April 3, 2007

VIA FEDERAL EXPRESS

Food and Drug Administration
Office of Generic Drugs, HFD-600
Attention: Gary J. Buehler
7500 Standish Place
Rockville, MD 20855

RE: Response to FDA Letter of March 28, 2007 Concerning Amlodipine Besylate (ANDA No. 77-080 and NDA No. 22-026)

Dear Mr. Buehler:

Synthon Laboratories, Inc. and Synthon Pharmaceuticals, Inc. (collectively referred to hereafter as "Synthon") hereby provide a joint response to the Food and Drug Administration's ("FDA's") March 28, 2007 letter concerning the regulatory and legal issues surrounding the approval of abbreviated new drug applications ("ANDAs") for amlodipine besylate. Synthon Pharmaceuticals, Inc. is the holder of a pending 505(b)(2) new drug application (NDA 22-026) that contains a paragraph III patent certification to patent number 4,879,303 (the '303 patent), and Synthon Laboratories, Inc. is the holder of a pending ANDA (ANDA 77-080) that contains a paragraph IV patent certification to the '303 patent.

Because the two independent Synthon entities filed different patent certifications, the Food and Drug Administration's ("FDA's") decision in this matter will likely affect each company differently. Nevertheless, Synthon is filing a joint response because both companies share a desire to see the applicable statues, regulations, and case law applied in an equitable and consistent manner, regardless of the facts surrounding Synthon's applications in this particular instance. Our response has three sections. Section I briefly sets forth some preliminary concerns and our proposed remedy to what we see as the novel issue in this matter. Section II provides direct answers to the questions presented. Section III sets for a summary of what we think should happen in this particular matter.

I. Preliminary Concerns

The FDA's questions treat the '303 patent as if the whole patent was held invalid. This is not the case. Only three of the eleven granted claims have been held invalid. Significantly claims four and five, which are directed to specific tablet compositions, remain valid. While Pfizer (ultimately) agreed that Apotex's, Synthon's, and Mylan's products do not infringe claims four and five, we understand that claims four and five cover Pfizer's Norvasc® drug product. Thus,

9000 Development Drive • P.O. Box 110487 • Research Triangle Park, North Carolina 27709
Phone +1 (919) 493-6006 • Fax +1 (919) 493-6104

the '303 patent would appear to remain a properly listed Orange Book patent, despite the invalidation of claims one, two and three; e.g., claims four and five cover the listed product and were not held invalid. Accordingly, we suggest that a more refined review than an "all or nothing" patent analysis is needed.

Next, we see the heart of the issue as follows: an NDA holder should not enjoy the benefit of a pediatric extension of exclusivity based on a patent proven to be invalid and/or not infringed, regardless of whether the legal determination occurs before or after patent expiration. The statutory scheme shows that a pediatric extension should not be countenanced on an invalid and/or not infringed patent; e.g., successful paragraph IV challenger is not encumbered by the six month exclusivity extension. But, under the FDA's policy of converting a paragraph IV certification to a paragraph II certification upon patent expiration, the pediatric exclusivity would appear to inadvertently apply to successful patent challengers simply because their victory came too late. This result is nonsensical: the statutory scheme does not suggest that pediatric exclusivity should apply to invalid patents differently, depending on when they were invalidated. Yet, this unforeseen and unintended consequence is a possibility given FDA's summary conversion of all patent certifications to a paragraph II upon patent expiration. The American people have been unduly denied lower-cost generics drugs by invalid patent claims while the appellate process has played out, the public should not be further harmed by FDA postponing the launch of those generic drug products by an additional six months beyond the expiration of invalid and/or not infringed patents.

To prevent the perversion of the statute, we propose that FDA permit patent challengers, when successful after patent expiration, to remove their patent certifications in favor of a "no relevant patents" statement. In this way, the literal trigger of 21 U.S.C. § 355a(c)(2)(A)(i) is avoided, the intent of the statutory scheme is preserved, and FDA does not have to revisit or revise its judicially approved policy of converting a patent certification from a paragraph IV to a paragraph II after patent expiration. Because a court has adjudged the patent not relevant (invalid or not infringed) for a particular ANDA applicant, the statement is accurate and reasonable for that ANDA, only. This approach also maintains FDA's policy of not reviewing patent scope, infringement, or invalidity issues: the statement would be based solely on the decision of the court and would not require FDA to consider the merits of the patent. Thus, by allowing former paragraph IV ANDA applicants that are successful in their patent challenge after patent expiration to use the no relevant patent statement, FDA would provide a narrowly tailored policy of limited applicability that effectuates the plain intent of the statutory scheme while resolving an apparent regulatory conflict therewith.

