DEPARTMENT OF HEALTH & HUMAN SERVICES

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

NOV 17 2014

Michael H. Hinckle
K&L Gates LLP
P.O. Box 14210
Research Triangle Park, NC 27709-4210

Re: Docket No. FDA-2013-P-0846

Dear Mr. Hinckle:

This letter responds to your citizen petition, which was received by the Food and Drug Administration (FDA or Agency) on July 11, 2013 (Petition). In the Petition, you request that FDA permit your client (a manufacturer intending to file an abbreviated new drug application (ANDA) referencing KUVAN (sapropterin dihydrochloride) 100 milligram tablets) to establish bioequivalence to KUVAN using product marketed in Israel under the name KUVAN rather than the U.S.-approved reference listed drug.

FDA has carefully considered the information submitted in the Petition and other relevant information available to the Agency, including the comment on the Petition submitted by Greenberg Traurig on December 19, 2013. Based on our review of these materials and for the reasons described below, the Petition is denied.

I. BACKGROUND

A. Kuvan

KUVAN is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). BioMarin Pharmaceutical, Inc. (BioMarin) is the new drug application (NDA) holder for KUVAN, which is available in both tablet form (NDA 22-181) and as powder for oral solution (NDA 20-5065).

B. Legal and Regulatory Framework for Abbreviated New Drug Applications

The ANDA approval process established by the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) is set forth in section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). To obtain approval, an ANDA applicant is not required to submit evidence establishing the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the "listed drug" referenced by the ANDA (the "reference listed drug," or RLD) is safe and effective.

"Listed drugs" are those that have been approved for safety and effectiveness under section 505(c) of the FD&C Act or approved under section 505(j) of the FD&C Act (section 505(j)(7) of the FD&C Act; 21 CFR 314.3). "Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*[1] (the list) or any current supplement thereto, as a drug with an effective approval" (21 CFR 314.3).

The scientific premise underlying the Hatch-Waxman amendments is that when products are *therapeutically equivalent*, meaning that they can be expected to have the same clinical effect and safety profile, they generally may be substituted for each other. Products are therapeutic equivalents only if they are both *pharmaceutically equivalent* and are *bioequivalent*, among other requirements.[2]

Pharmaceutically equivalent drug products are those "in identical dosage forms that contain identical amounts of the identical active drug ingredient [...] and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates" (21 CFR 320.1).[3] A 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 under similar experimental conditions in either a single dose or multiple doses" (section 505(j)(8)(B)(i) of the FD&C Act). The purpose of demonstrating bioequivalence to the RLD is to determine whether changes in the formulation of the proposed generic product affect the rate at or extent to which the active ingredient reaches the site of drug action.

II. DISCUSSION

Your petition states that BioMarin has implemented a voluntary restrictive distribution scheme for KUVAN, and that under this program, KUVAN is available only through specialty mail order pharmacies after a prescription has been reviewed and approved by the "BioMarin Patient and Physician Support" group (Petition at 3). You indicate that as a result of this program, KUVAN is not available through the wholesale distribution channels typically used by ANDA applicants to obtain product supplies for bioequivalence testing (id.). You state that BioMarin has not yet responded to your client's request to buy product supplies from it directly, notwithstanding your client's assurances that the product would not be sold to any patients and that bioequivalence testing would be done in accordance with all applicable FDA requirements (id.).

---

[1] The publication is commonly referred to as the *Orange Book*.

[2] Orange Book, Preface, at vii.

[3] See also Orange Book, Preface, at vi-vii ("Drug products 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").

You request that your client therefore be permitted to demonstrate bioequivalence using drug product approved and marketed in Israel as KUVAN rather than the U.S. RLD. In support of this request, you contend that it is possible to demonstrate that a product obtained in a foreign country is the same as the RLD (Petition at 5). You argue that the KUVAN tablets approved in Israel are materially the same as those approved in the U.S. (Petition at 6-7), noting that the KUVAN labeling posted on the www.kuvan.com Web site indicates that the U.S. RLD was manufactured by EXCELLA GmbH in Feucht, Germany, and that the Israeli Ministry of Health's Israel Drug Registry lists what appears to be the same company (though spelled slightly differently) in Feucht, Germany as the manufacturer of the KUVAN product marketed in Israel (Petition at 4). You also note that the package insert for the KUVAN product marketed in Israel lists the same active ingredients and tablet imprint as the U.S. RLD, and that both tablets are off-white to light yellow (Petition at 4, 6). Accordingly, you claim that your client should be able to use drug product obtained in Israel in place of the U.S. RLD in bioequivalence testing.

As explained above, section 505(j)(2)(A)(iv) of the FD&C Act requires ANDA applicants to include information showing that their proposed new drug is bioequivalent to a previously approved "listed drug." Listed drugs are those that have been approved for safety and effectiveness under section 505(c) of the FD&C Act or approved under section 505(j) of the FD&C Act (section 505(j)(7) of the FD&C Act; 21 CFR 314.3). The Israeli-approved version of KUVAN has not been approved under section 505(c) or (j) of the FD&C Act, and is, therefore, not a listed drug within the statutory meaning. While your petition provides information suggesting that the Israeli-approved product may be the same as the U.S. RLD, the Petition does not establish that the two products are in fact the same.

Because of the potential for bioequivalence inconsistencies that may result from even slight differences between a foreign-approved product and the domestic RLD, it is Agency policy not to accept bioequivalence studies based on a foreign-approved product to show that a drug is bioequivalent to the U.S. RLD.[4] For example, small differences in critical specifications (or even excipients) could potentially affect critical performance characteristics such as dissolution. For this reason, we deny your request that FDA allow your client to establish bioequivalence to KUVAN using product approved in Israel rather than the U.S.-approved RLD.

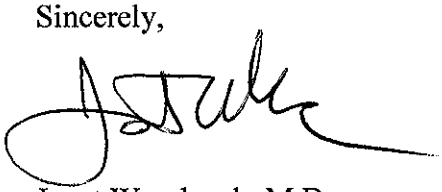
If you believe that BioMarin's failure to respond to your client's inquiries regarding sale of product supplies constitutes anticompetitive behavior, we encourage you to raise the matter with the Federal Trade Commission, which is responsible for addressing anticompetitive practices.

[4] In some circumstances where the original listed drug is no longer marketed, FDA will designate another generic drug as the reference standard. In these cases, however, the product designated as the reference standard has already been demonstrated to be bioequivalent to the original RLD. No such bridge has been created here: your petition requests that your client be permitted to demonstrate bioequivalence to a product that has not been established to be the same as the RLD and has never been shown to be bioequivalent to the RLD.

III. CONCLUSION

For the reasons described above, the Petition is denied.

Sincerely,



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