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Division of Dockets Management
Food and Drug Administration
Room 1061 (HFA-305)
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. 2007N-0123 - Amlodipine Abbreviated New Drug Application Approvals

Dear Sir or Madam:

Medco Health Solutions, Inc. ("Medco"), a leading pharmacy benefit manager with the nation's largest mail order pharmacy operations, submits these comments in response to the Food and Drug Administration's ("FDA's") solicitation of views concerning the Agency's ability to approve Abbreviated New Drug Applications ("ANDAs") for amlodipine besylate tablets.[1] Medco's interest in the issues presented in this case stems from the company's business objective of ensuring that Americans have access to affordable, high quality prescription drugs.

As explained below in Medco's response to each of the five sets of FDA's questions, the Agency should grant final approval to tentatively approved ANDAs for amlodipine besylate, because neither (1) the now-expired 180-day exclusivity period applicable to Mylan's ANDA #76-418, nor (2) Pfizer's pediatric exclusivity applicable to United States Patent No. 4,879,303 ("the '303 patent") listed in the Orange Book as

[1] Medco is also submitting a copy of the company's views to the FDA dockets established pursuant to the submission of three citizen petitions concerning amlodipine exclusivity issues, Docket Nos. 2007P-0110 and 2007P-0111 (submitted by Pfizer Inc. ("Pfizer")), and 2007P-0116 (submitted by Mylan Pharmaceuticals Inc. ("Mylan")).

covering NORVASC (amlodipine besylate) 2.5mg, 5mg, and 10mg Tablets, provides a legal basis to delay further generic competition.

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 [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?

March 22, 2007 is the date that controls FDA's giving effect to the Apotex decision; and as of that date, FDA should treat the '303 patent as invalid for purposes of triggering the start of Mylan's 180-day exclusivity period, the eligibility of other generic applicants with tentative approvals for final approval, and for determining the inapplicability of Pfizer's pediatric exclusivity.[2] FDA need not await the issuance of a mandate from the Federal Circuit.

Section 505(j)(5)(B)(iii)(II)(aa) (2006) of the FDC Act states, in pertinent part, that an ANDA with a paragraph IV patent certification (and the sponsor of which was sued by the NDA holder/patent owner for patent infringement within 45 days of receiving notice of that certification, and if the district court decides before the end of the 30-month stay that the patent has been infringed and the judgment is appealed) "shall be made effective on the date on which the court of appeals decides that the patent is invalid or not infringed . . . ." FDC Act § 505(j)(5)(B)(iii)(II)(aa)(AA) (2006) (emphasis added).[3]

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[2] FDA approved ANDA #76-418 on October 3, 2005 after Mylan notified the Agency that no action for patent infringement was brought by the NDA/patent holder. ANDA #76-418 was submitted to FDA prior to the enactment of Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA"), Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003). As such, the triggering of Mylan's 180-day exclusivity is governed by the pre-MMA version of § 505(j)(5)(B)(iv)(I)-(II) of the Federal Food, Drug, and Cosmetic Act ("FDC Act"). The approval of amlodipine ANDAs is governed by the post-MMA version of FDC Act § 505(j)(5)(B)(iii). All post-MMA FDC Act references in this letter are identified with a "2006" notation. It is noteworthy that if this were a post-MMA case involving the triggering of 180-day exclusivity, Mylan would almost certainly have forfeited its exclusivity. Mylan began commercial marketing on March 23, 2007, which is the latest possible date on which Mylan's 180-day exclusivity was triggered. Mylan's 180-day exclusivity expired, however, on March 25, 2007 when the '303 patent expired.

[3] Pfizer argues that FDC Act § 505(j)(5)(B)(iii)(II)(aa)(AA) (2006) does not apply in this case, because "the 30-month stay of Apotex's ANDA expired on January 7, 2006 –prior

Thus, Congress clearly intended "the date on which the court of appeals decides" to be the controlling date for purposes of giving effect to a decision that a patent is invalid or not infringed, and not the date of the issuance of a court of appeals mandate.