II. FDA's Questions and Synthon's Responses

To enhance the readability of our response, we have restated the Agency's question in italicized text, followed by our response in normal text.

1. What date controls FDA's giving effect to the decision in Pfizer Inc. v. Apotex, Inc., No. 2006-1261 (Fed. Cir. March 22, 2007) ("Apotex decision") holding that Pfizer's patent 4,879,303 ("the '303 patent") is invalid? Can FDA treat the '303 patent as invalid as of March 22, 2007, or must FDA await the issuance of the mandate? Is the answer the same for all purposes, that is, for determining the applicability of pediatric exclusivity, the triggering of 180-day exclusivity, and the eligibility of other ANDA applicants for final approval?

FDA's decisions under Federal Food, Drug, and Cosmetic Act ("FFDCA") must be transparent and consistent in order to avoid unnecessary confusion and litigation. While this is true for all Agency actions under the FFDCA, it is particularly applicable to actions concerning paragraph IV litigation under the Hatch-Waxman Amendments (the "H-W Act"). Both the innovator and generic industries need assurance that FDA actions will be final and not subject to change. There is simply too much at stake to base agency action on preliminary decisions. In order to provide this type of certainty, FDA must wait until the Court of Appeals issues its final "mandate" before taking any agency action under the FFDCA that is triggered by an appellate decision. Until the mandate issues, FDA is constrained to operate as if there were no appellate decision in the matter.

The applicable law provides FDA with no option but to wait for the court's mandate. The Federal Rules of Appellate Procedure leave no doubt as to when a Court of Appeals decision is "final" and binding on the parties. *See* F.R.A.P. 41(c) (stating that mandates are effective when issued). It is the court's mandate that fixes the obligations of the parties and renders the decision "final." *See* Advisory Committee Notes to F.R.A.P. 41. Prior to issuance of the mandate, the obligations of the parties are subject to change through a variety of procedural avenues (e.g., petition for rehearing *en banc*). Thus, FDA need not search for a definition of "final appellate decision." The F.R.A.P. provides an unambiguous answer to the Agency's question – the Apotex decision is not "final" until the Federal Circuit issues its mandate. To rely on any other date to trigger the H-W Act events would conflict with the F.R.A.P. and would potentially entangle FDA in a quagmire of litigation in those instances where the Federal Circuit's initial decision is reversed.

With regard to the current amlodipine matter, FDA should withhold all agency action relating to the Apotex decision until the court issues its mandate. The application of this policy to the various types of amlodipine applicants is set forth below:

a) <u>Paragraph IV ANDAs with final approval as of the date of the Apotex decision (i.e., the first-filer).</u>

The first-filer in this matter was not sued by the NDA holder prior to the expiration of the 45-day period set forth in FFDCA § 505(j)(5)(B)(iii).[1] As a result, the first-filer received

[1] Because the first ANDA containing a paragraph IV certification for amlodipine was filed prior to December 8, 2003, the amendments to FFDCA § 505(j) enacted as part of the Medicare Prescription Drug, Improvement, and Modernization Act ("MMA") are not applicable to this matter (except that the "court decision" trigger for 180-day

"final" ANDA approval at the completion of the scientific review of its application. Subsequently, a U.S. District Court ruled that the '303 patent was valid and infringed by the first filer. Thus, at the time of the Apotex decision, the first filer held a "final" ANDA approval and an adverse District Court decision. The relevant case law squarely addresses this exact set of facts and compels FDA to convert the first filer's ANDA approval from "final" to "tentative." See Mylan Labs., Inc. v. Thompson, 332 F.Supp.2d 106 (D.D.C. 2004), aff'd 389 F.3d 1272 (D.C. Cir. 2004).[2] Once the approval is converted to "tentative," the first filer has an obligation to keep its patent certification accurate and therefore must convert its paragraph IV certification to a paragraph II certification upon the expiration of the '303 patent. See 21 C.F.R. § 314.94(a)(12)(viii)(C)(1). See also Ranbaxy Labs. Ltd. v. FDA, 307 F.Supp.2d 15 (D.D.C. 2004), aff'd 96 Fed. Appx. 1 (D.C. Cir.2004). Without a paragraph IV certification, the first filer would lose the potential for 180-day exclusivity as soon as its paragraph IV certification is converted to a paragraph II certification. See FFDCA § 505(j)(5)(B)(iv) (stating that exclusivity attaches to an ANDA "containing" a paragraph IV certification); Dr. Reddy's Labs., Inc. v. Thompson, 302 F.Supp. 2d 340, 353-55 (D.N.J. 2003). Consequently, the first-filer's ANDA would no longer block the approval of other ANDAs that previously contained a paragraph IV certification (and were likewise converted to paragraph II certifications). Furthermore, the final approval of the first-filer's ANDA would be blocked by the pediatric exclusivity that attaches to the '303 patent. See FDCA § 505A(c)(2)(A)(i); Mylan Labs., Inc., 389 F.3d at 1281-84; Ranbaxy Labs. Ltd., 307 F.Supp2d at 21. As explained in greater detail in our response to the question 3 below, the first-filer could obtain final approval of its ANDA when the Federal Circuit's mandate issues by changing its paragraph II certification to a "no relevant patents" statement.

