirm that Andrx intends to market (if and when it receives approval) a product that will differ from the one that was the subject of its original patent certification. Upon making the determination, the Commissioner must refuse to approve Andrx's ANDA 75-401 until Andrx has perfected its patent certification obligations.

C. Environmental Impact

Biovail claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

D. Economic impact

This information will be provided upon request of the Commissioner.

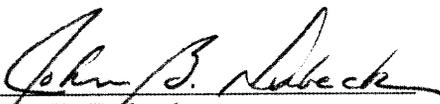
E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Declaration of Diane Servello (dated April 9, 2001), filed in *Andrx Pharm., v. Biovail Corp. Int'l.*, Case No. 01-6194-Civ-Dimitrouleas (S.D. Fla.) (relevant pages provided as Attachment 2).

²⁰ At the end of September 2001, Biovail provided to FDA detailed information (covered by a protective order issued by a U.S. District Court judge) that documented the known changes to Andrx's ANDA formulation. As demonstrated in that submission, it is beyond dispute that Andrx's original patent certification cannot be "accurate" since the information presented in its original notice of patent certification described a product with different characteristics.

Respectfully submitted,



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Attachments (4)