



Generic Pharmaceutical Association

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March 11, 2002

VIA OVERNIGHT COURIER

Dockets Management Branch
U.S. Food and Drug Administration
5630 Fishers Lane
Room 1061 - HFA-305
Rockville, Maryland 20852

Re: Docket No. 02P-0001
Comments of The Generic Pharmaceutical Association

The Generic Pharmaceutical Association (GPhA) files these comments in opposition to the Citizen Petition filed on January 2, 2002, on behalf of Biovail Corporation ("Biovail") in the above-referenced docket. In its petition, Biovail asks FDA: (1) to require Abbreviated New Drug Application ("ANDA") applicants who have previously filed a "Paragraph IV" patent certification to submit a new Paragraph IV Certification every time the applicant submits a change to the Chemistry, Manufacturing and Controls ("CMC") sections of an ANDA; and (2) to refuse to approve Andrx's ANDA No. 75-401 (diltiazem HCl extended release capsules) until Andrx submits a new patent certification to its ANDA.

For the reasons discussed below, FDA should deny the Biovail petition because the relief it seeks: (a) is unauthorized by, and would violate, the Federal Food, Drug, and Cosmetic Act ("FDCA") and FDA's implementing regulations under the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman")¹; and (b) would serve no useful function with respect to FDA's review of ANDAs, or with the courts' handling of Paragraph IV patent litigation. This is especially true for Paragraph IV ANDAs that are based on invalidity arguments, since CMC changes would have no effect under any circumstances on the issue of a patent's validity. Moreover, Biovail's proposal is ludicrous because it would result in FDA receiving a flood of multiple unnecessary re-certifications that could constantly re-scramble the order of filing, and thus exclusivity eligibility, among various applicants and further strain the Agency's already overburdened resources for no legitimate purpose. Biovail's proposal would also significantly increase the already egregious delays in generic drug approvals, to the detriment of American consumers, and would further erode the balance Congress sought to achieve in Hatch-Waxman between the intellectual property interests of innovator companies and the rights of generic companies (and the public) to prompt market access to affordable generic drugs.

¹ Public Law No. 97-417 (September 24, 1984), as codified at 21 U.S.C. §355(j), et seq.

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I. Duplicative Paragraph IV Certifications Would Violate The Plain Language of Section 505(j)(2) and FDA's Implementing Regulations

Hatch-Waxman created a careful public policy compromise between encouraging the availability of low-priced, safe and effective generic pharmaceuticals on the one hand and creating incentives for brand name companies to continue to conduct research to uncover new therapeutics. Congress, in enacting Hatch-Waxman, understood that the balance it sought depended, in large measure, on creating a system that was as predictable as possible in how it affected the development plans of both generic and brand name companies. Thus, it attempted to ensure certainty in the process for generic firms by spelling out with specificity the statutory criteria for what a generic applicant had to show to secure ANDA approval.

Thus, the statutory ANDA provisions make clear that an ANDA must contain certain information, set forth at 21 U.S.C. § 355(j)(2)(A)(i) through (viii) (e.g., information showing that the generic drug is the same as the brand name product with respect to active ingredients, route of administration, strength, dosage form, and labeling; and that it also contains "a" patent certification with respect to each relevant patent). But, just as importantly, 21 U.S.C. § 355(j)(2) also clearly provides that FDA "may not require that an ANDA contain information in addition to that required by clauses (i) through (viii)." (emphasis added). Thus, the threshold issue here is whether an applicant whose ANDA already contains "a" Paragraph IV Certification to a listed patent – thus satisfying the requirement of clause (vii) – must submit another Paragraph IV Certification to the same patent simply because the applicant made a change to the CMC section of the ANDA prior to approval. The answer is emphatically "**No**" because the filing of another Paragraph IV Certification to a patent that is already the subject of a Paragraph IV Certification by the same applicant would constitute "information in addition to that required" under 21 U.S.C. § 355(j)(2)(A)(i) through (viii). Thus, Biovail's requested rule would violate the plain language of the FDCA and cannot be adopted. See *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984).