Synthon notes that, in this instance, the first-filer claims to have triggered its 180-day exclusivity via the "commercial marketing" trigger prior to the expiration of the '303 patent. We also understand that FDA did not convert the first-filer's "final" approval to a "tentative" approval when the patent expired due to court order staying any FDA action on the matter. We believe the granting of a stay of FDA action in that matter was inappropriate. Nevertheless, the presence of a final approval on the patent expiry date does not change the outcome with respect to 180-day exclusivity. Assuming the first-

---

exclusivity is at the Appellate Court rather than the District Court). Therefore, all statutory references in these comments are to the pre-MMA statute, unless otherwise noted.

[2] Indeed, once the amended district court judgment was issued delaying the approval date of the first filer's ANDA, the status of the first filer's ANDA was necessarily a "tentative" and not a "final" one. This is true regardless of the later applied for and received stay from the Federal Circuit. The day after the district court's judgment, the first filer's ANDA was only tentatively approved by definition. See 21 C.F.R. § 314.105(a). This legal fact could not be revoked by the later stay. To regain final approval would require substantive review by the FDA. See Barr Laboratories, Inc. v. Thompson, 238 F.Supp.2d 236, 245-50 (D.D.C. 2002) (affirming FDA decision that an approval with a delayed effective date is tentative and does not give an applicant the right to enter the market on a date certain without further FDA action); Ranbaxy Labs., Ltd. 307 F.Supp.2d at 19-20 (upholding FDA determination that ANDA approvals do not become effective automatically). See also 21 C.F.R. § 314.107(b)(3)(v) (stating final approval letter from FDA required to convert tentative approval to final approval).

filer's ANDA approval remains effective and that the 180-day exclusivity period commenced prior to the patent expiration date, the first-filer's exclusivity only prohibited approval of other ANDAs prior to the patent expiration date. After that date, the exclusivity has no effect on the approval of the other ANDAs. As noted above, once the patent expires, all patent certifications to the '303 patent contained in pending ANDAs must convert to paragraph II certifications. The 180-day exclusivity provision in the FFDCA only blocks the approval of a subsequently filed ANDA if such an application "contains a [paragraph IV] certification." FFDCA § 505(j)(5)(B)(iv).[3] Thus, the plain language of the statute does not allow FDA to apply the 180-day exclusivity provision to ANDAs that no longer contain a paragraph IV certification. See Response to Question 3, below.

b) Paragraph IV ANDAs without final approval as of the date of the Apotex decision (i.e., subsequent filers)

All of the ANDA applicants who filed paragraph IV certifications to the '303 patent were sued by the NDA holder within the required 45 days; therefore, the "final" approval of those applications was subject to a "30 month stay." Additionally, these ANDAs could not receive "final" approval until the first-filer's 180-exclusivity expired or was rendered ineffective by a change in patent certification.[4] Therefore, none of the "subsequently filed" paragraph IV ANDAs had received final approval as of the expiration date of the '303 patent. Under the Mylan and Ranbaxy cases, the patent certifications in these applications automatically converted to paragraph II certifications on the patent expiry date. See Mylan Labs., Inc., 389 F.3d at 2181-84; Ranbaxy Labs., Ltd., 307 F.Supp.2d at 21. With paragraph II certifications, the ANDAs are no longer blocked by 180-day exclusivity; however, they remained blocked by pediatric exclusivity until the patent certifications are removed or the patent is delisted.

c) Paragraph III ANDAs

The ANDAs submitted paragraph III certifications to the '303 patent will also be deemed to contain "paragraph II" certifications when the patent expires. 21 C.F.R. § 314.94(a)(12)(viii)(C)(1). Under section 505A of the FFDCA, FDA cannot make the approval of these ANDAs "effective" until six months after the expiration of the '303 patent. This barrier to final approval remains effective as long as the '303 patent remains listed in the Orange Book.

