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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this petition on behalf of one of its generic drug manufacturer clients pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and in accordance with 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs take the actions described below.

I. Action Requested

We respectfully request that the Food and Drug Administration ("FDA") permit our client, a manufacturer that is planning to file an abbreviated new drug application ("ANDA") seeking approval of a generic version of the KUVAN™ (sapropterin dihydrochloride) tablets, 100 mg drug product ("KUVAN"), to establish the *in vivo* bioequivalence of its proposed generic drug product and the KUVAN drug product with bioequivalence studies using the KUVAN drug product obtained in Israel as the reference product based on evidence that the KUVAN drug product marketed in Israel is the same, in all material respects, as the KUVAN product described in the applicable approved New Drug Application ("NDA"). Because BioMarin Pharmaceutical Inc. ("BioMarin"), the holder of the approved NDA for KUVAN, has voluntarily implemented a restrictive distribution scheme and refuses to sell KUVAN samples to our client, the requested relief is necessary for an affordable generic version of KUVAN to be made available to patients in the United States.

II. Statement of Grounds

A. Regulatory Background

The ANDA process under which "generic" drugs are approved and marketed in the United States is codified in Section 505(j) of the FDCA. Under this statutory construct, an

ANDA applicant may obtain FDA approval of a drug that is the "same" as a previously approved drug without conducting the full battery of clinical and non-clinical studies that are required for a NDA.[1] An ANDA applicant is allowed to rely upon a prior FDA finding of safety and efficacy for the approved brand drug that is referenced by the ANDA applicant, provided that the proposed generic drug is the "same" as the approved brand drug with regard to active ingredients, dosage form, route of administration, strength, and labeling.[2] Additionally, the proposed generic drug must be demonstrated to be "bioequivalent" to the referenced brand drug.[3]

Not all currently marketed brand drugs may be referenced in an ANDA. Rather, the statute requires ANDA applicants to reference a "listed drug."[4] FDA's regulations define a "listed drug" as a drug that is the subject of an approved NDA that has not been withdrawn for safety or effectiveness reasons.[5] The regulations further explain that "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 (the list) or any current supplement thereto, as a drug with an effective approval."[6] The particular "listed drug identified by FDA as the drug product upon which an [ANDA] applicant relies" is further defined as the "reference listed drug" ("RLD").[7] Therefore, application of the applicable FDCA provisions and FDA regulations results in ANDA applicants being required to demonstrate the "bioequivalence" of the proposed generic drug and the corresponding RLD that is designated in the Orange Book.

In general, a generic drug is "bioequivalent" to the applicable RLD if, in single-dose or multiple dose clinical studies, the "rate and extent of absorption" of the two drugs are not significantly different.[8] For most systemically absorbed drug products, bioequivalence is demonstrated by *in vivo* comparative bioavailability studies that compare the proposed generic drug (*i.e.*, the "test" drug) and the RLD (the "reference" drug) under fasting and fed conditions

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[1] *See generally* FDCA § 505(j).

[2] FDCA § 505(j)(2)(A)(i), (ii), (iii), and (v).

[3] FDCA § 505(j)(2)(A)(iv); 21 C.F.R. § 314.127(a)(6)(i).

[4] FDCA § 505(j)(2)(A).

[5] 21 C.F.R. § 314.3(b).

[6] *See id.* FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" is commonly referred to as the "Orange Book."

[7] 21 C.F.R. § 314.3(b).

[8] *See* FDCA § 505(j)(8)(B).

(referred to as "bioequivalence studies").[9] In order to complete the required bioequivalence studies, ANDA applicants must first obtain sufficient quantities of the RLD product to dose the study subjects and maintain sufficient reserve samples.[10]

We understand that it is FDA's current policy that an ANDA applicant should use RLD obtained from a U.S. source as the reference product for the applicant's bioequivalence studies. However, we are unaware of any formal statement of such an agency policy.