In addition, Biovail's argument that a CMC change makes a previously submitted Paragraph IV Certification "inaccurate" and in need of "amendment" is nonsensical and is not supported by the governing regulations. A Paragraph IV Certification must be filed in a specific format as required by FDA's regulations, and the specified language makes no reference to the bases for the applicant's patent challenge, nor to the contents of the ANDA itself. Indeed, as FDA has emphatically stated over the years, it has no capability, or desire, to evaluate the substantive merits of listed patents. Thus, Paragraph IV Notifications, which must contain substantive patent arguments, go directly to the patent holder and no copy is ever sent to FDA. In contrast, all Paragraph IV Certifications must simply state "*I (name of applicant), certify that Patent No. _____ (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this application is submitted.*" 21 C.F.R. § 314.94(a)(12)(i)(A)(4). "A certification in any other form will not be accepted by the

agency as a paragraph IV certification.” 54 Fed. Reg. 28872, 28885 (July 10, 1989). Given this mandated language of Paragraph IV Certifications, an “amended” certification under Biovail’s proposal would actually be exactly the same as the certification it replaced. Thus, it simply cannot be true, as Biovail argues, *Pet.* at 1, 2, 5, that its proposal would merely involve enforcement of 21 C.F.R. § 314.94(a)(12)(viii)(C)(1), because: (1) if the “new” certification is accurate, an identical prior certification must also be accurate, and (2) if an applicant submits a new identical certification, it cannot be deemed to have amended the prior certification.

Moreover, It is also clear that this regulation was not intended, and in fact does not operate, to require the re-submission of an identical Paragraph IV Certification as requested by Biovail. The certification amendment regulations, 21 C.F.R. § 314.94(a)(12)(viii), clearly use the term “amendment” to mean a change from one type of certification to another, and not as Biovail suggests, an “amendment” involving the resubmission of an identical certification that does not change the status of the ANDA vis-à-vis the patent. Specifically:

- ◆ The introductory paragraph of section 314.94(a)(12)(viii), captioned “*Amended certifications*,” provides that a certification “may be amended at any time” with the limitation that “an applicant who has submitted a Paragraph IV patent certification may not change it to a Paragraph III certification if a patent infringement suit has been filed against another Paragraph IV applicant...”
- ◆ Similarly, section 314.94(a)(12)(viii)(A) (“*After finding of infringement*”) requires that an applicant who originally submitted a Paragraph IV Certification but subsequently lost its patent infringement action “shall amend the certification. . . .In the amended certification, the applicant shall certify under paragraph (a)(12)(i)(A)(3)...that the patent will expire on a specific date,” i.e., the certification shall be “amended” from a Paragraph IV Certification to a Paragraph III Certification. (A “IV→III” amendment)
- ◆ Likewise, section 314.94(a)(12)(viii)(B) (“*After removal of a patent from the list*”) requires that when a patent is removed from the Orange Book (usually due to a court decision of invalidity), ANDA applicants with Paragraph IV or Paragraph III certifications must amend their patent certification to either state that no relevant patents claim the drug (pursuant to 21 C.F.R. § 314.94(a)(12)(ii)), or to refer only to remaining listed patents. (a “IV→(ii)” or “III→(ii)” amendment).
- ◆ Finally, section 314.94(a)(12)(viii)(C) (“*Other amendments*”), upon which Biovail relies, provides 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,” but

specifically exempts applicants from making amendments in response to a new patent being listed in the Orange Book after approval of the ANDA.

Thus, in the context of patent certifications, FDA's regulations clearly and consistently use the term "amended" or "amend" to mean a change from one certification type to another type. Biovail's twisting of this clear regulatory meaning further reflects the fallacy of its Petition.

Biovail also argues that every change to the CMC section of an ANDA creates a new "drug for which the application is submitted," thus requiring a new Paragraph IV Certification for each such change. See *Pet.* at 5-7. There is simply no basis to support Biovail's contention. As FDA's regulations make clear, for purposes of Paragraph IV Certifications, reference to the "drug for which the application is submitted" means the established name of the drug (e.g., in this case, "Diltiazem Hydrochloride Extended-Release Capsules USP"). See 21 C.F.R. § 314.94(a)(12)(i)(A)(4) (Paragraph IV Certifications refer only to the "name of the proposed drug product" and not to any particular formulation or manufacturing process used by the applicant). The Paragraph IV Notification regulations also do not define "drug" with respect to CMC or manufacturing issues, but rather by reference to "the established name... of the proposed drug product." 21 C.F.R. § 314.95(c)(3), (4) (emphasis added). The Notification must also identify "the active ingredient, strength, and dosage form of the proposed drug product," but the regulations do not require information about CMC or manufacturing processes.