Indeed, this interpretation is supported by other provisions in FDC Act § 505(j)(5)(B)(iii) (2006). For example, one provision states that "if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under [35 U.S.C. § 271(e)(4)(A)]." Id. § 505(j)(5)(B)(iii)(II)(bb) (2006) (emphasis added). Other provisions state that ANDA approval "shall be made effective on the date on which the [district] court enters judgment reflecting the decision; or the date of a settlement order or consent decree signed and entered by the [district] court stating that the patent . . . is invalid or not infringed." Id. § 505(j)(5)(B)(iii)(I)(aa)-(bb) (2006) (emphasis added). If Congress intended the date of the issuance of a mandate to be controlling, as opposed to "the date on which the court of appeals decides," then it would have identified this date with particularity as it did in other FDC Act § 505(j)(5)(B)(iii) (2006) provisions. But it did not. Thus, the date that controls FDA's giving effect to the Apotex decision, and the date Congress intended, is March 22, 2007.

FDA's guidance document, "Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act" (Mar. 2000) (hereinafter "Court Decisions Guidance"), states, in relevant part, that "[i]f the district court finds the patent is infringed, but that decision is reversed on appeal, the Agency may approve the ANDA on the date the district court issues a judgment that the patent is invalid, unenforceable, or not infringed pursuant to a mandate issued by the court of appeals." Id. at 4 (emphasis added). FDA issued this guidance document prior to the enactment of the MMA and in the wake of the decisions in TorPharm Inc., v. Shalala, No. 97-1925, 1997 WL 33472411 (D.D.C. Sep. 15, 1997), appeal withdrawn and remanded, 1998 WL 135491 (D.C. Cir. Feb. 5, 1998), and Mylan Pharma., Inc. v. Shalala, 81 F. Supp. 2d 30 (D.D.C. 2000), in which the plaintiffs successfully challenged the Agency's interpretation of the definition of the term "court

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to the district court decision on January 29, 2006." Pfizer Comments, Docket No. 2007N-0123, at 3 (Mar. 25, 2007). Pfizer later argues that if FDC Act § 505(j)(5)(B)(iii)(II)(aa)(AA) (2006) applies "it does not authorize FDA to approve Apotex's ANDA based on the non-final ruling of the Federal Circuit issued on March 22[, 2007]." Id. Because FDA did not (and could not) make the approval of Apotex's ANDA "effective upon the expiration of the thirty-month period," FDC Act § 505(j)(5)(B)(iii)(II)(aa)(AA) (2006) must control in this case. It is the only applicable provision in FDC Act § 505(j)(5)(B)(iii) (2006).

decision" in the FDC Act provisions (pre-MMA) governing the timing of ANDA approvals and the triggering of 180-day exclusivity.

As a result of the decisions cited above, FDA also withdrew the Agency's regulations at 21 C.F.R. §§ 314.107(e)(1) and (2)(i)-(iii), promulgated in 1994, concerning court decisions for purposes of establishing the effective date of ANDA approval. See FDA, Interim Rule, Court Decisions, ANDA Approvals, and 180-Day Exclusivity, 65 Fed. Reg. 43,233, 43,235 (July 13, 2000). Section 314.107(e)(2)(iii) stated that "[i]f the district court enters a decision that the patent is infringed, and the decision is appealed, the date on which the district court enters a judgment that the patent is invalid, unenforceable, or not infringed pursuant to a mandate issued by a court of appeals" will be deemed to be the date of the final decision of the court. 21 C.F.R. § 314.107(e)(2)(iii) (1999) (emphasis added). Although § 314.107(e)(2)(iii) was removed from FDA's regulations, the Court Decisions Guidance states that the Agency will continue to apply "the same process as described in . . . § 314.107(e)(2)(iii)." Court Decisions Guidance at 4 n. 9; see also 65 Fed. Reg. at 43,234.[4] However, FDA's "mandate policy" described in the Court Decisions Guidance, even if it was an appropriate interpretation in March 2000 (an issue that is questionable given the clear "date of the court decision" statutory language), applies only to the pre-MMA version of FDC Act § 505(j)(5)(B)(iii) and is not a valid interpretation of the current version of FDC Act § 505(j)(5)(B)(iii) (2006), which applies in this case.[5]

