



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUL 11 2006

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Charles J. Raubicheck
Frommer Lawrence & Haug LLP
745 Fifth Avenue
New York, NY 10151

Re: Docket No. 2004P-0339/CP1

Dear Mr. Raubicheck:

This letter responds to your citizen petition, dated July 28, 2004, requesting that the Food and Drug Administration (FDA) refuse to accept for filing¹ any abbreviated new drug application (ANDA) for amlodipine besylate-benazepril hydrochloride (HCl) (amlodipine-benazepril) unless the ANDA contains a study assessing bioequivalence to Lotrel, the reference listed drug, under both fed and fasting conditions. FDA has considered the information in the petition, the December 2, 2004, comments submitted to the FDA from Dr. Reddy's Laboratories (Reddy) opposing the petition, and other information available to the Agency. For the reasons set forth below, your petition is granted.

I. BACKGROUND

A. Lotrel

Lotrel is a combination of amlodipine besylate (a calcium channel blocker) and benazepril HCl (an angiotensin-converting enzyme inhibitor). Lotrel is indicated for the treatment of hypertension. Novartis Pharmaceuticals Corporation is the holder of new drug application (NDA) 20-364 for Lotrel Capsules. The capsules are formulated in four different strengths for oral administration with a combination of amlodipine besylate equivalent to 2.5 milligrams (mg), 5 mg, or 10 mg, with 10 mg, 20 mg, or 40 mg of benazepril HCl providing for the following available combinations: 2.5/10 mg, 5/10 mg, 5/20 mg, 5/40 mg, 10/20 mg, and 10/40 mg. The 2.5/10-mg, 5/10-mg, and 5/20-mg combinations were approved on March 3, 1995. The 10/20-mg combination was approved on June 20, 2002. The 5/40-mg and 10/40-mg combinations were approved on April 11, 2006.

B. Statutory and Regulatory Basis for Approval of ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug,

¹ Your petition refers to the "filing" of an ANDA. Under 21 CFR 314.101, an ANDA is not *filed* by FDA but rather is *received*.

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and Cosmetic Act (the Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. To gain approval, the ANDA applicant generally must show, among other things, that with respect to a listed drug (i.e., a drug product previously approved for safety and effectiveness), the generic drug product² has the same active ingredient or ingredients, the same dosage form, same route of administration, the same strength, and has the same labeling, and is bioequivalent. The specific listed drug to which an ANDA refers is known as the reference listed drug (RLD). The scientific premise underlying the Hatch-Waxman Amendments is that a drug product that meets the approval requirements of section 505(j) is as safe and effective as the RLD. In most cases, drug products approved under section 505(j) may be substituted for the RLD as therapeutic equivalents. Therapeutic equivalence requires, among other things, a showing that the products are pharmaceutical equivalents (see 21 CFR 320.1(c)) and are bioequivalent (FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), Preface at vi, 26th edition).

Under the Act, a generic drug product is bioequivalent to the RLD "if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient" (section 505(j)(8)(B)(i) of the Act).

FDA regulations at 21 CFR 320.1(e) specify that two drug products are bioequivalent if there is an

absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.³

FDA regulations at 21 CFR 320.24 discuss the types of evidence appropriate for establishing bioequivalence. These include pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, and in vitro studies. The regulations list the various methodologies in order of accuracy, sensitivity, and reproducibility (21 CFR 320.24). It is well-accepted that FDA has considerable discretion in determining how the bioequivalence requirement is met. FDA's discretion need only be based on a "reasonable and scientifically supported criterion, whether [the Agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs" (*Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 218 (D.D.C. 1996) (quoting *Schering v. Sullivan Corp.*, 782 F. Supp. 645, 651 (D.D.C. 1992), *vacated as moot sub nom. Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993))). Courts have expressly upheld FDA's regulatory implementation of the Act's BE requirements (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3rd Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994)).

² The term *generic drug* is used in this petition response to refer to drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act.

³ See also 21 CFR 320.23(b).

