March 31, 2020

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

CITIZEN PETITION

Belcher Pharmaceuticals, LLC ("Belcher" or "the Company") submits this Citizen Petition ("Petition") pursuant to § 505(j)[1] of the Federal Food, Drug, and Cosmetic Act ("FFDCA" or "the Act") and 21 C.F.R. §10.20, §10.30, and Part 320 to request that the Commissioner of Food and Drugs ("Commissioner") require that current holders of abbreviated new drug applications ("ANDAs") for tacrolimus oral capsule drug products demonstrate that those drugs meet the more stringent bioequivalence requirements that the U.S. Food and Drug Administration ("FDA" or "the Agency") has imposed since their approval. If those products are not bioequivalent under the current requirements, then FDA should change the therapeutic equivalence rating of those ANDAs from "AB" to "BX."

A. ACTION REQUESTED

For the reasons more fully discussed herein, Belcher respectfully requests that the Commissioner make the following findings:

(1) Require the sponsors of tacrolimus oral capsule ANDAs which were approved prior to December 2012 to test their products according to FDA's December 2012 Draft Guidance on Tacrolimus ("2012 Tacrolimus Guidance"), which requires both fasting and fed bioequivalence studies designed as single-dose, four-way, fully-replicated crossover studies *in vivo*. This action is necessary to maintain an AB therapeutic equivalence rating in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") because the Agency made significant testing changes in the 2012 Tacrolimus Guidance to acknowledge that tacrolimus is a narrow therapeutic index ("NTI") drug product.

(2) If such sponsors do not test their products against the current 2012 Tacrolimus Guidance requirements, or if the results of such testing demonstrate that the drugs are not bioequivalent, then FDA should change the therapeutic equivalence rating for these ANDAs from AB to BX because they are not bioequivalent to post-December 2012

[1] *Codified at* 21 U.S.C. § 355(j).

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ANDAs. If the products are not bioequivalent, then they are not therapeutically equivalent and are not substitutable.

B. STATEMENT OF GROUNDS

Belcher submits this Petition based upon the grounds set forth below.

I. INTEREST OF BELCHER

FDA approved Belcher's ANDA 206651 for tacrolimus oral capsules (0.5 mg; 1 mg; 5 mg) on November 30, 2017. Prograf®, the reference listed drug ("RLD"), was approved on April 8, 1994.[2] FDA has approved numerous ANDAs,[3] most of which were approved before the end of 2012. Those ANDAs that were approved prior to December 2012 were required to comply with an earlier version of FDA's Tacrolimus Guidance. These pre-December 2012 approvals were granted based on different and less-rigorous bioequivalence testing than Belcher and any other post-December 2012 sponsor was required to perform.

Accordingly, as the sponsor of ANDA 206651, Belcher has an interest in ensuring that all generic tacrolimus oral capsule drug product sponsors adhere to the same NTI drug bioequivalence testing standards that the Company followed. If any of the pre-December 2012 products are in fact not bioequivalent to the RLD based upon these new test requirements, then patients' safety may be at risk if products are substituted for each other. Changing their therapeutic equivalence rating from AB to BX will alert physicians and pharmacists to this fact.

II. TACROLIMUS BIOEQUIVALENCE GUIDANCE DOCUMENT

FDA first issued a draft bioequivalence guidance for tacrolimus oral capsule drug products in 2006 ("2006 Tacrolimus Guidance"). At that time, FDA recommended two studies conducted in normal healthy males and females:

(1) One fasting, single-dose, two-treatment, two-period crossover *in vivo* bioequivalence study comparing 5 mg tacrolimus capsules to the RLD; and

(2) One fed, single-dose, two-treatment, two-period crossover *in vivo* bioequivalence study comparing 5 mg tacrolimus capsules to the RLD.

According to the 2006 document, FDA would waive bioequivalence studies on the 0.5 mg and 1 mg dosage strengths provided that the 5 mg strength studies were acceptable; the three dosage

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[2] NDA 50708.

[3] ANDA 65461 (approved August 10, 2009); ANDA 90509 (approved May 12, 2010); ANDA 90596 (approved September 17, 2010); ANDA 91195 (approved August 31, 2011); ANDA 90802 (approved September 28, 2012); ANDA 90687 (approved July 22, 2014).

6911 Bryan Dairy Road | Largo, FL 33777 | Tel: 727-471-0850 | Fax: 727-471-0858

strengths were proportionally similar in formulation; and all three strengths had acceptable *in vitro* dissolution testing results. There was no statement that tacrolimus is an NTI drug.

In September 2009, FDA finalized this draft guidance document ("2009 Tacrolimus Guidance"), retaining the same study designs as were in the 2006 version.[4] Again, FDA made no mention about the NTI drug status of tacrolimus.

The 2009 document was revised again in December 2012 and published as a draft (which it remains today).[5] In the 2012 Tacrolimus Guidance, FDA amended the bioequivalence study requirements as follows:

(1) One fasting, single-dose, four-way, fully-replicated crossover design *in vivo* bioequivalence study comparing 5 mg tacrolimus capsules to the RLD; and

(2) One fed, single-dose, four-way, fully-replicated crossover design *in vivo* bioequivalence study comparing 5 mg tacrolimus capsules to the RLD.