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[4] FDA's Court Decisions Guidance is but one example of the Agency's attempt to regulate directly from the FDC Act. FDA announced that the Agency would "regulate directly from the statute, and will make decisions on 180-day generic drug exclusivity on a case-by-case basis" in the wake of the decisions in Mova Pharm. Corp. v. Shalala, 140 F.3d 1060 (D.C. Cir. 1998), and Granutec, Inc. v. Shalala, 1998 U.S. App. LEXIS 6685 (4th Cir. 1998) (unpublished opinion). FDA, Guidance or Industry, "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act," (June 1998) at 4 (hereinafter "180-Day Guidance"); see also FDA, Proposed Rule, 180-Day Generic Drug Exclusivity for ANDAs, 64 Fed. Reg. 42,873, 42,876 (Aug. 6, 1999) (withdrawn 67 Fed. Reg. 66,593 (Nov. 1, 2002) ("The removal of the successful defense requirement has resulted in a fragmented regulatory framework, forcing the agency to modify not only the regulatory language in certain parts but also . . . its interpretation of language that is to remain."). These cases and others ─e.g., Mylan Pharma., Inc. v. Shalala, 81 F. Supp. 2d 30 (D.D.C. 2000) (invalidating FDA regulation defining "court decision")─ struck down other aspects of FDA's 1994 ANDA regulations because an actual conflict existed between the FDC Act and the Agency's implementing regulations. Similarly, FDA's "mandate policy" based on now-removed 21 C.F.R. § 314.107(e)(2)(iii) (1999) and the pre-MMA version of FDC Act § 505(j)(5)(B)(iii) conflicts with the clear and unambiguous text of the post-MMA FDC Act version applicable in this case and should not be followed.

[5] The MMA amended FDC Act § 505(j)(5)(B)(iii). The amendments to this provision

FDA's "mandate policy" described in the Court Decisions Guidance would not withstand scrutiny under Chevron, U.S.A., Inc. v. National Resources Defense Council, 467 U.S. 837 (1984) in the post-MMA context. FDA's power to interpret the FDC Act is "not the power to make law. Rather, it is the power to adopt regulations [and policies] to carry into effect the will of Congress as expressed by the statute." Ernst & Ernst v. Hochfelder, 425 U.S. 185, 213-14 (1976) (citation and internal quotation omitted). Under Chevron, FDA is entitled to "deference," but only if the statute is unclear or ambiguous; "[i]f the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of the Congress." Chevron at 842-43. FDA's pre-MMA "mandate policy" is contrary to the clear language of FDC Act § 505(j)(5)(B)(iii)(II)(aa)(AA) (2006). Congress unambiguously stated that ANDA approval "shall be made effective on the date on which the court of appeals decides that the patent is invalid or not infringed . . . ." In this case, that date is March 22, 2007.[6] This reading is supported by other provisions in FDC Act § 505(j)(5)(B)(iii) (2006) that specifically identify the dates on which ANDA approval becomes effective. Had Congress intended to link ANDA approval with the issuance of a court of appeals mandate, it would have done so.

March 22, 2007 is also the date that controls FDA's giving effect to Mylan's 180-day exclusivity period and for determining the inapplicability of Pfizer's pediatric exclusivity. FDC Act § 505(j)(5)(B)(iv) states that 180-day exclusivity may be triggered by "the date of a decision of a court . . . holding the patent which is the subject of the [paragraph IV] certification to be invalid or not infringed." FDC Act

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apply to all ANDAs pending on or after December 8, 2003. Prior to the MMA, FDC Act 505(j)(5)(B)(iii) stated, in relevant part, "if before the expiration of [the 30-month stay] the court decides that such patent is invalid or not infringed, the approval [of an ANDA containing a paragraph IV certification] shall be made effective on the date of the court decision." FDC Act § 505(j)(5)(B)(iii)(I) (emphasis added). Even here, given the statutory language identifying a specific date, FDA's pre-MMA "mandate policy" is questionable. The post-MMA version of FDC Act § 505(j)(5)(B)(iii), however, removes any doubt given the surrounding provisions that specifically identify the dates on which ANDA approval becomes effective.