B. Factual Background

FDA approved the KUVAN drug product on December 13, 2007.[11] When approving the KUVAN product, FDA required the NDA holder, BioMarin, to design and implement a patient registry to collect clinical status information from KUVAN patients for at least 15 years.[12] However, FDA did not approve a specific Risk Evaluation and Mitigation Strategy ("REMS") for the KUVAN product. Nevertheless, BioMarin has voluntarily limited the distribution of the drug. KUVAN is available only through "specialty" mail order pharmacies after the prescription has been reviewed and approved by the "BioMarin Patient and Physician Support" ("BPPS") group.[13] Consequently, KUVAN is not available through the prescription drug wholesale distribution channels that are typically used by ANDA applicants to obtain reference product for bioequivalence testing.

Furthermore, BioMarin refuses to sell the KUVAN product directly to potential ANDA applicants. Our client has directly contacted BioMarin and requested to purchase a sufficient quantity of KUVAN to conduct the requisite bioequivalence testing to obtain ANDA approval. In its request, our client assured BioMarin that the drug would not be sold to any patients and that the bioequivalence testing would be conducted in accordance with all applicable FDA requirements. As of the date of this petition, BioMarin has not responded to our client's request.

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[9] *See* 21 C.F.R. § 320.24(b)(1)(i).

[10] 21 C.F.R. § 320.63 (Retention of bioequivalence samples).

[11] NDA No. 022181.

[12] 12/13/2007 NDA Approval Letter at 2.

[13] *See* http://www.kuvan.com/patients/parent-caregivers-order-kuvan-from-a-specialty-pharmacy.html (viewed July 9, 2013) ("KUVAN is not available at your neighborhood pharmacy. Instead, it is conveniently dispensed by a specialty pharmacy. BioMarin Patient and Physician Support (BPPS) will arrange for the specialty pharmacy to ship KUVAN to your home.")

The KUVAN labeling obtained from the "www.kuvan.com" website, maintained by BioMarin exclusively for U.S. residents, states that the drug is manufactured by EXCELLA GmbH in Feucht, Germany.[14] The Israeli Ministry of Health's Israel Drug Registry website confirms that the KUVAN product marketed by a third party labeler in Israel is also manufactured by EXCELLA GmbH in Feucht, Germany.[15] The package insert for the KUVAN product distributed in Israel lists the same inactive ingredients and the same tablet imprint (i.e., "177") as the KUVAN product distributed in the United States.[16]

C. Argument

1. The FDCA does not mandate the use of reference drugs sourced in the United States.

An ANDA applicant bears the burden of demonstrating that its proposed drug is bioequivalent to the RLD.[17] In order to meet that burden, an applicant must first demonstrate that the reference product that was used in the applicant's bioequivalence study was the actual RLD product.[18] FDA has the statutory authority to permit ANDA applicants to demonstrate that the

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[14] KUVAN package insert (Rev. Date 12/2007) ("KUVAN PI") at 4 (attached as Exhibit 1); *see also* KUVAN labeling and manufacturing information published on the U.S. National Library of Medicine's "DailyMed" website, *available at* http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=af38711e-8873-4790-a92d-4d583e23fb89 (viewed July 9, 2013) (stating that KUVAN is manufactured by "EXCELLA GmbH, Nürnberger Strasse 12, 90537 FEUCHT Germany").

[15] Although the Israeli Ministry of Health's Israel Drug Registry website spells the manufacture site for the Israeli KUVAN tablets as "EXELLA GMBH, GERMANY," the addresses for both "EXELLA GMBH" and "EXCELLA GMBH" are the same – Nürnberger Strasse 12, Feucht 90537, Germany. *See* Israeli KUVAN drug information from Israel Drug Registry, *available at* http://www.old.health.gov.il/units/pharmacy/trufot/PerutTrufa.asp?Reg_Number=144%2023%2033052%2000&safa=h (viewed July 9, 2013) ("Israel Drug Registry") (attached as Exhibit 2) *and* KUVAN PI at 4. Therefore, the slight variation in spelling of the manufacturer's name is not material to this analysis and we submit that "EXELLA GMBH" and "EXCELLA GMBH" are the same manufacturer.