---

[3] Interpretation of the 180-day exclusivity period as limited by the patent expiration date is consistent with FDA's longstanding policy. See 59 Fed. Reg. 50338, 50348 (Oct. 3, 1994) (stating that, for exclusivity purposes, "a patent is deemed to be relevant until the end of the term of the patent or applicable 180-day period, whichever occurs first").

[4] An adverse appellate decision obligates an ANDA applicant to change its certification from paragraph IV to paragraph III, thus rendering the potential exclusivity ineffective because the application "will no longer be considered to be one containing a [paragraph IV certification]". 21 C.F.R. § 314.94(a)(12)(viii)(A).

2. If FDA must await the issuance of the mandate, does pediatric exclusivity bar the approval of all unapproved ANDAs in the meantime?

As noted above, FDA should not act upon a Court of Appeals decision until the court's mandate issues. Therefore, all patent certifications to the '303 patent should be converted to "paragraph II" certifications as of the expiration date of the patent. The plain language of Section 505A states that ANDAs with paragraph II certifications to a patent that has received pediatric exclusivity cannot receive final approval until 6 months after the patent expiration date. FFDCA § 505A(c)(2)(A)(i). FDA should apply this unambiguous language until either (a) the relevant ANDAs no longer contain a certification to the '303 patent; or (b) the '303 patent is "delisted" from the Orange Book.

3. If and when the Apotex decision is implemented, what is the effect of the decision that the '303 patent is invalid on the obligation of an ANDA applicant to change its certification? Must Pfizer delist its patent, so that certifications can be withdrawn? Or can FDA treat an invalid patent as delisted as a matter of law, and presume the withdrawal of the certifications? Or must the ANDA applicants file paragraph II certifications stating that the '303 patent has expired?

We will address each part of the Agency's question below:

(a) *What is the effect of the decision that the '303 patent is invalid on the obligation of an ANDA applicant to change its certification?*

If the Federal Circuit issues a mandate holding that claims one, two, and three of the '303 patent are invalid, the ANDA applicants who originally filed paragraph IV certifications to the '303 patent (which were subsequently converted to paragraph II certifications), will be entitled to remove the certifications to the '303 patent and file a "no relevant patents" statement. Section 505(j)(2)(vii) of the FFDCA requires ANDA applicants to certify to each patent "which claims the listed drug" identified in the ANDA. Once the Federal Circuit invalidates all of the claims that have been asserted against the paragraph IV applicants, the '303 patent will no longer be a patent to which those applicants are required to certify. Rather, the appropriate amendment will be the "no relevant patent" statement described in 21 C.F.R. § 314.94(a)(12)(ii). In contrast, the paragraph III applicants will not be eligible to remove their patent certification because claims four and five of the '303 patent remain valid and the NDA holder never had an opportunity to assert those claims against the paragraph III applicants.

Allowing a "no relevant patents" statement for the former paragraph IV applicants is the only approach that strikes an appropriate balance between consumer access to generic drugs and the innovator's patent and pediatric exclusivity rights. It is axiomatic that an invalid patent should not block the public's access to affordable generic drugs. It naturally follows that a period of pediatric exclusivity attached to an invalid patent (and therefore assuming the same character of the patent) should not delay generic market entry. However, the statute does not specifically address the situation where the asserted claims in a patent are found invalid after the patent expires and ANDAs are no longer permitted to contain paragraph IV certifications. Fortunately,

FDA's regulations provide a remedy in the "no relevant patents" statement. Applying the "no relevant patents" statement to the narrow set of facts presented in this matter will prevent the unnecessary delay of generic drugs while simultaneously preserving the innovator's pediatric exclusivity as to those applicants against whom the innovator never had the opportunity to assert the patent claims that remain valid.

(b) *Must Pfizer delist its patent, so that certifications can be withdrawn?*

Pfizer is *required* to list the '303 patent as long as the patent "claims [the Norvasc drug product] or a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by [Pfizer] engaged in the manufacture, use, or sale of the drug." FFDCA § 505(b)(1). The Apotex decision invalidates only claims one, two, and three. Claims four and five will remain valid after the court's mandate issues. Therefore, if Pfizer determines that the '303 patent continues to meet the statutory requirements for listing, the company will be prohibited from delisting the patent.