6 Black's Law Dictionary defines the term "decision" to mean, generally, "[a] determination arrived at after consideration of facts, and, in legal context, law. A popular rather than technical or legal word; a comprehensive term having no fixed, legal meaning." Black's Law Dictionary, 6th Ed. at 407. Unless specifically defined, a court must presume that Congress intended the ordinary meaning of a term when it is used in a statute. See Chevron at 860. Thus, the use of the term "decision" in this case must mean the date on which the Federal Circuit ruled the '303 patent invalid.

§ 505(j)(5)(B)(iv)(II) (emphasis added).[7] The date of such a "decision of a court" is "the date on which the court of appeals decides that the patent is invalid or not infringed," in this case, March 22, 2007. Id. § 505(j)(5)(B)(iii)(II)(aa)(AA) (2006) (emphasis added). These two provisions must be read consistently.[8] As such, because the date in this case under FDC Act § 505(j)(5)(B)(iii)(II)(aa)(AA) (2006) is March 22, 2007, the date triggering Mylan's 180-day exclusivity under FDC Act § 505(j)(5)(B)(iv)(II) must also be March 22, 2007.

Although not as explicit as the statutory provisions controlling ANDA approval and the triggering of 180-day exclusivity, the provisions for determining the applicability of Pfizer's pediatric exclusivity must also be read to identify March 22, 2007 as the controlling date in this case. FDC Act § 505A(c)(2)(B) (2006) states:

> if the drug is the subject of a listed patent for which a [paragraph IV] certification has been submitted . . . , 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).

FDC Act § 505A(c)(2)(B) (2006) (emphasis added).

The "court [that] determines that the patent is valid and would be infringed" is the same court referred to in FDC Act §§ 505(j)(5)(B)(iii)(II)(aa)(AA) (2006) and 505(j)(5)(B)(iv)(II). In this case, the Federal Circuit decided that the '303 patent is invalid. Thus, Pfizer is not entitled to pediatric exclusivity with respect to that patent ─pediatric exclusivity does not apply to an invalid patent. As such, March 22, 2007 is also the date for purposes of determining the applicability (or inapplicability as the case is) of Pfizer's pediatric exclusivity.

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[7] 180-day exclusivity may also be triggered on the date of "first commercial marketing." FDC Act § 505(j)(5)(B)(iv)(I). In this case, Mylan began commercially marketing on March 23, 2007, which is the latest possible date on which Mylan's 180-day exclusivity was triggered.

[8] See e.g., National Pharm. Alliance v. Henney, 47 F. Supp. 2d 37, 39 (D.D.C. 1999) (upholding FDA's interpretation that pediatric exclusivity granted under FDC Act § 505A applies to all of a sponsor's approved drug products containing the studied "active moiety" rather than a specific drug product as "consistent with the overall structure of regulation of generic drugs, as set forth in the Hatch-Waxman Amendments, Pub. L. 98-417, 98 Stat. 1585 (1984).").

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

If FDA must await the issuance of the Federal Circuit's mandate (which Medco does not believe is the case), then Pfizer's pediatric exclusivity applicable to the '303 patent would prevent the Agency from fully approving tentatively approved ANDAs containing a paragraph III or paragraph IV certification to that patent. See FDC Act §§ 505A(c)(2)(A)(ii), (B) (2006). However, once the Federal Circuit's mandate is issued declaring the '303 patent invalid, FDA should treat the patent as "delisted" as a matter of law as of the date of the court of appeals decision on March 22, 2007, and any paragraph III or IV certifications to that patent as changed to a certification that there are no relevant patents. See 21 C.F.R. § 314.94(a)(12)(ii).

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?