We further note that the Israeli KUVAN package insert ("Israeli KUVAN PI") lists "Merck Serono S.A., Geneva, Switzerland" as the "manufacturer." *See* Israeli KUVAN PI at 1 (attached as Exhibit 3). Based on our understanding, Merck Serono S.A. in Geneva, Switzerland refers to one of the company's headquarters addresses and not the actual manufacturing site for KUVAN. As the Israel Drug Registry confirms, the actual manufacturing site is EXCELLA GMBH in Feucht, Germany.

[16] *See* Israeli KUVAN PI at 1 *and* KUVAN PI at 4.

[17] FDCA § 505(j)(2)(A)(iv); 21 C.F.R. § 320.21(b).

[18] We note that establishing the "sameness" of the proposed product labeling does not present the same issue because the FDA-approved labeling for the RLD product is available on FDA's internet website. In fact, FDA

reference drug used in the applicant's bioequivalence study is the proper RLD. It is certainly possible to demonstrate that a product obtained in a foreign country is the same as the RLD product sold in the United States. Our understanding of FDA's current policy, however, is that the agency permits only one means of meeting that initial burden, namely obtaining the RLD product from a source in the United States. However, neither the FDCA nor FDA's regulations *compel* such a rigid regulatory policy, and the realities of the modern pharmaceutical business necessitate a more flexible scheme, as explained below.

2. Flexibility in determining acceptable sources of reference listed drugs is necessary to prevent abuses of the Hatch-Waxman system.

Providing flexibility to generic manufacturers in obtaining RLD products is essential to uphold the purposes of the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) ("Hatch-Waxman Act"). When Congress passed the Hatch-Waxman Act, it created a delicate balance between timely and low-cost entry of generic drug products into the market and innovator intellectual property protection interests.[19] To encourage generic market entry and promote competition, the Hatch-Waxman Act created the ANDA process for generic manufacturers.[20] However, when NDA holders voluntarily implement restrictive distribution schemes and refuse to sell RLD products to potential ANDA applicants, they undermine the Hatch-Waxman process by indefinitely forestalling generic competition.[21, 22]

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requires ANDA applicants to design their product labeling to match the labeling on FDA's website rather than the labeling that is actually distributed with the RLD product in the United States.

[19] The Hatch-Waxman provisions "emerged from Congress' efforts to balance two conflicting policy objectives: to induce name brand pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market." *Mylan Pharm., Inc. v. Thompson*, 268 F.3d 1323, 1326 (Fed. Cir. 2001) (internal quotations and citation omitted), *superseded by statute on different grounds*. *See also Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 132 S.Ct. 1670, 1676 (2012) ("this process is designed to speed the introduction of low-cost generic drugs to market").

[20] The ANDA procedure "implement[ed] the policy objective of getting safe and effective generic substitutes on the market as quickly as possible after the expiration of the [brand drug] patent." H.R. Rep. No. 98-857, Pt. 2, at 9.

[21] FDA has recognized the importance of generic manufacturers obtaining RLD products for bioequivalence testing even under REMS, which is a more stringent regulatory construct than the voluntary restrictive distribution scheme at issue here. For instance, following an explicit statement in the 2007 Food and Drug Administration Amendments Act (FDAAA), 21 U.S.C. § 355-1(f)(8), that no holder of a REMS-covered drug can use REMS to "block or delay approval" of an ANDA, FDA publicly stated that REMS programs should not "block or delay generic competition" and asked for suggestions for how to meet this goal. FDA, Risk Evaluation and Mitigation Strategies; Notice of Public Meeting; Reopening of Comment Period, 75 Fed. Reg. 34453, at 34456 (June 17, 2010). Similarly, the Federal Trade Commission found that distribution restrictions – whether under a REMS or under a voluntary scheme – "raise serious competitive concerns" and, if used improperly, "threaten[] to undermine the careful balance created by the Hatch-Waxman Act and potentially preserve a brand firm's monopoly indefinitely." *See* Fed. Trade

