DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Ave
Building 51
Silver Spring, MD 20993

NOV 1 3 2013

Emmalyn Caoili
Regulatory Affairs Manager
BioKey, Inc.
44370 Old Warm Springs Blvd.
Fremont, CA 94538

Re: Docket No. FDA-2013-P-0299

Dear Ms. Caoili:

This responds to your citizen petition received on March 13, 2013 (Petition), submitted on behalf of Trigen Laboratories (Trigen). Your Petition requests that the Food and Drug Administration (FDA or the Agency) amend FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) to assign a second reference listed drug (RLD) for bisoprolol fumarate tablets (Petition at 1). Specifically, you request that FDA designate Sandoz Inc.'s (Sandoz) abbreviated new drug application (ANDA) 075643 for bisoprolol fumarate tablets and/or Mylan Pharmaceuticals, Inc.'s (Mylan) ANDA 075831 for bisoprolol fumarate tablets as RLD(s). Your request is based on your assertion that the current RLD, Zebeta (bisoprolol fumarate) 10 milligram (mg) tablets (NDA 019982),[1] for which Teva Women's Health Inc. (Teva) is the new drug application (NDA) holder, is not available for commercial distribution.

For the reasons stated below, your Petition is denied.

I. BACKGROUND

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, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)). The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[2] Section 505(j) of the FD&C Act established an abbreviated approval pathway for a drug product that is the same as a previously

[1] Zebeta (bisoprolol fumarate) is also available in 5 mg tablets.

[2] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

approved drug (i.e., RLD) with respect to active ingredient, dosage form, route of administration, strength, and, with certain exceptions, labeling and conditions of use, among other characteristics. An RLD is the listed drug[3] identified by FDA as the drug product on which an ANDA applicant relies in seeking approval of its application.[4] An ANDA applicant also must demonstrate that its proposed product is bioequivalent to the RLD. An applicant that meets the requirements under section 505(j) for approval may reference the Agency's finding of safety and effectiveness for the RLD and need not repeat the extensive nonclinical and clinical investigations required for approval of a stand-alone NDA submitted under section 505(b)(1) of the FD&C Act.

Our policy on the designation of RLDs is stated in the preamble to the 1992 final rule establishing the requirements for ANDAs.[5] In response to comments asking us to explain how we determine which drugs should be reference listed drugs, we stated:[6]

> FDA will designate all reference listed drugs. Generally, the reference listed drug will be the NDA drug product for a single source drug product. For multiple source NDA drug products or multiple source drug products without an NDA, the reference listed drug generally will be the market leader as determined by FDA on the basis of commercial data. FDA recognizes that, for multiple source products, a product not designated as the listed drug and not shown bioequivalent to the listed drug may be shielded from direct generic competition. If an applicant believes that there are sound reasons for designating another drug as a reference listed drug, it should consult FDA.

II. DISCUSSION

BioKey, Inc. (BioKey) asserts that, for over a period of almost 24 months, BioKey and Trigen have attempted to procure Zebeta to support an ANDA submission without success (Petition at 2). BioKey states that wholesale distributors have indicated that Zebeta 5 mg and 10 mg tablets are not available for commercial distribution (Petition at 2). Accordingly, BioKey requested that FDA designate Sandoz's bisoprolol fumarate tablets and/or Mylan's bisoprolol fumarate tablets as RLD(s), because these two products are available in the 5 mg and 10 mg strengths and are "always in stock and readily available in the market" (Petition at 2).

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[3] A listed drug is a drug product that has an effective approval under section 505(c) of the FD&C Act for safety and effectiveness or under section 505(j), that has not been withdrawn or suspended under section 505(e)(1) through (5) or (j)(6) of the FD&C Act, and that has not been withdrawn from sale for reasons of safety or effectiveness. See 21 CFR 314.3. Listed drugs are identified as drugs with an effective approval in the Orange Book.

[4] 21 CFR 314.3.

[5] See 57 Fed. Reg. 17950 (April 28, 1992).

[6] 57 Fed. Reg. at 17958.

As a preliminary matter, we note that the RLD generally is a drug product approved under section 505(c) of the FD&C Act based on full reports of investigations of safety and effectiveness.[7] Accordingly, Teva's NDA 019982 for Zebeta (bisoprolol fumarate) 10 mg tablets is the RLD and would be the basis for submission of an ANDA for bisoprolol fumarate tablets, 5 mg and/or 10 mg. FDA previously has designated a second NDA drug product as an RLD so that it would not be shielded from direct competition by requiring an ANDA applicant to cite the other innovator drug product as the basis for its ANDA submission.[8] However, since FDA has not approved another NDA for bisoprolol fumarate tablets, there would be no reason to designate a second RLD because our statutory and regulatory scheme for generic drugs would require an ANDA applicant to demonstrate bioequivalence to the first RLD.[9] Accordingly, we interpret your request to designate a second RLD as a request to move Zebeta to the discontinued section of the Orange Book, and designate a therapeutically equivalent product[10] as the reference standard for a proposed generic drug product to use to assess bioequivalence to the RLD (Zebeta).[11]

FDA does not agree that Zebeta should be moved to the discontinued section of the Orange Book or that Sandoz's or Mylan's bisoprolol fumarate tablets should be designated as the reference standard at this time. Based on our records, Teva or Duramed

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[7] See November 28, 2008 letter from Janet Woodcock, Director, CDER, to Mark S. Aikman, Docket No. FDA-2008-P-0329 (Velafaxine Petition 1); January 21, 2010 letter from Janet Woodcock, Director, CDER, to Mark S. Aikman, Docket No. FDA-2009-P-0356.

[8] See, e.g., January 30, 2013 letter from Janet Woodcock, Director, Center for Drug Evaluation and Research (CDER), to David L. Rosen, Docket No. FDA-2012-P-1043; April 18, 2005 letter from Steven K. Galson, Acting Director, CDER, to Robert W. Pollock, Docket No. FDA-2004-P-0466.

[9] See November 28, 2008 letter from Janet Woodcock, Director, CDER, to Mark S. Aikman, Docket No. FDA-2008-P-0329.

[10] According to the Orange Book,

> FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured incompliance with Current Good Manufacturing Practice regulations.

See Orange Book at vii, available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf.

[11] See, e.g., Abbreviated New Drug Application Regulations; Proposed Rule (54 FR 28872 at 28882, July 10, 1989) ("Currently, the agency uses one product as a reference standard against which the bioequivalence of the applicant's product is compared. The agency intends to continue that practice. Usually that reference product is the innovator's product, which would also usually be the listed drug referred to by the applicant.")

Pharmaceuticals, Inc. (Duramed), the company listed in Zebeta's labeling as the manufacturer, packer, or distributor, are marketing small amounts of the 10 mg tablets of Zebeta. Until Zebeta is discontinued from marketing, it will remain listed in the Orange Book as both the RLD and be considered the reference standard.

If you continue to have difficulty obtaining Zebeta, you should provide the Office of Generic Drugs with more detailed information regarding your efforts to obtain the product, including any documents received from Teva or Duramed restricting your purchase of this product for purposes of your proposed generic drug development program.

III. CONCLUSION

For the reasons stated above, your Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research