(c) *Can FDA treat an invalid patent as delisted as a matter of law, and presume the withdrawal of the certifications?*

FDA has historically taken the position that it does not determine whether a patent must be listed, or delisted, in the Orange Book. Although the Agency now requires more detailed certifications with patent listings, it has not deviated from its position that FDA's role in patent listing is purely "ministerial." See 21 C.F.R. § 314.53(f) (stating "[u]nless the patent owner withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list"). There is no justification to deviate from that longstanding position in this instance. It has always been, and should remain, the NDA holder's responsibility to delist patents that no longer meet the statutory qualifications for listing.[5] While it is true that the failure to promptly delist a patent after it has been invalidated could have an adverse effect on the timeliness of generic competition, the Federal Antitrust Laws provide a sufficient deterrent for this type of anticompetitive "gaming" of the system.

(d) *Must the ANDA applicants file paragraph II certifications stating that the '303 patent has expired?*

It is not necessary for each applicant to amend its application to add a paragraph II certification. The courts have upheld FDA's authority to automatically convert the certifications to paragraph II upon patent expiry. See Dr. Reddy's Labs., Inc., 302 F.Supp.2d at 355. Whether the ANDA applicants actually file a paragraph II certification, or FDA "deems" the certification to have been changed to paragraph II, the outcome is the same.

[5] The single exception to this policy is the instance where a patent has been found invalid and an ANDA applicant is eligible for 180-day exclusivity. In that limited situation, FDA's regulations prohibit the delisting of the invalid patent during the 180-day exclusivity period. 21 C.F.R. § 314.50(h)(i)(6)(ii).

4. If and when the Apotex decision is implemented and the patent is treated as invalid, does pediatric exclusivity attach to the '303 patent with respect to any unapproved ANDAs? Does it matter whether the ANDA applicant filed a paragraph III or IV certification before patent expiration?

Pediatric exclusivity will remain effective for the '303 patent as long as: (a) the '303 patent remains listed in the Orange Book; and (b) the relevant ANDA contains a paragraph II certification (which all ANDAs will contain after the patent expiration date).[6] The final disposition of the ANDAs will hinge on whether the application originally contained a paragraph III or a paragraph IV certification. As set forth above, those applications that contained a paragraph IV certification should be permitted to remove their patent certification and file a "no relevant patents" statement as soon as the Apotex decision and/or their own appeal is final and applied to the particular ANDA applicant's District Court decision. The ANDAs that originally contained a paragraph III certification, should not be permitted to remove their certification because Pfizer was never given an opportunity to assert claims four and five of the '303 patent against those applicants.

5. Does 180-day exclusivity triggered before a patent expires continue to bar approvals of other ANDAs after the patent expires, even if other ANDA applicants change their certifications to paragraph II or withdraw their certifications altogether?

The 180-day exclusivity should not be given effect after the patent upon which it is based has expired. FDA has long taken the position that the 180-day exclusivity period cannot extend past the patent expiration date. See 59 Fed. Reg. 50338, 50348 (Oct. 3, 1994). Likewise, Congress has recognized that generic competition should not be delayed past the expiration of the patents that form the basis for exclusivity. In the MMA, Congress specifically stated that the 180-day exclusivity period shall be "forfeited" if "[a]ll of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired." 21 U.S.C. 355(j)(5)(D)(i)(VI) (2006) (post-MMA). The same public policy rationale applies to the pre-MMA statutory construct – there should be no exclusivity after patent expiration.

Additionally, as noted above, the plain language of the pre-MMA 180-day exclusivity provision states that, during the exclusivity period, FDA is prohibited from approving a subsequently filed ANDA that "contains" a paragraph IV certification. FFDCA § 505(j)(5)(B)(iv). There is no prohibition on approving ANDAs during the exclusivity period that contain a paragraph II certification. Furthermore, the word "contains" leaves no doubt that the subsequent ANDA must

[6] If FDA adopts the position that the first filer retained its final ANDA approval as of the patent expiration date, it would follow that the first filer would not be required to remove its paragraph IV certification. See 21 C.F.R. § 314.94(a)(12)(viii)(C)(1) (stating ANDA applicant not required to amend patent certification after receiving final approval). In such a circumstance, the pediatric exclusivity would not apply to the first filer's ANDA because it would contain a paragraph IV certification with a favorable court decision (as of the date of the court's mandate and application to the first filer's District Court decision). However, for the reasons set forth in this letter, Synthon believes that the first filer's final approval should have been converted to "tentative" because the Apotex decision was not final at the time of patent expiry.

