Daiichi-Sankyo

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BY UPS - 1Z 05F 9A7 01 9638 4709
Gary J. Buehler, Director
Food and Drug Administration
Office of Generic Drugs, HFD-600
7519 Standish Place
Rockville, MD 20855

Re: Docket No. 2007N-0123 -- FDA solicitation for comments regarding amlodipine 180 day exclusivity and pediatric exclusivity issues

Dear Mr. Buehler:

Daiichi Sankyo Inc. ("Daiichi Sankyo") submits this response to FDA's request for comments regarding decisions FDA will be making on the issues of 180 day exclusivity and pediatric exclusivity for amlodipine applications. Daiichi Sankyo is an interested party, because we have a pending 505 (b)(2) application (a "paper NDA") for a combination drug containing amlodipine besylate as one of the active ingredients. Daiichi Sankyo has filed a paragraph III certification regarding Pfizer's U.S. Patent 4,879,303 ("the '303 patent"), and currently cannot gain a final approval of our paper NDA prior to the expiration of Pfizer's pediatric exclusivity on September 25, 2007. A decision on Pfizer's pediatric exclusivity for amlodipine applies with equal force to both ANDAs and 505(b)(2) applications, since the pediatric exclusivity statute applies pediatric exclusivity identically to both ANDAs and 505(b)(2) applications. FDA's decision will clearly impact us, because it could lead to a date of final approval earlier than September 25, 2007 for our paper NDA for our amlodipine combination, as well as other similarly situated paper NDAs for amlodipine combinations.

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?

At the outset, it should be noted that there is an erroneous assumption underlying several of the questions posed in FDA's notice that Pfizer's patent (i.e., all claims of Pfizer's patent) was declared invalid. The ***patent*** was not declared invalid—***only claims 1-3 of the patent*** were declared invalid. Pfizer v. Apotex, 2007 WL 851203 (Fed. Cir. 2007; No. 2006-1261) at pages 1, 5 and 20. This distinction is significant, because **the '303 patent has 11 claims**, claims 4-11 of which were apparently not pursued in the litigation by Pfizer as having been infringed by Apotex, and thus were not addressed by the Federal Circuit in the Apotex decision. Please see our response to the other questions regarding how the existence of these other claims affects the issue of pediatric exclusivity.

We have no comments on whether FDA must await the issuance of a mandate and whether FDA must apply the mandate (or lack of mandate) standard consistently for all purposes.

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

We assume FDA's reference to "unapproved ANDAs" means tentatively approved ANDAs and ANDAs that have not yet received tentative approval. If FDA must await the issuance of the mandate, pediatric exclusivity bars approval of all unapproved ANDAs and 505(b)(2) applications (i.e., ANDAs and 505(b)(2) applications that have tentative approval, and those which have not yet received tentative approval).

The answer to this question is governed by Section 505A of the Food and Drug Act (21 U.S.C. 355a). Subsections (c)(2)(A) and (c)(2)(B) of section 505A expressly provide that the type of certification determines whether or not an ANDA or 505(b)(2) application can be approved:

> (2)(A) if the drug is the subject of—
> (i) a listed patent for *which a certification has been submitted* under **[paragraph II]** and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or
> (ii) a listed patent for *which a certification has been submitted* under **[paragraph III]**,
> the period during which an application may not be approved under section 505(c)(3) or section 505(j)(5)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions); or
> (B) if the drug is the subject of a listed patent *for which a certification has been submitted* under **[paragraph IV]**, and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under section 505(c)(3) or section 505(j)(5)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions). [emphasis added].[1]

It is clear from the consistent reference in these subsections to "the drug … for which a certification has been submitted", that whether or not an NDA/patent owner's pediatric exclusivity prohibits final approval of an ANDA or 505(b)(2) application must be addressed in the context of each individual ANDA or 505(b)(2) application and the specific accompanying certifications. This construction flows logically from the use of the word "or" in separating the different certification (paragraphs II, III, or IV) scenarios under which approval of "an application" may be

[1] Subsections (c)(2)(A) and (c)(2)(B) of 505A apply, because Norvasc was an "already marketed drug" approved prior to enactment of section 505A. Subsections (b)(2)(A) and (b)(2)(B) are identical to subsections (c)(2)(A) and (c)(2)(B), but apply to drugs that were not approved as of the date that section 505A was enacted.

