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BY FEDERAL EXPRESS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20857

Re: Citizen Petition 02P.0447-CP1; Amlodipine Maleate

Ladies/Gentlemen:

As a law firm representing an interested pharmaceutical manufacturer, we hereby submit, pursuant to 21 CFR §10.30(d), the following comments concerning the above-identified pending Citizen Petition submitted by Morgan Lewis & Bockius on behalf of Pfizer Inc. on October 11, 2002. This Citizen Petition asks FDA to refuse approval of a Section 505(b)(2) new drug application (NDA) filed by Dr. Reddy's Laboratories, Inc. for the drug amlodipine maleate.

1. Studies Authorized for Reference Under Section 505(b)(2)

A Section 505(b)(2) NDA is a pre-market approval application for a drug incorporating a change or modification in a drug previously approved via a Section 505(b)(1) NDA, which must include data to support the change. 21 CFR § 314.54. For safety and effectiveness, a 505(b)(2) NDA may rely on the basic safety and effectiveness data submitted for the originally approved drug. See FDA's "Guidance for Industry: Applications Covered by Section 505(b)(2)"(October 1999, hereafter "FDA's 505(b)(2) Guidance"), at 2-3.

A 505(b)(2) NDA can include or refer to "investigations ... not conducted by or for the applicant and for which the applicant has not obtained a right of reference from the person by or for whom the investigations were conducted." 21 U.S.C. § 355(b)(2). This statutory language is sufficiently broad to permit a 505(b)(2) applicant's reliance on studies conducted by another person or entity (including but not limited to studies conducted by a pertinent 505(b)(1) NDA holder), whether or not such studies have been published.

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2. Pfizer's Proprietary Data on Amlodipine Maleate Cannot Automatically Be Relied Upon in Dr. Reddy's 505(b)(2) NDA

Despite the foregoing, Dr. Reddy's Section 505(b)(2) NDA for amlodipine maleate should not necessarily be permitted to rely upon preliminary safety and effectiveness clinical studies of amlodipine maleate submitted in Pfizer's NDA, which was ultimately approved for the drug amlodipine besylate.

Pfizer's approved NDA covers the besylate salt of amlodipine, not the maleate salt. Under FDA regulations, amlodipine maleate and amlodipine besylate, as different salts of the same pharmacologically active moiety, are separate and distinct drug substances. See 21 CFR § 314.108(a); FDA's 505(b)(2) Guidance, *supra*, at 5.

As noted in the Citizen Petition, while Pfizer's NDA initially sought approval of the maleate salt, Pfizer was compelled to change to the besylate salt, due to a degradation impurity which developed in the maleate salt and affected stability. Pfizer's NDA includes separate safety and efficacy clinical studies on the besylate salt.

By submission of a 505(b)(2) NDA for the maleate salt, Dr. Reddy's is evidently attempting to reference basic safety and effectiveness clinical data on the maleate salt in Pfizer's NDA. This should not be countenanced by FDA, to the extent that Pfizer's data on the maleate salt did not constitute a basis for approval of Pfizer's NDA on the besylate salt.

Safety and effectiveness data submitted to FDA in an NDA constitute trade secrets and/or confidential commercial information. 21 CFR § 20.61. FDA has recognized that such data qualify as proprietary intellectual property belonging to the NDA sponsor. See 21 CFR § 314.430; Tri-Bio Laboratories, Inc. v. United States, 836 F.2d 135, 139 (3d Cir. 1987). Proprietary safety and effectiveness data submitted in a 505(b)(1) NDA, which for whatever reason were not relied upon by FDA in approving that NDA, should not be permitted serve as a basis for approval of a Section 505(b)(2) NDA to which the 505(b)(2) application refers. To allow otherwise would vitiate vital intellectual property interests of the 505(b)(1) sponsor. It would also contravene the 505(b)(2) exception to FDA's general rule of proprietary information protection, which most certainly permits a 505(b)(2) applicant to rely upon another applicant's data *only where such data have been accepted by FDA as the basis for approval of a prior 505(b)(1) NDA.* See 21 U.S.C. § 355(b)(2); FDA's 505(b)(2) Guidance, *supra.*

3. **Dr. Reddy's Should Be Required to Submit Independent Toxicity Data in its Section 505(b)(2) NDA for Amlodipine Maleate**

Furthermore, FDA should require Dr. Reddy's to: (a) identify any impurities in Reddy's amlodipine maleate drug product; (b) demonstrate that the levels of such impurities can be sufficiently controlled by Reddy's manufacturing processes and controls; and (c) conduct independent *in vitro* and animal studies demonstrating that there is no toxicity associated with those impurities. Pfizer's experience shows that at least one impurity was identified in its amlodipine maleate product, creating a stability problem that forced Pfizer to switch to the besylate salt. In this regard, FDA's "Guidance for Industry: Impurities in New Drug Substances" (ICH Q3A, 1996) directs that the biological safety of impurities/degradants above a 0.1% threshold must be adequately demonstrated.

Respectfully submitted,

Charles J. Raubicheck

CJR:bav