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Via Hand Delivery

Dockets Management Branch (HFA-305)
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CITIZEN PETITION

On behalf of our client, Biovail Corporation, this Citizen Petition is being submitted under 21 C.F.R. §10.30 as a means of calling to the attention of the Commissioner of Food and Drugs a practice that is occurring within the Office of Generic Drugs which fails to assure that all dosage strengths of certain extended release generic drugs are bioequivalent to the reference listed drug (RLD). As described in more detail below, low dose forms of extended-release drug product formulations that depend upon a blend of a limited number of bead types with different dissolution characteristics to achieve the desired extended release profile cannot be assumed to be bioequivalent just because high dose forms of the product are bioequivalent. For products with such multi-bead populations, it is scientifically inappropriate to grant waivers of bioequivalence data for the low dose forms. Diltiazem extended release products manufactured by both Andrx Pharmaceuticals and Purepac Pharmaceutical Co. are believed to rely upon such technology.

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A. ACTION REQUESTED

This Petition requests that the Commissioner refrain from granting approval to Abbreviated New Drug Applications (ANDAs) for extended-release generic drugs consisting of a blend of a small number of different types of beads containing active ingredients with intentionally different release characteristics unless bioequivalence has been demonstrated for both the highest and lowest dose form of the product, or until alternate methods are available to assure that a demonstration of bioequivalence at one dose will assure bioequivalence at all other doses. Previously issued approvals should be reevaluated and, as necessary, additional data requested to ensure that all generic doses are bioequivalent to the corresponding dose for the RLD. FDA is requested to take these considerations into account in evaluating the adequacy of the bioequivalence data contained in ANDA No. 75-401 submitted by Andrx. We believe this product is composed of different types of beads containing active ingredients with different release characteristics, analogous to Andrx's currently-marketed generic equivalent of Cardizem CD.

B. STATEMENT OF GROUNDS

FDA regulations provide the following criteria for waiver of evidence of bioequivalence data:

- § 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.
- (a) Any person submitting a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in § 320.21(c), may request FDA to waive the requirement for the submission of evidence demonstrating the in vivo bioavailability or bioequivalence of the drug product that is the subject of the application. An applicant shall submit a request for waiver with the application. Except as provided in paragraph (g) of this section, FDA shall waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence if the drug product meets any of the provisions of paragraphs (b), (c), (d), or (e) of this section.
 - (b) ...
 - (c) ...

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(d) For certain drug products, bioavailability or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo data. FDA shall waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability of the drug product if the drug product meets one of the following criteria:

(1) [Reserved]

(2) The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) of this section are met:

(i) The bioavailability of this other drug product has been demonstrated;

(ii) Both drug products meet an appropriate in vitro test approved by FDA; and

(iii) The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

(iv) This subparagraph does not apply to enteric coated or controlled release dosage forms.

(3) The drug product is, on the basis of scientific evidence submitted in the application, shown to meet an in vitro test that has been correlated with in vivo data....

21 C.F.R. § 320.22. Wisely, the regulation leaves discretion for FDA to require additional evidence of bioequivalence for controlled release dosage forms. However, in its *Guidance for Industry: BA and BE Studies for Orally Administered Drug Products — General Considerations* (DRAFT GUIDANCE, August 1999), single (highest) dose comparisons are encouraged with additional criteria for waivers for lower strengths of the same dosage form — even for modified-release products. (Section V.D)

It is our understanding that waivers for bioequivalence (BE) studies are, in fact, often granted for lower dose controlled release products as long as the studies done at the highest level establish bioequivalence and the other criteria of the available guidance documents have been met. For most drug products, this practice poses no concern and represents a prudent technique to limit unnecessary exposure. Our concern is only with regard to those extended release products where the dose is comprised of a blend of a small number of bead types with intentionally different dissolution characteristics.

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This concern arose from further reflection regarding FDA's request last year for public comment on a draft document titled "Guidance for Industry - ANDAs: Blend Uniformity Analysis" ("BUA Guidance"). The scope of the BUA Guidance states that it is "recommended for those drug products for which the U.S. Pharmacopeia (USP) requires content uniformity analysis." BUA Guidance at 2. These dosage forms are identified as follows:

- Coated tablets, other than film coated tablets
- Transdermal systems
- Suspensions in single-unit containers or in soft capsules
- Pressurized metered-dose inhalers
- Suppositories

The acceptance criteria defined in the BUA Guidance are limited to determining that the active ingredient is appropriately close to the expected level based on statistical criteria. The BUA Guidance does note that "[f]or complex dosage forms, such as modified-release tablets or capsules, and complex processes (e.g., multistep granulation processes), applicants are advised to consult the appropriate chemistry reviewing division to determine if BUA is recommended." BUA Guidance at 2 - 3 (underlining added).

The implication in the BUA Guidance that blend uniformity analysis may not always be required for modified-release tablets or capsules is of concern. In fact, blend uniformity analysis with regard to extended-release formulations of generic drugs that are comprised of two or more types of "beads" of active ingredients with intentionally different release characteristics is extremely critical to assuring a consistent bioavailability profile. The BUA Guidance does not even purport to deal with this situation since it establishes as the only acceptance criteria a comparison to expected levels of the active ingredient rather than focusing on the need for

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acceptance criteria based on the expected amount of active present in each bead type in the blended controlled release formulation.

A multi-bead BUA which quantitates the presence of each bead type is critical to bioequivalence as demonstrated by the following situation. Assume a product which is available in a low dose of 120 mg and a high dose of 360 mg (a three-fold range). The acceptable criteria for BE is 80-125% of the dose. The 360 mg dosage strength is used for bioequivalence tests and it just meets the criteria, *i.e.*, C_{max} is 82-123%. It is well known that relative standard deviation (RSD) is inversely proportional to the dose (USP 24, page 2001). The range observed in the bioequivalence study with the high dose obviously includes (on an additive basis) the variance that is attributable to the ratio of the constituent beads. Since the significance of this variance will be three times higher in a product with one third the dose, the low dose product is virtually guaranteed to have an RSD that is outside the acceptable range for bioequivalence unless the RSD for the multi-bead BUA is close to zero for the ratios of the various bead types. It is obviously non-conservative to assume such uniformity in the absence of a rigorous analysis, but that is essentially what is being done if BE testing is waived for the low dose.

Finally, dissolution results cannot be claimed as proof of homogeneity and, therefore, cannot be used as evidence of bioequivalence for lower strengths not subject to bioavailability testing. The dissolution specifications that are established are driven by expected lot to lot variations during manufacturing and by stability results. The limits are too wide to ensure proper homogeneity of multiple bead types.

We submit that waivers of bioavailability studies for lower dose extended release products with a blend of a limited number of bead types should not be granted based on successful bioequivalence with highest dose product.

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C. ENVIRONMENTAL IMPACT

This Petition claims a categorical exclusion under 21 C.F.R. § 25.31.

D. ECONOMIC IMPACT

This information will be provided if requested by the Commissioner.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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