Generic manufacturers are then essentially foreclosed from the ANDA process and, instead, are forced to file NDAs, a procedure that the Hatch-Waxman Act sought to eliminate for generic manufacturers.[23] Giving flexibility to generic manufacturers in obtaining RLD products that are the "same" as the NDA-approved products but sold outside the United States would allow generic manufacturers to conduct the required bioequivalence testing, proceed through the ANDA pathway, and thus uphold the principles of the Hatch-Waxman system.[24]

3. The KUVAN tablets distributed in Israel are the same as the KUVAN tablets distributed in the United States.

A review of the KUVAN PI, Israeli KUVAN PI, and the Israel Drug Registry demonstrate that the KUVAN drug product marketed in Israel is materially the same as the KUVAN drug product marketed in the United States as described in BioMarin's approved NDA. First, both KUVAN products are manufactured by EXCELLA GmbH in Feucht, Germany.[25] Second, the package inserts for both KUVAN products list the same inactive ingredients: ascorbic acid, crospovidone, dibasic calcium phosphate, mannitol, riboflavin, and sodium stearyl fumarate.[26] Third, both KUVAN products are off-white to light yellow tablets that show the same tablet imprint ("177").[27] Accordingly, our client should be allowed to utilize the KUVAN

Comm'n *Amicus* Brief at 1-2, 8, *Actelion Pharm. Ltd. v. Apotex*, Case No: 1:12-cv-05743-NLH-AMD (D.N.J. Mar. 11, 2013).

[22] We recognize that courts are currently reviewing whether brand name drug manufacturers may improperly use restricted drug distribution programs to refuse to sell brand products to generic drug manufacturers for bioequivalence testing. *See, e.g.*, *Actelion Pharm. Ltd. v. Apotex*, Case No.: 1:12-cv-05743-NLH-AMD (D.N.J.). However, there is no certainty as to when and how the courts will rule. While these cases are pending, FDA has the authority to rule more quickly on this issue and foster generic competition.

[23] As Representative Henry Waxman explained in his 2005 *amicus* brief, "the purpose of [the Hatch-Waxman Act's] provisions concerning generic drugs was clear: 'to make available more low cost generic drugs by establishing a generic drug approval process for pioneer drugs first approved after 1962.' H.R. Rep. No. 98-857, Pt. 1, at 14 (June 21, 1984). The Act reflected the concern that then-existing FDA procedures, which required generic drug manufacturers to complete the lengthy procedures for new drug approval once patents protecting the name-brand drug expired, 'had serious anti-competitive effects,' the result of which was 'the practical extension of the monopoly position of the patent holder beyond the expiration of the patent.' H.R. Rep. No. 98-857, Pt. 2, at 4 (Aug. 1, 1984)." *See* Waxman *Amicus* Brief at 4, *Fed. Trade Comm'n v. Schering-Plough Corp., et al.*, No. 05-273 (S.Ct. 2005).

[24] Flexibility would not prejudice brand name manufacturers who could still utilize voluntary restrictive distribution schemes, yet would allow generic manufacturers to perform the bioequivalence testing as mandated by the Hatch-Waxman system.

[25] *See* KUVAN PI at 4 *with* Israel Drug Registry at 2.

[26] *Compare* KUVAN PI at 4 *with* Israeli KUVAN PI at 1.

[27] *Compare* KUVAN PI at 4 *with* Israeli KUVAN PI at 1.

drug product obtained from Israel in place of the KUVAN drug product marketed in the United States in conducting its bioequivalence testing.

D. Conclusion

On behalf of our client, we respectfully request FDA to allow ANDA applicants seeking approval of a generic version of KUVAN to establish the required bioequivalence of their proposed generic drug product by using KUVAN drug product obtained in Israel, which is the "same" in all material respects to the KUVAN product described in the approved NDA. Such flexibility would circumvent abuses of the Hatch-Waxman system stemming from brand manufacturers' misuse of restrictive distribution schemes and uphold Congress' intent of increasing generic competition while preserving incentives for brand innovations.

III. Environmental Impact

This petition is categorically exempt from the requirement for an environmental assessment or an environmental impact statement pursuant to 21 C.F.R. §§ 25.30 and 25.31.

IV. Economic Impact

Information on the economic impact of the petition will be provided upon request.

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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