DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

Dear ANDA Applicant:

This letter is in reference to your pending or approved abbreviated new drug application ("ANDA") for amlodipine besylate tablets ("amlodipine"). By letter dated June 14, 2007, Pfizer, the sponsor of Norvasc, the product that is the reference listed drug for your ANDA, notified FDA that U.S. Patent No. 4,879,303 (the '303 patent) no longer meets the criteria for listing in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") and requested that FDA remove the '303 patent from the listings for Norvasc, NDA 19-787.[1] On June 22, 2007, FDA removed the '303 patent from the Orange Book listing for Norvasc. Because FDA had previously established a docket regarding administrative issues related to the amlodipine ANDAs, see Docket No. 2007N-0123, FDA is providing notice of this supplemental determination to all of the ANDA applicants, and posting this letter in that docket.

As you are aware, on March 22, 2007, the Federal Circuit issued an opinion finding that Apotex Inc.'s amlodipine product did not infringe claims 1-3 of the '303 patent because those claims were invalid for obviousness. *Pfizer Inc. v. Apotex, Inc.*, 2007 U.S. App. LEXIS 6623, 2007 WL 851203 (Fed. Cir.. Fed. Mar. 22, 2007). Although the patent expired shortly thereafter on March 25, 2007, the patent continued to be potentially relevant to the timing of the approval of the amlodipine ANDAs because of certain exclusivity claims. Those issues have been the subject of litigation. *Mylan Labs, Inc. v. Leavitt.*, 484 F. Supp. 2d 109 (D.D.C. 2007), *appeal pending*, 07-5156 (D.C. Cir.). On May 21, 2007, the Federal Circuit issued the mandate regarding its decision on the '303 patent.

After receipt of Pfizer's June 14 letter, FDA determined to remove the '303 patent from the Orange Book listing for Norvasc, consistent with FDA's ministerial role in patent listing, because there was no bar to its removal. FDA's role in patent listing and delisting is generally ministerial. The agency will defer to the NDA holder's judgment as to whether a patent must or must not be listed. *Apotex, Inc. v. Thompson*, 347 F.3d 1335 (Fed. Cir. 2003); *aaiPharma Inc. v. Thompson*, 296 F.3d 227 (4th Cir. 2003); *Alphapharm PTY Ltd. v. Thompson*, 330 F. Supp. 2d 1 (D.D.C. 2004). Exceptions to this ministerial approach are set out at 21 CFR 314.94(a)(12)(viii), which describes certain situations in which a patent will not be removed from the Orange Book. It provides that "[a] patent that is the subject of a lawsuit under § 314.107(c) shall not be removed from the list 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

[1] Pfizer also requested that we remove the '303 patent from the Orange Book entry for NDA 21-540 for Caduet.

period of delay in effective dates of approval is ended."[2] Mylan Labs was eligible for 180-day exclusivity for amlodipine tablets with respect to the '303 patent by virtue of having been the first ANDA applicant to submit a paragraph IV certification to that patent. However, as FDA previously determined, and the federal district court for the District of Columbia upheld, Mylan's exclusivity with respect to that patent expired with the patent expiration on March 25, 2007. *Mylan v. Leavitt*, 484 F. Supp. 2d 109. Therefore, under the express provisions of 21 CFR 314.94(a)(12)(viii), there is no bar to removal of the '303 patent from the Orange Book pursuant to Pfizer's request.[3]

As a result of this delisting, applicants with pending applications that reference Norvasc should amend their patent certification as described in 21 CFR 314.94(a)(12)(viii). ANDAs referencing Norvasc will no longer contain certifications to the '303 patent. Therefore, under 21 U.S.C. 355a, there is no pediatric exclusivity barrier to approval of ANDAs for amlodipine. A threshold requirement for pediatric exclusivity associated with a patent is the existence of "a listed patent." 21 U.S.C. 355a(b)(2) and (c)(2). When there is no listed patent, there is no patent to which pediatric exclusivity may attach.

If you have any questions, please contact Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 240-276-9310.

Sincerely,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: Pfizer, Inc.

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[2] In a recent decision, a federal court of appeals determined that FDA also must leave a patent listed in the Orange Book, notwithstanding an NDA holder's request to delist, if an ANDA applicant is eligible for 180-day exclusivity because it submitted the first paragraph IV challenge to the patent, even if the first applicant is not sued as a result of the certification. *Ranbaxy v. Leavitt*, 469 F.3d 120 (D.C.Cir. 2006) This extension of the bar against delisting is not relevant here, where Mylan was sued and, more importantly, where the patent has expired.

[3] The exception created by section 314.94(a)(12)(viii) applies, by its express terms (by reference to section 314.107(c)), to litigation over 180-day exclusivity, not to litigation over pediatric exclusivity. In addition, because Pfizer, as the innovator company who submitted pediatric studies, is the entity Congress intended to benefit with the pediatric exclusivity award, Pfizer may waive pediatric exclusivity, and other ANDA applicants are not within the statutory zone of interest to challenge that waiver.

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/s/

Gary Buehler
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