C. Brief Overview of Food-Effect and Fed Studies From Guidance Document at Issue

In the *Federal Register* of January 31, 2003 (68 FR 5026), the Agency announced the availability of a guidance for industry entitled *Food-Effect Bioavailability and Fed Bioequivalence Studies* (the food effect guidance).⁴ The guidance provides recommendations to sponsors and/or applicants of immediate-release and modified-release drug products planning to conduct food-effect bioavailability (BA) and fed bioequivalence (BE) studies for orally administered drug products as part of investigational new drug applications, NDAs, ANDAs, and supplemental applications. The food effect guidance also provides information on when food-effect BA and fed BE studies should be performed, and addresses how to meet the BA and BE requirements in 21 CFR part 320, and §§ 314.50(d)(3), and 314.94(a)(7) as they apply to oral dosage forms.

The food effect guidance gives a brief overview on the effects of food on bioavailability and bioequivalence. Pharmaceutical companies usually conduct food-effect BA studies for new drugs and drug products in early drug development to assess the effects of food on the rate and extent of absorption of a drug product administered shortly after a meal (fed conditions), as compared to administration under fasting conditions. ANDA applicants conduct fed studies to demonstrate bioequivalence to the RLD under fed conditions.

Food administered with a drug product may change bioavailability by affecting either the drug substance or the drug product. In practice, it is difficult to determine the exact mechanism by which food changes the BA of a drug product without conducting specific mechanistic studies. The food effect on bioavailability is least likely to occur with rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances (BCS Class I)⁵ because absorption of highly soluble and highly permeable drug substances is usually pH- and site-independent and, thus, insensitive to differences in dissolution. In some cases, excipients or interactions between excipients and the food-induced changes in gut physiology can contribute to these food effects and influence the demonstration of bioequivalence.

For immediate-release drug products in BCS Classes II, III, and IV, and for all modified-release drug products, food effects are most likely to result from a more complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance. In these cases, the relative direction and magnitude of food effects on formulation bioavailability and the effects on the demonstration of bioequivalence are difficult, if not impossible, to predict without conducting a fed BE study.

⁴ Available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>.

⁵ See the guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*.

As articulated in the food effect guidance, the Office of Generic Drugs (OGD) requests fed and fasting BE studies for ANDAs for orally administered immediate release dosage forms, except for those that meet one of the exceptions listed in the food effect guidance. Accordingly, in the case of Lotrel, OGD would have expected fed and fasting studies from ANDA sponsors independent of the arguments raised in support of this petition.

II. ANALYSIS

A. ANDAs for Amlodipine-Benazepril Do Not Meet the Exceptions for Excluding a Fed Study as Set Forth in the Food Effect Guidance

You base your request that a fed study be made a condition for receipt of an ANDA for amlodipine-benazepril on the food effect guidance. The food effect guidance recommends that ANDA applicants of orally administered immediate-release drug products conduct fed studies to demonstrate bioequivalence unless one of the following exceptions applies (pp. 3-4):

- When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I), or
- When the DOSAGE AND ADMINISTRATION section of the RLD label states that the product should be taken only on an empty stomach, or
- When the RLD label does not make any statements about the effect of food on absorption or administration.

You claim that none of the exceptions listed above applies to applicants for generic amlodipine-benazepril drug products for which Lotrel is the RLD (Petition at 2).

Specifically, you state that “Benazepril is not a BCS Class 1 drug substance, the labeling of Lotrel does not recommend administration on an empty stomach, and the Lotrel labeling contains a statement that absorption of the individual active drug substances is not influenced by the presence of food in the gastrointestinal tract” (Petition at 2). For these reasons, you conclude that none of the exceptions applies and therefore you ask that a fed study be conducted.

FDA agrees with both the petition and Reddy’s comment that Lotrel does not meet exceptions one and two. Benazepril HCl is a highly soluble drug with low oral bioavailability (about 37 percent), and amlodipine besylate is slightly soluble in aqueous media. Therefore, the combination of amlodipine-benazepril is not considered a BCS Class I drug and fails to meet exception one. Exception two is not met because the dosage and administration section of the Lotrel labeling does not recommend administration only on an empty stomach.

FDA has also concluded that the third exception does not apply here, and, thus recommends that a bioequivalence study under fed (in addition to fasting) conditions be conducted to meet the bioequivalence requirement.⁶

As reflected in the food effect guidance, the third exception turns on the language of the RLD's label as to whether fed studies are expected for demonstrating the bioequivalence of two orally administered immediate-release drug products. The relevant language from Lotrel's labeling⁷ states:

The rate and extent of absorption of benazepril and amlodipine from Lotrel are not significantly different, respectively, from the rate and extent of absorption of benazepril and amlodipine from individual tablet formulations. Absorption from the individual tablets is not influenced by the presence of food in the gastrointestinal tract; food effects on absorption from Lotrel have not been studied.