delayed by an additional six month period commencing six months after the original date of patent expiration. To adopt a contrary construction wherein "*an* application" is interpreted to mean "*every* application" would lead to an absurd result: if *any* ANDA has made a paragraph III certification, approval of *all* ANDAs would be delayed by pediatric exclusivity. Given a choice between the plain reading of the words of the statute that leads to a reasonable result, and a construction suggested nowhere in the legislative history that would produce an illogical result, the plain reading and reasonable result construction must prevail. *See Clinton v. City of New York*, 524 U.S. 417, 429, 118 S.Ct. 2091, 141 L.Ed.2d 393 (1998) (refusing to adopt a statutory reading that "would produce an absurd and unjust result which Congress could not have intended."). Moreover, had Congress truly intended that pediatric exclusivity would not apply selectively as described above, it could have drafted the statute without any reference to the different types of certifications, and simply stated that no ANDA or 505(b)(2) application will be approved during the pediatric exclusivity period, unless prior to the original date of patent expiration, there is a judgment declaring the patent invalid or non-infringed.

Thus, pediatric exclusivity is not an all or nothing proposition--it does not necessarily block approval of all ANDAs and 505(b)(2) applications; there are some instances where it will block some, but not all ANDAs and 505(b)(2) applications. Moreover, pediatric exclusivity only blocks *approval* of applications that have not received final approval (both tentatively approved and unapproved applications).[2]

Applications Having Paragraph III Certifications

For ANDAs and 505(b) applications that have submitted a paragraph III certification (i.e., a certification that the applicant "is not seeking approval prior to the

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[2] Of course, there are situations in which an application receives final approval, and the final approval is subsequently converted into a tentative approval. One such situation occurs when an ANDA applicant has lost a litigation resulting from a paragraph IV certification, and the district court issues an injunction under 35 U.S.C. § 271(e)(4)(A) prior to the original expiration date of the patent. An application in that situation is then subject to, and blocked by pediatric exclusivity.

expiration of the listed patent"), the statute clearly and unambiguously provides that the period during which the application may not be approved "shall be extended by a period of six months after the date the patent expires (including any patent extensions)." *Id.* In other words, with respect to ANDAs for amlodipine and 505(b)(2) applications that reference Pfizer's NDA for amlodipine and contain a paragraph III certification regarding the '303 patent, those applications can not receive a final approval until the expiration of pediatric exclusivity on September 25, 2007. Even if these applications were deemed to have been converted by operation of law into applications containing paragraph II certifications (i.e., certification that "the patent has expired") upon the '303 patent's original expiration date of March 25, 2007, the result is still the same, because like an application having a paragraph III certification, an application with a paragraph II certification can not receive approval until after the expiration of pediatric exclusivity.

Applications Having Paragraph IV Certifications

If FDA requires a mandate, and not merely a Federal Circuit decision reversing a district court decision, then clear and established case law provides that for any tentatively approved 505(b)(2) applicant or ANDA applicant that submitted a paragraph IV certification as of the original expiration date of the '303 patent, but which had failed to ***personally obtain*** a decision from a district court declaring the patent invalid or not infringed, or a mandate to that effect from the Federal Circuit prior to the original expiration date of the '303 patent ***in litigation resulting from that individual applicant's paragraph IV certification***, the application must be deemed to have converted into an application with a paragraph II certification (i.e., a certification that "the patent has expired"). *Mylan Laboratories, Inc. v. Thompson*, 389 F.3d 1272 (C.A. D.C. Circuit 2004); *Ranbaxy Laboratories, Ltd. v. FDA*, 307 F. Supp.2d 15 (D. D.C. 2004), *aff'd* 2004 WL 886333 (C.A.D.C. 2004). It thus cannot receive final approval until Pfizer's pediatric exclusivity expires on September 25, 2007. Even if FDA does not require a mandate, and will accept a Federal Circuit decision reversing a district court decision, the only beneficiary of that decision is the

individual applicant who obtained it. Any other applicant with a tentative approval (and a paragraph IV certification) that desires immunity from the pediatric exclusivity bar to final approval must ***personally obtain*** a court decision declaring that any claims of the patent asserted by Pfizer against it are invalid or not infringed.[3]

This conclusion is compelled by the construction of section 505A, discussed above. Whether "an application" can receive final approval when there is pediatric exclusivity will depend on what type of certification the applicant made. If a tentatively approved application has made a paragraph IV certification, and "in ***the*** patent infringement litigation resulting from ***the certification*** the court determines that the patent is valid and would be infringed," the tentatively approved application can not receive final approval until expiration of pediatric exclusivity. *505A(c)(2)(B)*(emphasis added).