The Federal Circuit's March 22, 2007 decision that the '303 patent is invalid should not require the applicant of a tentatively approved ANDA to amend its patent certification to a paragraph II, or cause FDA to consider a paragraph IV certification to be effectively changed to a paragraph II to which Pfizer's pediatric exclusivity attaches.[9] Instead, FDA should treat the '303 patent as "delisted" from the Orange Book as a matter of law, either effectively change ─*nunc pro tunc*─ any paragraph III or IV patent certifications to the '303 patent to a certification that there are no relevant patents or

[9] FDA has, in other cases, effectively converted a paragraph IV patent certification to a paragraph II to which pediatric exclusivity attaches and delays ANDA approval. See e.g., Mylan Labs., Inc. v. Thompson, 389 F.3d 1272 (D.C. Cir. 2004); Ranbaxy Labs. Ltd. v. FDA, 307 F. Supp. 2d 15 (D.D.C. 2004), aff'd, 307 Fed. Appx. 1 (D.C. Cir. 2004). However, these cases differ significantly from the current case in that there was no court decision on patent invalidity. As such, the rulings in these cases cannot serve as precedent for FDA to determine the applicability of Pfizer's pediatric exclusivity to ANDA applicants.

accept such a change submitted by an ANDA applicant pursuant to 21 C.F.R. § 314.94(a)(12)(viii)(C), and fully approve any tentatively approved ANDAs previously containing a paragraph III or IV certification to the '303 patent. Indeed, FDA can take these actions because the '303 patent is invalid and has expired and, as discussed below in response to question set #5, Mylan's 180-day exclusivity has expired.

FDA's regulation at 21 C.F.R. § 314.94(a)(12)(viii)(B) governs the "delisting" of invalid patents from the Orange Book, and states, in relevant part:

> If a patent is removed from the [Orange Book], any applicant with a pending application (including a tentatively approved application with a delayed effective date) who has made a certification with respect to such patent shall amend its certification. The applicant shall certify under [21 C.F.R. § 314.94(a)(12)(ii)] that no patents described in [21 C.F.R. § 314.94(a)(12)(i)] claim the drug or, if other relevant patents claim the drug, shall amend the certification to refer only to those relevant patents. . . . A patent that is the subject of a lawsuit under [21 C.F.R. § 314.107(c)] shall not be removed from the [Orange Book] until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended.

FDA explained this provision in the 1994 preamble to the Agency's final ANDA regulations:

> An applicant may change its certification at any time. Although there is no need for the agency to pronounce such changes in certification nunc pro tunc [(now for then)], the agency agrees that the protection offered by 180-day exclusivity should not be undermined by changes from paragraph IV certification or by the filing of original certifications other than paragraph IV certifications. . . . To ensure that this does not occur, the agency has required that a patent remain [in the Orange Book] after being declared invalid or unenforceable <u>until the end of any applicable 180-day exclusivity period</u>. This means that a patent is deemed to be relevant under § 314.94(a)(12)(ii) <u>until the end of the term of the patent or applicable 180-day exclusivity period, whichever occurs first</u>. Thus, where there is a patent that has been challenged by a paragraph IV applicant, a subsequent applicant will not be able to file a certification that there is no relevant patent or seek an immediately effective approval <u>until either the patent or the 180-day exclusivity period expires</u>. The agency has amended § 314.94(a)(12)(viii)(B) and made a similar change to § 314.50(i)(6)(ii) to reflect this position.

FDA, Final Rule, ANDA Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,348 (Oct. 3, 1994) (emphasis added).[10]

In this case, the '303 patent has been ruled invalid (and therefore, there is no pediatric exclusivity with respect to the patent) and Mylan's 180-day exclusivity has expired. The appropriate certification when there are no relevant patents is a certification under 21 C.F.R. § 314.94(a)(12)(ii). Pediatric exclusivity does not attach to such a certification. See FDC Act § 505A(c)(2).[11] In the absence of any existing and applicable patents or exclusivities, FDA must fully approve tentatively approved ANDAs.

