

COVINGTON & BURLING LLP

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202.662.6000
FAX 202.662.6291
WWW.COV.COM

WASHINGTON
NEW YORK
SAN FRANCISCO
LONDON
BRUSSELS

PETER O. SAFIR
TEL 202.662.5162
FAX 202.778.5162
PSAFIR@COV.COM

December 21, 2006

VIA FEDERAL EXPRESS

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Comments to Suitability Petition, Docket No. 2006P-0397/CP1

Dear Sirs and Madam:

The undersigned, on behalf of sanofi-aventis U.S. (Sanofi), submits these comments to request that the Food and Drug Administration (FDA) deny the suitability petition submitted by Lupin Pharmaceuticals, Inc. (Lupin) on September 28, 2006. The Lupin petition seeks a determination under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FDCA) that the drug products Fexofenadine Hydrochloride for Oral Suspension, 30 mg/5 mL and 60 mg/5 mL, are suitable for submission under an abbreviated new drug application (ANDA), even though the proposed drug products are of both different strength and dosage form from the listed drug cited in the petition. The petition cites as the reference listed drug for both of its proposed products a drug manufactured by Sanofi: Allegra[®] (fexofenadine hydrochloride) Tablets 180 mg.

As described more fully below, the petition must be denied with respect to both proposed products because the listed drug it cites is inappropriate for each. The appropriate reference listed drug with which the proposed 30 mg/5 mL product must be shown to be bioequivalent is Allegra[®] Oral Suspension 30 mg/5 mL (6mg/L) because they share the same strength and dosage form; a suitability determination for this proposed product is improper. In addition, Lupin's proposed 60 mg/5 mL product shares the same strength as Allegra[®] Oral Capsules 60 mg, which is accordingly the appropriate reference listed drug for the proposed 60 mg/5 mL product.

2006P-0397

CI

Ordinarily the listed drug cited in an ANDA will be “the drug product selected by the agency as the reference standard for conducting bioequivalence testing.”¹ FDA has identified Allegra[®] Oral Suspension 30 mg/5 mL² and Allegra[®] Oral Capsules 60 mg³ as reference listed drugs. Lupin’s petition cites as the reference listed drug Allegra[®] Tablets 180 mg – a drug that has neither the same strength nor the same dosage form as either of Lupin’s proposed products. In contrast, Allegra[®] Oral Suspension 30 mg/5 mL and Lupin’s proposed 30 mg/5 mL product share the same strength and dosage form; a suitability determination permitting a deviation between the proposed drug and its reference listed product is thus not warranted. Further, Allegra[®] Oral Capsules 60 mg is the appropriate reference listed drug for Lupin’s proposed 60 mg/5 mL product because the drugs share the same strength, making it the appropriate comparison product for bioequivalence testing. The recommended dose of Allegra[®] for adults is the 60 mg tablet twice a day, or the 180 mg tablet once a day.

If the comparison drug cited in an ANDA is not a reference listed drug that is the same as or the most similar to the proposed drug, the FDCA is contravened and the carefully crafted Hatch Waxman exclusivity scheme is subverted. The FDCA requires ANDAs to include “information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug” cited in the application.⁴ The limited circumstance in which an ANDA need not refer to a listed drug that is the

¹ 21 C.F.R. § 314.94(a)(3). See also 21 C.F.R. § 314.94(3)(i) (“For an abbreviated new drug application based on an approved petition . . . the reference listed drug must be the same as the listed drug approved in the petition.”).

² FDA, Approved Drug Products with Therapeutic Equivalence Evaluations (“Orange Book”) (Oct. 2006) (“Allegra”), available at <http://www.fda.gov/cder/orange/default.htm>. FDA approved a new drug application for Sanofi’s Allegra[®] Oral Suspension 30 mg/ 5mL on October 26, 2006, approximately one month after Lupin submitted its petition. A drug is deemed to be listed on the date of its approval. FDCA § 505 (j)(7)(B), 21 C.F.R. § 314.3 (“listed drug”). Allegra[®] Oral Suspension 30 mg/5 mL is expected to be available in early 2007.

³ Orange Book (“Allegra”). Sanofi discontinued production of Allegra[®] Oral Capsules 60 mg for reasons unrelated to safety or efficacy in 2004. The 60 mg capsule formulation is discussed in the Clinical Pharmacology section of the current prescribing information for Allegra[®] products.