We would expect that a proposed amlodipine- benazepril drug product would meet exception three of the food effect guidance if the RLD labeling includes no statement at all about the effect of food on absorption or administration. We would not consider exception three to have been met, however, if the RLD makes any statement, positive or negative, about a food effect, that is, states that there is a food effect or there is no food effect.

FDA reviewed the Lotrel labeling. The Lotrel labeling makes statements about the effect of food on the absorption or administration of individual tablets (i.e., amlodipine besylate tablets and benazepril tablets). Food effect studies were not conducted on Lotrel, as described in the next section, because there was sufficient information available to FDA to provide appropriate labeling for Lotrel. One of the scientific premises underlying generic drug approvals is that the ANDA product is expected to have the clinical effect as that described in the RLD labeling. In this case, the Lotrel labeling includes statements about the effect of food on absorption or administration. We therefore expect ANDA applicants to assess whether food influences the absorption of the proposed generic product in the same manner as food influences the absorption of the RLD. Thus, exception three is not met and FDA expects that fed bioequivalence studies for proposed generic amlodipine-benazepril drug products be conducted to meet the bioequivalence requirement.

⁶ Reddy's comment on the citizen petition contends that food-effect studies are unnecessary because "amlodipine-benazepril ANDAs meet a relevant exemption" (Comment at 2). To support its contention, Reddy observes that the Petitioner, in justifying why exception three does not apply to generic amlodipine-benazepril products, omitted from the petition the following statement from the Lotrel labeling: "food effects on absorption from Lotrel have not been studied." Reddy claims that this omitted statement is crucial, and that "[g]iven the fact that food effects on Lotrel have not been studied, there is no reasonable basis to require ANDA applicants using Lotrel as the RLD to conduct such studies" (Comment at 3-4). We disagree with Reddy's comment, as explained above.

⁷ See Product Labeling for Lotrel approved on April 11, 2006.

Further, an ANDA applicant seeking approval of proposed benazepril HCl tablets would be expected to perform a fed bioequivalence study because the RLD (Lotensin) labeling states: "The extent of absorption is at least 37% as determined by urinary recovery and is not significantly influenced by the presence of food in the GI tract." An ANDA applicant seeking approval of proposed amlodipine besylate tablets would also be expected to perform a fed bioequivalence study because the RLD (Norvasc) labeling states: "The bioavailability of [amlodipine besylate tablets] is not altered by the presence of food." FDA's expectation of a fed bioequivalence study for generic versions of Lotrel is consistent with its expectation for the individual products (i.e., amlodipine tablets and benazepril tablets).

B. Reddy's Claim of "Unequal Treatment" Is Without Merit

Reddy claims that because the labeling states that food effects have not been conducted on Lotrel, the RLD, it would be unequal treatment to require sponsors of generic drug products to conduct fed studies. Principally, Reddy relies on *Bracco Diagnostics, Inc., v. Shalala*, 963 F. Supp. 20 (D.D.C. 1997) to support its claim that FDA is purportedly treating similarly situated parties differently and is therefore being arbitrary and capricious. Reddy's reliance on *Bracco* is misplaced.

FDA is not treating similarly situated parties differently. The instant matter involves approval requirements for two different types of drug applications, NDAs and ANDAs. As stated previously, the Act sets forth the requirements for FDA approval of drug products. The Act requires a demonstration of safety and effectiveness generally through submission of clinical studies for a product to be approved under an NDA, and requires (among other things) a demonstration of bioequivalence for a generic drug to be approved under an ANDA. Thus, it is inherent in the Act that the Agency use different standards for evaluating NDAs and ANDAs. A showing of bioequivalence is required and necessary for a product submitted for approval under section 505(j) of the Act because it helps to ensure that the generic drug and RLD are therapeutically equivalent.

FDA disagrees with Reddy's claim that it is "unequal treatment" to require sponsors of proposed generic amlodipine-benazepril drug products to conduct fed bioequivalence studies when the sponsor of Lotrel has not (as reflected in the labeling) conducted food-effect studies on Lotrel. Although Lotrel's labeling states that food-effect studies have not been conducted on Lotrel, FDA did not expect food-effect studies to be conducted on Lotrel because there was sufficient information available to FDA from (among other things) studies conducted by the NDA sponsor that compared Lotrel to the individual tablets, and clinical data establishing the utility of the combination to provide appropriate labeling of Lotrel.