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 Apotex decision, which invalidated the '303 patent effective as of March 22, 2007, and which provides FDA with a basis to treat the '303 patent as "delisted" from the Orange Book, means that Pfizer's pediatric exclusivity should not attach to any

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[10] See also 21 C.F.R. § 314.50(i)(6)(ii) ("A patent that is the subject of a lawsuit under [21 C.F.R. § 314.107(c)] shall not be removed from the [Orange Book] until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended."). While the '303 patent could remain listed in the Orange Book until the expiration of Mylan's 180-day exclusivity (i.e., March 25, 2007 ─the same date the '303 patent expired), because the Federal Circuit ruled that the '303 patent is invalid on March 22, 2007, Pfizer's pediatric exclusivity is inapplicable with respect to the '303 patent as of that date.

[11] FDA's authority to "delist" the '303 patent from the Orange Book in this case is not affected by the recent decision of the United States Court of Appeals for the District of Columbia in Ranbaxy Labs. Ltd v. Leavitt, Case No. 06-5154 (D.C. Cir., Nov. 14, 2006). That case concerned "whether the FDA may delist a patent upon the request of the NDA holder after a generic manufacturer has filed an ANDA containing a paragraph IV certification so that the effect of delisting is to deprive the applicant of a period of marketing exclusivity." Id. at 10. Mylan's 180-day exclusivity has already been triggered and run (i.e., as of March 25, 2007 when the '303 patent expired). Indeed, the court specifically stated that "[w]e need not address the question of patent expiration in this case. We note, however, . . . the text and structure of the [FDC Act] suggest a distinction between expiration and delisting such that the first generic applicant may no longer retain exclusivity when the patent has expired." Id. at 11 (note) (emphasis added).

tentatively approved ANDA containing a paragraph III or IV certification to the '303 patent, because such certifications have effectively changed (or via an ANDA amendment) to a certification that there are no relevant patents.

FDC Act §§ 505A(c)(2)(A) and (B) (2006) extend the period during which FDA cannot approve an ANDA (or a 505(b)(2) application) that includes a paragraph II or paragraph III patent certification, or a paragraph IV patent certification that concerns a patent that a court has determined is valid and would be infringed by the manufacture, use, or sale of a product that is the subject of an ANDA (or 505(b)(2) application). See FDC Act § 505A(c)(2) (2006). Because the '303 patent is invalid as of March 22, 2007 and has otherwise expired (and furthermore, because there is no blocking period of 180-day exclusivity), FDA may "delist" the patent from the Orange Book, and Pfizer's pediatric exclusivity is inapplicable.

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?

Mylan's period of 180-day exclusivity expired on March 25, 2007 when the '303 patent expired. As such, FDA should fully approve all tentatively approved ANDAs previously containing either a paragraph III or IV certification to the '303 patent (and that now effectively contain a certification that there are no relevant patents). Interpreting the FDC Act to prevent the full approval of pending, tentatively approved ANDAs until 180-days after Mylan's exclusivity was triggered (or until September 22, 2007) is not in the interest of the public, is contrary to Congress' intent in creating the 180-day exclusivity period, and is contrary to long-standing FDA policy.

FDC Act § 505(j)(5)(B)(iv) states, in relevant part, that "[i]f the application contains a [paragraph IV certification] . . . and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification, the application shall be made effective not earlier than [180] days after" the earlier of (1) the first commercial marketing of the approved generic drug product, or (2) a court decision finding that the patent on which 180-day exclusivity based to be invalid and/or not infringed. See FDC Act §§ 505(j)(5)(B)(iv)(I)-(II) (emphasis added).

Congress' intent in adding this provision was to reward applicants for designing around and challenging relevant patents on brand name drugs. When there is no longer a relevant patent, however, the broader objective of the Hatch-Waxman Act ─to "make available more low costs generic drugs"─ is controlling. H.R. Rep. No. 857, 98th Cong.

1st Sess., pt. 1, at 14 (1984), reprinted in 1984 U.S.C.C.A.N. 2647.[12] FDA's interpretation of FDC Act § 505(j)(5)(B)(iv) with respect to the approval of subsequent ANDA applicants when a patent on which 180-day exclusivity is based expires must, and does, take into account this broader Congressional objective.