⁴ FDCA § 505(j)(2)(A)(iii). See also 21 C.F.R. 314.92(a)(1) (stating that ANDAs are suitable for drug products that “are the same as a listed drug.” The regulation defines “same as” to mean “identical in active ingredients(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted.”).

Division of Dockets Management Branch

December 21, 2006

Page 3 of 4

“same” with regard to dosage form or strength is when an application is filed pursuant to the approval of a petition filed under section 505(j)(2)(C).⁵ These provisions ensure that the bioequivalence of a proposed drug that is the subject of an ANDA is evaluated against a listed drug that is the same (or the most similar) with regard to characteristics that could affect bioavailability.⁶ Further, because the patent status of the listed drug cited in an ANDA determines whether a manufacturer will be given notice when an applicant believes a patent is invalid or not infringed, the objectives of the Hatch Waxman amendments are met only when ANDAs cite the appropriate reference listed drug.⁷

In addition to being required by statute, citing in an ANDA or suitability petition the listed drug that has the same or most similar dosage form and strength as the proposed drug accords with FDA guidance. When an ANDA is submitted for a product that has multiple strengths and for which there is more than one reference listed drug, “FDA considers each strength to represent a different drug product and will require an ANDA applicant to demonstrate that each proposed drug product is bioequivalent to its corresponding reference listed drug.”⁸ FDA has advised that “[w]hen the Orange Book identifies as a separate listed drug a product with the characteristics (e.g., active ingredient, dosage form, route of administration) for which the [ANDA] applicant is seeking approval, the applicant should submit a separate ANDA referencing the corresponding listed drug.”⁹ Similarly, with regard to 505(b)(2) applications, the agency has explained that “[i]f there is a listed drug that is the

⁵ FDCA § 505(j)(2)(A)(iii); 21 C.F.R. §§ 314.92(a)(3), 314.93.

⁶ An ANDA must include “(i) Information that shows that the drug product is bioequivalent to the reference listed drug upon which the applicant relies; or (ii) If the abbreviated new drug application is submitted under a petition approved under §314.93, the results of any bioavailability of bioequivalence testing required by the agency, or any other information required by the agency to show that the active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those in the reference listed drug and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug.” 21 C.F.R. § 314.94(a)(7).

⁷ See generally FDCA § 505(j)(2)(A), (B).

⁸ 57 Fed. Reg. 17950, 17954 (1992). FDA further clarified that “strength” refers to “the amount of the product’s active ingredient and is usually expressed in terms of weight. For example, a drug that is available as a 50 milligram (mg) tablet and a 100 mg tablet has two ‘strengths.’” *Id.* at 17956.

⁹ FDA, Draft Guidance for Industry: Listed Drugs, 30-Month Stays, and Approval of ANDAs and 505(b)(2) Applications Under Hatch-Waxman, as Amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 Questions and Answers (Oct. 2004), at 3.

Division of Dockets Management Branch

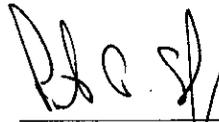
December 21, 2006

Page 4 of 4

pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug.”¹⁰

For the reasons stated above, Allegra[®] Oral Suspension 30 mg/5 mL and Allegra[®] Oral Capsules 60 mg are the proper reference listed drugs for Lupin’s proposed 30 mg/5 mL and 60 mg/5 mL products, respectively. Lupin’s proposed 30 mg/5 mL product is allegedly the same as this listed drug, therefore FDA need not approve a suitability determination to enable the submission of an ANDA for this proposed product. Any suitability petition for Lupin’s proposed 60 mg/5 mL product should cite Allegra[®] Oral Capsules 60 mg as the reference listed drug because the drugs share the same strength. Due to the potential effect of strength and dosage form on bioavailability, the above-captioned petition that cites Allegra[®] Tablets 180 mg as the reference listed drug for Lupin’s proposed products must be denied.

Respectfully submitted,



Peter O. Safir

Attorney for sanofi-aventis U.S.

Covington & Burling LLP
1201 Pennsylvania Ave., N.W.
Washington, D.C. 20004-2401

¹⁰ FDA, Draft Guidance for Industry: Applications Covered by Section 505(b)(2) (Oct. 1999), at 8. Drugs are considered pharmaceutical equivalents if they contain “the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration.” FDA, Orange Book, at V, available at <http://www.fda.gov/cder/orange/obannual.pdf>.