GPhA is especially concerned that if FDA were to adopt Biovail's narrow definition of "drug" for purposes of requiring new Paragraph IV Certifications, every amendment of any kind to an ANDA would result in a "new drug for which the applicant is seeking approval." Although Biovail argues that its proposed requirement should only apply for CMC changes, it offers no coherent regulatory reason that would support FDA applying this definition of "drug" only in cases of CMC changes, but not in cases involving other changes to ANDAs. It is hard to imagine any ANDA being granted final approval in exactly the same form as when originally filed. In practice, as FDA and Biovail know well,² many amendments of various types are usually required prior to final approval of an ANDA, and if each such change required a new Paragraph IV Certification, the potential for delay through serial imposition of new 30-month stays would be magnified exponentially. This result was obviously not the intent of Congress or FDA, and it should be avoided here by denying Biovail's petition.

² Biovail's own ANDA 74-485 for diltiazem HCl 60, 90, and 120 mg. extended-release capsules involved seven amendments during its two and a half year review. See September 15, 1999 FDA approval letter to John Dubeck, Esq., Keller & Heckman, as U.S. agent for Biovail Corporation.

In addition, Biovail's proposal to require patent certifications based on CMC changes would create a highly anomalous and imbalanced situation that Congress could not possibly have intended. It is well-settled that process/manufacturing patents are not permitted to be listed in the Orange Book, and thus patent holders cannot impose a 30-month stay on ANDAs based on such patents. This reflects Congress' intent to limit the Paragraph IV patent challenge system to compound and method of use issues. Although Biovail feels aggrieved by a situation in which it asserts that a manufacturing change implicates its non-process patent, the "solution" it proposes would operate across the board to all CMC changes, thus effectively interjecting a new and unauthorized basis for patent holders to delay generic competition and further harm consumers.

II. Duplicative Paragraph IV Certifications Are Unnecessary For FDA And The Federal Courts To Discharge Their Obligations Under Hatch-Waxman

Not only does the plain language of the FDCA prohibit Biovail's proposed requirement that ANDA applicants file multiple Paragraph IV Certifications to the same patent, such duplicative certifications are entirely unnecessary under the Hatch-Waxman patent challenge system. The patent certification and notification provisions were not enacted to serve as a constant update service to the brandname company on matters relating to the progress of the ANDA applicant's journey through the generic drug approval process. Rather, they are designed to provide, at the outset of that ANDA review, notice to the brandname company that its patent will be challenged by the ANDA applicant. Paragraph IV Certifications serve only limited functions under Hatch-Waxman. First, from the standpoint of FDA's role in the Paragraph IV patent challenge system, Paragraph IV Certifications serve simply to inform FDA of the applicant's intent to challenge the patent based on the applicant's belief that the patent is invalid, unenforceable, or that it would not be infringed by the applicant's product once marketed. FDA's only administrative obligation in response to such a certification is to delay approval of the ANDA for 30 months if the patent holder brings a patent infringement action within 45 days of its receipt of the applicant's notification of the filing of the Paragraph IV Certification. 21 U.S.C. § 355(j)(5)(B)(iii).³

The only other relevant purpose of the Paragraph IV Certification is to provide a jurisdictional basis for the courts to adjudicate the validity, enforceability, or future infringement of the patent. Specifically, the Patent Code provides Article III jurisdiction for the federal courts by defining as an "artificial" act of infringement⁴ the submission of

³ The order of Paragraph IV Certifications filed by different ANDA applicants is also, of course, relevant to eligibility for the 180-day exclusivity period, but that issue is not directly relevant to the issues raised by Biovail's petition.

⁴ See *Eli Lilly v. Medtronic*, 496 U.S. 661 (1990).