FDA's regulations at 21 C.F.R. § 314.94 interpret FDC Act § 505(j)(5)(B)(iv) to mean that 180-day exclusivity is tied to patent expiry ─regardless of whether an ANDA applicant is eligible for 180-day exclusivity or whether that period has been triggered:

> If a patent is removed from the [Orange Book], any applicant with a pending application (including a tentatively approved application with a delayed effective date) who has made a certification with respect to such patent shall amend its certification. The applicant shall certify under [21 C.F.R. § 314.94(a)(12)(ii)] that no patents described in [21 C.F.R. § 314.94(a)(12)(i)] claim the drug or, if other relevant patents claim the drug, shall amend the certification to refer only to those relevant patents. . . . A patent that is the subject of a lawsuit under [21 C.F.R. § 314.107(c)] shall not be removed from the [Orange Book] until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended.

21 C.F.R. § 314.94(a)(12)(viii)(B) (emphasis added).[13]

FDA explained this provision in the 1994 preamble to the Agency's final ANDA regulations:

> To ensure that [the protection offered by 180-day exclusivity is not undermined by changes from paragraph IV certification or by the filing of

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[12] See also Mead Johnson Pharm. Group v. Bowen, 838 F.2d 1332, 1333 (D.C. Cir. 1988) ("The purpose of [the Hatch-Waxman Act is] to increase competition in the drug industry by facilitating the approval of generic copies of drugs.").

[13] See also 21 C.F.R. § 314.50(i)(6)(ii) ("A patent that is the subject of a lawsuit under [21 C.F.R. §] 314.107(c) shall not be removed from the [Orange Book] until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended.") (emphasis added). While the '303 patent could remain listed in the Orange Book until the expiration of Mylan's 180-day exclusivity (i.e., March 25, 2007), Pfizer's pediatric exclusivity is inapplicable with respect to the '303 patent, because the Federal Circuit ruled that the '303 patent is invalid on March 22, 2007.

> original certifications other than paragraph IV certifications], the agency has required that a patent remain on the list after being declared invalid or unenforceable until the end of any applicable 180-day exclusivity period. This means that a patent is deemed to be relevant under § 314.94(a)(12)(ii) until the end of the term of the patent or applicable 180-day exclusivity period, whichever occurs first. Thus, where there is a patent that has been challenged by a paragraph IV applicant, a subsequent applicant will not be able to file a certification that there is no relevant patent or seek an immediately effective approval until either the patent or the 180-day exclusivity period expires.

59 Fed. Reg. at 50,348 (emphasis added).

FDA reiterated this position in the preamble to the Agency's 1999 proposed rule on triggering 180-day exclusivity:

> The agency is clarifying that once the patent for which the first applicant filed a paragraph IV certification expires, the first applicant is no longer eligible for exclusivity. When the first applicant is no longer eligible for exclusivity, FDA may approve all otherwise eligible ANDA's. FDA regulations at [21 C.F.R. § 314.94(a)(12)(viii)] currently provide that exclusivity cannot extend beyond the term of the patent.

64 Fed. Reg. at 42,877.[14]

FDA, the courts, and Congress have also, on several occasions, expressed their views that 180-day exclusivity cannot extend beyond the date of expiration of the patent for which a paragraph IV certification has been made (and on which 180-day exclusivity is based):

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[14] FDA's proposal was intended to respond to some of the issues created as a result of the Mova and Granutec court decisions. Under one such proposal, FDA would "delay the effective date of approval of a subsequent ANDA for up to 180 days from the date described in paragraph (c)(1) of this section only when the first applicant is eligible for 180-day exclusivity." 64 Fed. Reg. at 42,886 (proposed 21 C.F.R. § 314.107(c)(2)). Thus, it has clearly been FDA's long-held position that 180-day exclusivity may not always extend for 180-days, and that the Agency may approve, under certain circumstances, subsequent ANDAs prior to the date that is 180-days after a first filer's ANDA approval.