It appears that the only tentatively approved ANDA or 505(b)(2) applicant that may not be blocked by Pfizer's pediatric exclusivity is Apotex (although Apotex could be blocked by 180 day exclusivity, if FDA determines that Mylan retains 180 day exclusivity). If FDA determines that a mandate was required, then Apotex cannot obtain approval prior to the expiration of Pfizer's pediatric exclusivity. Because Apotex failed to obtain a mandate prior to the original expiration date of the patent, it was blocked under 505A(c)(2)(B), and upon the original expiration date of the patent on March 25, 2007, its paragraph IV certification transformed by operation of law into a paragraph II certification, leaving Apotex permanently blocked by Pfizer's pediatric exclusivity. *Mylan*, *supra*; *Ranbaxy*, *supra*. If, however, FDA determines that a

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[3] It is conceivable that one or more ANDA or 505(b)(2) applicants may have attempted to change their paragraph III certifications to paragraph IV certifications after the recent Federal Circuit decision in *Apotex v Pfizer*. To the extent there are such applicants, they could not possibly have procured a judgment of invalidity prior to the expiration of the '303 patent, and upon expiration of the '303 patent, those applications must be deemed to have converted into applications containing a paragraph II certification.

mandate was not required and a Federal Circuit decision reversing a district court decision is sufficient, then Apotex has obtained such a decision, and is not blocked by pediatric exclusivity (because 505A(c)(2)(B) no longer applies).

The foregoing interpretation is consistent with, and strikes a fair balance between the policies of the pediatric exclusivity law and the Hatch-Waxman Act. FDA has acknowledged that "[t]he pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date." S . Rep. 107-79 at 5 (2001) (citing FDA's January 2001 Status Report to Congress). To allow ANDA or paper NDA applicants to gain approval during the pediatric exclusivity period when such applicants have sat back and have not personally procured a judgment of invalidity or non-infringement (or a mandate, if FDA determines that a mandate is required) would seriously undermine the incentive for NDA holders to carry out pediatric studies. The ANDA or 505(b)(2) applicants who should be permitted to market during a pediatric exclusivity period should be limited, consistent with the plain language of the statute, to those who diligently maintained a paragraph IV certification and were successful in obtaining a judgment of invalidity or non-infringement (or a mandate, if FDA determines that a mandate is required) prior to the original expiration date of the listed patent.

3. If and when the Apotex decision is implemented, what is the effect of the decision that the '303 patent is invalid on the obligations 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?

The underlying premise of this question—that Pfizer's patent (i.e., all claims of Pfizer's patent) was declared invalid—is wrong. The ***patent*** was not declared invalid—***only claims 1-3 of the patent*** were declared invalid. Pfizer v. Apotex, 2007

WL 851203 (Fed. Cir. 2007; No. 2006-1261) at pages 1, 5 and 20. This distinction is significant, because **the '303 patent has 11 claims**, claims 4-11 of which were apparently not asserted by Pfizer to have been infringed by Apotex, and thus were not addressed by the Federal Circuit in the Apotex decision. *Id.*; see U.S. Patent 4,879,303 (attached) at column 6, lines 29-64. Claims 4-11 of the '303 patent remained valid through the March 25, 2007 original expiration date, having never been declared invalid by any court. Claims 4-5 cover pharmaceutical formulations in the form of tablets containing amlodipine besylate together with specific excipients, and claims 6-8 cover pharmaceutical formulations in the form of tablets containing amlodipine besylate together with specific excipients.

Claims 1-11 are set forth below:

1. The besylate salt of amlodipine.

2. A pharmaceutical composition comprising an antihypertensive, antiischaemic or angina - alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 together with a pharmaceutically acceptable diluent or carrier.

3. A tablet formulation comprising an anti-hypertensive, antiischaemic or angina - alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 in admixture with excipients.

4. A tablet formulation as claimed in claim 3 wherein the excipients comprise a compression and, an additive to provide sheen to the tablet, a disintegrant and a lubricant.

5. A tablet formulation as claimed in claim 4 wherein the excipients comprise microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycollate and magnesium stearate.

6. A capsule formulation comprising an antihypertensive, antiischaemic or angina - alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 in admixture with excipients.

7. A capsule formulation as claimed in claim 6 wherein the excipients comprise an inert diluent, a dried disintegrant and a lubricant.

8. A capsule formulation as claimed in claim 7 wherein the excipients comprise microcrystalline cellulose, dried maize starch and magnesium stearate.

9. A sterile aqueous solution comprising an antihypertensive, antiischaemic or angina - alleviating effective amount of the besylate salt of amlodipine for parenteral administration.