The concern for an ANDA application is whether or not food influences the absorption of a generic product in the same manner as food influences the absorption of the RLD. The effect of food on bioavailability and bioequivalence can be dependent on the inactive ingredients in a drug product's formulation. Although generic drug products that are pharmaceutical equivalents must contain, among other things, the same active ingredient,

they are not necessarily required to contain the same inactive ingredients (see 21 CFR 320.1(c)). ANDA sponsors are generally permitted to change both the type and amount of inactive ingredients provided that the differences do not affect the safety or efficacy of the proposed product (see generally 21 CFR 314.94(a)(9), 314.127(a)(8)). For this reason, among others, as noted elsewhere, the Agency generally expects that food effect studies be conducted to meet the bioequivalence requirement. The Agency identified in the food effect guidance, however, three circumstances in which food effect studies can be excluded even if there are differences in inactive ingredients. Because it is not self-evident that a generic drug product will demonstrate the same food effect as the RLD if one of these exceptions is not met, the Agency expects ANDA applicants to conduct studies to demonstrate that the generic drug product exhibits equivalent in vivo performance to the RLD in the presence or absence of food. Therefore, conditioning approval of a generic amlodipine-benazepril drug product on a demonstration of bioequivalence to the RLD under fed conditions is not unequal treatment as Reddy claims. Because of the differences in framework for ANDA and NDA approvals, it is entirely reasonable for FDA to expect ANDA applicants for generic versions of Lotrel to conduct a fed BE study to meet the bioequivalence requirement and, at the same time, *not* expect the NDA applicant for Lotrel to conduct a fed BE study for NDA approval.

C. FDA May Refuse to Receive an ANDA for Review Based on Incomplete Bioequivalence Data

The Agency's regulation governing the receipt of an ANDA is set forth in 21 CFR 314.101. Under § 314.101(b)(1), FDA reviews an ANDA to determine whether it may be received, that is, accepted for substantive review. The reasons that FDA may not consider an ANDA to be received are set forth in § 314.101(d) and (e). Under § 314.101(b)(2), if FDA finds that none of the reasons in § 314.101(d) or (e) applies for refusing to receive an ANDA, the Agency will receive the application. Receipt of an ANDA means that FDA has made a threshold determination that the ANDA is sufficiently complete to permit a substantive review (§ 314.101(b)(1)). Although § 314.101(d) and (e) set forth several bases on which the Agency may refuse to receive an ANDA, the relevant one that pertains to your petition request is in § 314.101(d)(3).

Under § 314.101(d)(3), the Agency may refuse to receive an ANDA if it is incomplete because it does not on its face contain information required under section 505(j) of the Act and § 314.94 of the Agency's regulations. Thus, the Agency would not receive an ANDA, for example, that contained incomplete bioequivalence data that could not support approval of the application. The "refuse to receive" policy seeks to avoid waste of Agency resources by directing those resources to applications sufficiently complete for substantive review.

As discussed previously, FDA's current position is that fed studies are expected to meet the bioequivalence requirement for generic amlodipine-benazepril products. Accordingly, FDA will consider an ANDA for amlodipine-benazepril that fails to include a fed study to be incomplete because it does not on its face contain information required under section 505(j) and § 314.94 to demonstrate bioequivalence to the RLD. Thus, FDA

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does not intend to receive such an ANDA because it would not be sufficiently complete for substantive review (§ 314.101(b) and (d)(3)).

III. CONCLUSION

FDA currently expects ANDA applicants for generic amlodipine besylate-benazepril drug products to conduct a fed (in addition to fasting) study to meet the bioequivalence requirement. An ANDA that fails to include a fed study would be incomplete on its face and not sufficiently complete to permit substantive review. FDA does not intend to receive for review an ANDA for a generic version of Lotrel that does not include a fed bioequivalence study comparing the generic product to Lotrel. Therefore, your petition is granted.

Sincerely,

A handwritten signature in black ink, appearing to read "Steven K. Galson".

Steven K. Galson, M.D., M.P.H.

Director

Center for Drug Evaluation and Research