- FDA Response, Docket No. 1999P-1271, at 4 (Aug. 2, 1999) ("Because [180-day] exclusivity cannot extend beyond the expiration of a patent, Pharmachemie lost its eligibility for exclusivity when the [patent] expired before either of the events described in [FDC Act §] 505(j)(5)(B)(iv)(I) and (II) occurred."); see also FDA Letter re: ANDA 75-347 (omeprazole) (Nov. 17, 2001) at 2 (discussing FDA's August 2, 1999 decision);

- Dr. Reddy's Labs., Inc. v. Thompson, 302 F. Supp. 2d 340, 351 (D.N.J. 2003) (approving FDA's interpretation of FDC Act § 505(j)(5)(B)(iv) that upon patent expiration a paragraph IV certification in a tentatively approved ANDA converts to a paragraph III and 180-day exclusivity is lost);

- Ranbaxy Labs. Ltd v. Leavitt, Case No. 06-5154, at 11 (note) (D.C. Cir., Nov. 14, 2006) ("We need not address the question of patent expiration in this case. We note, however, . . . the text and structure of the [FDC Act] suggest a distinction between expiration and delisting such that the first generic applicant may no longer retain exclusivity when the patent has expired.") (emphasis added); and

- In December 2003, Congress passed the MMA, which amended the FDC Act to add certain provisions that cause a "first applicant" submitting an ANDA with a paragraph IV patent certification to forfeit 180-day exclusivity. See FDC Act § 505(j)(5)(D)(i) (2006). One such provision states that exclusivity is 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." Id. § 505(j)(5)(D)(i)(VI). Although Congress did not make this provision retroactive to pre-MMA cases, such as the current case involving amlodipine, FDA can carry out Congress' intent in creating FDC Act § 505(j)(5)(D)(i)(VI) in this case by considering Mylan's 180-day period to have expired on March 25, 2007 when the '303 patient expired.

Not only is FDA's view that 180-day exclusivity is tied to patent expiry (both in the cases of tentatively approved and fully approved ANDAs) a long-standing policy, but it is a reasonable interpretation of the ambiguous language of FDC Act § 505(j)(5)(B)(iv) that should survive Chevron scrutiny.

Under Chevron, a court must uphold an agency interpretation if "the intent of Congress is clear" as to the "precise question at issue" and the agency's interpretation follows that intent. 467 U.S. at 842. Chevron also directs courts to defer to agency interpretations when Congress' intent is unclear and the agency's interpretation "is based

on a permissible construction of the statute." Id. at 843. Importantly, "[i]f the agency's reading fills a gap or defines a term in a reasonable way in light of the Legislature's design," a court must "give that reading controlling weight, even if it is not the answer 'the court would have reached if the question initially had arisen in judicial proceeding.'" Regions Hosp. v. Shalala, 522 U.S. 448, 457 (1998) (quoting Chevron, 467 U.S. at 843 n. 11); see also Whitman v. Am. Trucking Assns., Inc., 531 U.S. 457 (2001).

One example of this principle is Young v. Community Nutrition Inst., 476 U.S. 974 (1986). In that case, the Court upheld FDA's interpretation of FDC Act § 406 (concerning tolerances for poisonous ingredients in food). While the Court acknowledged that the interpretation adopted by the court of appeals (and the Community Nutrition Institute) "may seem to some to be the more natural interpretation," the Court noted that "the phrasing of [FDC Act § 406] admits of either respondents' or petitioner's reading of the statute," and therefore sustained FDA's interpretation. Id. at 980. Young demonstrates that a reviewing court would have to uphold FDA's interpretation of FDC Act § 505(j)(5)(B)(iv) unless the statutory provision is incapable of being read to permit the expiry of 180-day exclusivity upon patent expiration. Because FDA's interpretation of FDC Act § 505(j)(5)(B)(iv) that 180-day exclusivity ends upon patent expiry is consistent with both the language of the statute and with the goal of Congress to get affordable generic drugs onto the market, FDA's current sensible interpretation is permissible.

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In sum, neither Mylan's expired 180-day exclusivity, nor Pfizer's inapplicable pediatric exclusivity with respect to the '303 patent provide a legal basis to delay further generic competition. FDA should immediately (or as soon as permitted to by a court) grant final approval to all tentatively approved ANDAs for amlodipine besylate tablets.

Respectfully Submitted,

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