“an application under section 505(j)...if the purpose of such submission is to obtain approval under [the FDCA] to engage in the commercial manufacture, use, or sale of a drug...claimed in a patent...before the expiration of such patent.” 35 U.S.C. § 271(e)(2) (emphasis added). Under the plain language of this provision, the courts retain jurisdiction over any disputes between the applicant and the patent holder relating to the ANDA so long as the applicant’s application continues to seek approval prior to the expiration of the patent, regardless of whether the applicant has made CMC, or any other, changes to its ANDA. Thus, there is no basis and no need, from an administrative or judicial standpoint, for an applicant to re-certify every time it makes a CMC change in the ANDA.

Even if, as Biovail asserts, some CMC changes have the potential to alter the substantive dispute between the parties as to infringement or non-infringement of the patent, the courts are the appropriate venue to address such issues, and they may do so without the ANDA applicant filing a new Paragraph IV Certification. Indeed, as Biovail notes, the Federal Circuit has recently reminded ANDA applicants of their obligation during litigation to keep the court and the patent holder apprised of any ANDA changes that would *materially* affect the patent issues involved in the case. *Pet.* at 6, citing *Biovail v. Andrx*, 239 F.3d 1297 (Fed. Cir. 2001). In addition, the Federal Circuit has more recently held that a final judgment of non-infringement arising from a pre-marketing Paragraph IV infringement action does not preclude the patent holder from later suing the same generic company for actual infringement if the marketed generic product is shown to infringe the patent. *Bayer AG v. Biovail*, Nos. 01-1329, and 1330 (Fed. Cir., Feb. 7, 2002). As the Court noted, “infringement under § 271(e)(2)(A) by submission of an ANDA is not synonymous with infringement under § 271(a) by a commercial product. Evidence of actual infringement (contrasted with evidence of a “hypothetical” infringement) may differ in substance and may become available only after manufacture of the composition.” Thus, regardless of how many changes, of whatever nature, are made to an ANDA during or after the FDA review period, the courts are well equipped to give innovators what Biovail speciously suggests is not available without its proposed rule – “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).” *Pet.* at 7.

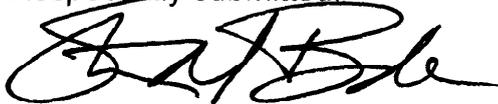
Finally, Biovail argues that its proposal will not disadvantage ANDA applicants because even if a new 30-month stay were imposed, the ANDA applicant could seek to have the stay shortened pursuant to 21 U.S.C. § 355(j)(5)(B)(iii). *Pet.* at 7-8. First, as GPhA has explained to FDA in the past, the statutory language and intent of Hatch-Waxman should be interpreted to limit 30-month stays to one stay per ANDA, regardless of how many patents are listed for the innovator drug. Biovail’s position that multiple stays are possible *for the same patent* is absurd and would further distort the true meaning and intent of the 30-month stay provision. Moreover, the “protection” offered up by Biovail of seeking to shorten such successive stays is cold comfort to any generic company that has been in the trenches of Hatch-Waxman patent litigation, where endless discovery and motions practice, and the courts’ overflowing case

dockets mean that resolution of even relatively straightforward preliminary matters can take months or years. And as a practical matter, this option would be of only marginal value as a curb on patent holder abuses. However, to the extent Biovail believes the courts' power to alter the term of a stay is a viable tool in these cases, it undermines Biovail's position that innovators are disadvantaged by the current lack of a requirement to re-certify based on CMC changes. Indeed, patent holders have all the procedural advantages in Paragraph IV infringement actions and should have little to fear from CMC changes in ANDAs. Not only can patent holders request a lengthened stay, they can also seek a preliminary injunction against the generic applicant for the remainder of the litigation. 21 U.S.C. § 355(j)(5)(B)(iii). And, as Biovail and the innovator industry all too often fail to mention, patent holders retain the alternative right to sue generic applicants for actual commercial infringement after marketing, and unlike in pre-approval Paragraph IV infringement actions, a prevailing patent holder can recover monetary damages, trebled if the infringement is shown to be willful.

Conclusion

Biovail's petition is without merit and should be denied.

Respectfully submitted,



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