contain a paragraph IV certification during the exclusivity period in order for the prohibition on approval to apply. If, at any time during the 180 days, a subsequent ANDA application no longer "contains" a paragraph IV certification, the approval of that ANDA is no longer blocked by the plain language of the exclusivity provision.[7]

In the amlodipine situation, the ANDAs that were not subject to final approval at the moment of patent expiration *cannot* maintain paragraph IV certifications after the patent expires. See Dr. Reddy's Labs., Inc., 302 F.Supp.2d at 355; Mylan Labs., Inc., 389 F.3d at 1281-84; Ranbaxy Labs., Ltd., 307 F.Supp.2d at 21. As a result, the final approval of those ANDAs *cannot* be blocked by the first-filer's 180-day exclusivity. In fact, even if FDA should deviate from its longstanding policy and determine that, in this instance, the 180-day exclusivity remains beyond the patent expiration date, the exclusivity will have *no effect* because the subsequently filed ANDAs are prohibited from containing a paragraph IV certification.[8]

III. Conclusion

FDA should adopt a position for the amlodipine ANDAs that is consistent with the plain language of the statute, applicable case law and agency precedent. As set forth above, the application of such a sound policy compels the following:

(1) the Apotex decision is not "final" until the court issues its mandate;

(2) the first-filer's final approval must be immediately and/or retroactively converted to a "tentative" approval;

(3) all patent certifications to the '303 patent are deemed to be paragraph II certifications as of expiration of the '303 patent, i.e., midnight on March 25, 2007;

(4) the first-filer's potential 180-day exclusivity does not run beyond the expiration of the '303 patent because the 180-day exclusivity is only relevant to ANDAs with a paragraph IV

[7] FDA regulations are consistent with this reading of the statute. In order to prevent potential gaming of the system, FDA's regulations do not allow an ANDA applicant to attempt to circumvent the 180-day exclusivity period by removing its paragraph IV certification. 21 C.F.R. § 314.94(a)(12)(viii). This regulation is also consistent with FDA's position that 180-day exclusivity does not extend beyond the patent life in that the limitation on removing a paragraph IV certification does not apply when the patent expires before the lawsuit is resolved or before the 180-day exclusivity expires. See id.

[8] We note that arguments attempting to apply FFDCA § 505A(k) to the amlodipine facts are wholly without merit. Section 505A(k) applies to the narrow fact pattern where the first-filer's 180-day exclusivity has been triggered by a "court decision," but the exclusivity holder is prohibited from getting final ANDA approval as a result of pediatric exclusivity that is attached to a different patent (to which the exclusivity holder filed a paragraph III or received an adverse court decision) or a period of market exclusivity. In that instance, Section 505A(k) prevents the loss of a portion, or all, of the exclusivity. It does not, as some have suggested, extend exclusivity beyond the expiration date of the patent upon which exclusivity is based. To the best of Synthon's knowledge, section 505A(k) has only been applied in one instance—the 180-day exclusivity for fluoxetine.

certification; i.e., all ANDAs were converted to paragraph II certifications after '303 patent expiration so no paragraph IV ANDAs remain to be blocked.

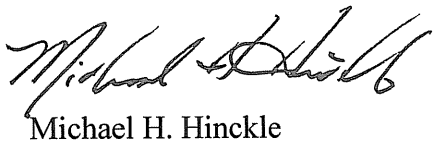
(5) the '303 patent must remain listed as long as claims four and five are valid and Pfizer asserts that they claim the Norvasc drug product;

(6) all ANDAs that contained a paragraph IV certification to the '303 patent prior to March 25, 2007, and whose holders' litigated claims one, two, and three, may be amended to remove the paragraph II certification and add a "no relevant patents" statement as soon as their successful challenge of the '303 patent is embodied in (i) a mandate from the appellate court in their appeal or (ii) a judgment from their District Court;

(7) all ANDAs (and 505(b)(2) NDAs) that contained a paragraph III certification to the '303 patent prior to March 25, 2007 must wait for either: (a) the pediatric exclusivity on the '303 patent to expire; or (b) the delisting of the '303 patent, before obtaining final FDA approval.

Thank you for the opportunity to comment on this matter. Should you have any questions concerning this submission, please contact me at (919) 536-1304 or via email at mhinckle@synthon.com.

Sincerely,



Michael H. Hinckle
Vice President & General Counsel
Synthon Pharmaceuticals, Inc.

cc: FDA Docket No. 2007P-0116