10. A sterile aqueous solution as claimed in claim 9 comprising from 10 to 40% w/v of propylene glycol.

11. A sterile aqueous solution as claimed in claim 9 or claim 10 comprising about 1% w/v sodium chloride.

Putting aside the hypothetical question of whether a patent for which all of its claims have been declared invalid still exists, or must be delisted, that simply is not the situation here. The patent certainly did still exist, even after the decision by the Federal Circuit declaring claims 1-3 invalid, because there were 8 other remaining claims. Moreover, because the patent still existed, and was still listed in the Orange Book, any tentatively approved or unapproved ANDA or 505(b)(2) applicant who wanted to gain final approval earlier than the expiration of Pfizer's pediatric exclusivity needed to file a paragraph IV certification before March 25, 2007, and send notice to Pfizer of the paragraph IV certification. The notice letter would have been required to include a full and detailed explanation of why each claim was not infringed, invalid and/or unenforceable. 21 C.F.R. § 314.52. But unless a tentatively approved 505(b)(2) application or ANDA contained such a paragraph IV certification as of the original expiration date of the '303 patent, and obtained a decision declaring the patent invalid or non-infringed in litigation resulting from its certification prior to the original expiration date of the '303 patent, the application must be deemed to have converted into an application with a paragraph II certification (i.e., a certification that "the patent has expired"), and cannot receive final approval until Pfizer's pediatric exclusivity expires on September 25, 2007. *Mylan*, *supra*; *Ranbaxy*, *supra*.

Regarding FDA's specific questions, the decision declaring claims 1-3 invalid did not create any obligations for ANDA applicants to change their certifications, because the patent was still properly listed in the Orange Book. Pfizer was not required to delist its patent, because there were 8 other presumptively valid claims in that patent (2 of which covered pharmaceutical formulations in the form of tablets containing amlodipine besylate together with specific excipients) that had never been declared invalid by any court. Regarding FDA's question of whether it can treat an invalid patent as delisted as a matter of law, and presume the withdrawal of the certifications, that is a purely hypothetical scenario that clearly does not apply here.

Regarding FDA's question whether the ANDA applicants must file paragraph II certifications stating that "the '303 patent has expired," we note that while 21 C. F.R. § 314.94(a)(12)(viii)(C)(i) states "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," FDA has in the past treated certifications that have become inaccurate due to subsequent events as automatically converting by operation of law into the correct certification. *Mylan*, *supra*; *Ranbaxy*, *supra*. We believe it is unnecessary for applicants to formally amend their certifications in view of FDA's practice regarding automatic conversion of inaccurate certifications. So, for example, any tentatively approved ANDA or 505(b)(2) applications having paragraph III certifications, or paragraph IV certifications (without having personally obtained a judgment of invalidity, or a mandate, if that is what FDA requires) will automatically convert to paragraph II certifications after March 25, 2007.

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?

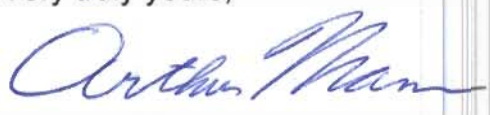
The underlying premise of this question—that Pfizer's patent (i.e., all claims of Pfizer's patent) was declared invalid—is wrong. See the detailed discussion of this issue in the comments to question 3, above. Even if hypothetically all claims of the patent had been declared invalid, pediatric exclusivity would apply on a case-by-case basis. No tentatively approved or unapproved ANDA or 505(b)(2) application with a paragraph III certification would receive final approval until after expiration of pediatric exclusivity on September 25, 2007. No tentatively approved or unapproved ANDA or 505(b)(2) application with a paragraph IV certification should receive final approval unless the applicant personally procured a judgment of invalidity or non-infringement (or a mandate, if FDA determines that a mandate is required) prior to the original expiration date of the patent. See the response to question 2 for the reasons supporting these conclusions.

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?

We have no comments on whether 180 day exclusivity triggered before a patent expires continues 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. However, we note that even in the absence of 180 day exclusivity, Pfizer's pediatric exclusivity bars approval of all tentatively approved ANDAs and 505(b)(2) applications, with the possible exception of Apotex (depending on how FDA resolves the mandate issue). Any ANDA or 505(b)(2) application that has changed its certification to a paragraph II certification would be barred from obtaining final approval by Pfizer's pediatric exclusivity. It would be improper for an

ANDA or 505(b)(2) applicant to withdraw its certification altogether. At the very least, an applicant should be required to maintain a paragraph II certification, which would bar the ANDA or 505(b)(2) applicant from obtaining final approval until after the expiration of Pfizer's pediatric exclusivity.

Very truly yours,



Arthur Mann
Executive Director of Intellectual Property
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cc: Dockets Management