The criteria for a waiver for the 0.5 mg and 1 mg dosage strengths remained the same.

Significantly, FDA concluded in the 2012 document that tacrolimus is an NTI drug. As a result, FDA now requires a fully-replicated crossover design to both scale bioequivalence limits to RLD variability, and to compare test product and RLD intra-subject variability. Finally, the Agency stated that sponsors should utilize the statistical methods found in the draft bioequivalence guidance for another NTI drug product, warfarin sodium.[6]

All but two ANDAs for tacrolimus oral capsules—the Belcher ANDA and one other[7]—were approved before these heightened bioequivalence requirements were issued in December 2012. Therefore, there is a clear distinction between how bioequivalence of tacrolimus oral capsule drug products pre-December 2012 and post-December 2012 was determined. Belcher is concerned that substitutions of these generic drugs will place the public at risk because FDA has now recognized that tacrolimus is an NTI drug—yet not all of these products have been tested using these heightened standards. This concern is the basis of the Company's Petition.

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[4] We note that the 2006 Tacrolimus Guidance did include an additional comment about the fasting and fed studies, which was eliminated from the 2009 Tacrolimus Guidance: "Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study."

[5] FDA, "Draft Guidance on Tacrolimus" (revised December 2012), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/psg/Tacrolimus_cap_50708_RV12-12.pdf.

[6] FDA, "Draft Guidance on Warfarin Sodium" (recommended December 2012), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/psg/Warfarin_Sodium_tab_09218_RC12-12.pdf.

[7] ANDA 90687 (approved July 22, 2014).

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III. FDA'S EVOLUTION ON NTI DRUG PRODUCT BIOEQUIVALENCE

FDA's view on bioequivalence requirements for NTI drugs has evolved in the last decade in conjunction with the recommendations of the Agency's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology ("Advisory Committee" or "the Committee"). In April 2010[8] and July 2011,[9] the Advisory Committee specifically discussed a number of NTI drug bioequivalence issues at FDA's request: (1) whether NTI drugs are a distinct group of products, how they should be defined, and if FDA should prepare a list; (2) whether the existing bioequivalence standards are sufficient for NTI drugs or how they should be revised; and (3) whether the assay potency standard should be tightened for NTI drugs.

In the case of bioequivalence standards, the Committee discussed whether the historic 90% confidence interval ("CI") range of 80–125% for both area under the curve ("AUC") and C_{max} measurements was appropriate, and how study design changes could improve reliability of BE assessments for these products. Because NTI drugs are characterized by narrow within-patient variability, both FDA and the Advisory Committee were concerned that the traditional 80%–125% limits would not ensure safe product substitution. At the 2010 meeting, the Committee reviewed FDA simulations of various bioequivalence approaches for NTI drugs,[10] and considered how other countries treat such products.[11] The Committee voted 11–2 that the current bioequivalence standards were not sufficient for NTI drugs. They specifically addressed a narrowed range of 90%–111.11% (including the 100% or 1.0 point), even though some members were concerned that FDA had not presented enough data to demonstrate that this particular range should be adopted for NTI drugs.[12] Although there was no formal 2010 Advisory Committee vote on a new 90% CI range of 90%–111.11%, FDA nonetheless voiced its support for this recommendation at the July 2011 meeting. This narrowed 90–111.11% range was "adopted" for discussions during the 2011 meeting without FDA asking for a vote.[13]

In the case of study design for NTI drugs, in 2011 the Committee recommended (by a 12–1 vote) that bioequivalence testing consist of a two-treatment, four-period, fully-replicated

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[8] *See generally* background materials for April 13, 2010 Advisory Committee meeting, *available at* http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm201700.htm.

[9] *See generally* background materials for July 26, 2011 Advisory Committee meeting, *available at* http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm240583.htm.

[10] Donald J. Schulmann, FDA, "Evaluation of Scaling Approaches to Demonstrate BE of NTI Drugs – OGD Simulation Efforts" (slides presented at July 26, 2011 meeting).

[11] Barbara M. Davit, FDA, "FDA Proposal for Bioequivalence of Generic Narrow Therapeutic Index Drugs" (slides presented at July 26, 2011 meeting).

[12] 2010 AC Minutes at 5.

[13] 2011 AC Transcript (July 26, 2011) at 245 (Dr. Yu, FDA: "[L]ast year, you already proposed a bioequivalence limit of 90 to 111.111 percent. We thought it was a good approach. So, therefore, we didn't ask you for additional deliberation and the vote here.").

6911 Bryan Dairy Road | Largo, FL 33777 | Tel: 727-471-0850 | Fax: 727-471-0858

crossover design.[14] A four-period design allows replicated testing of both the test and reference products to obtain separate estimates of their variance. This approach provides an assessment of the pharmaceutical quality of each formulation,[15] and this design was viewed as providing valuable information about the test and reference drugs. Second, the Committee voted unanimously (with one abstention) to adopt a reference-scaled average bioequivalence approach.[16] Products with both high and low within-subject variability can be tested using reference scaling, which adjusts the bioequivalence limits by scaling to within-subject variability of the reference product.[17] The reference-scaled approach, which FDA first developed in 2004,[18] permits within-patient variations to be considered during product testing and has supported several FDA approvals of highly-variable generic drugs as well.[19]

It is clear that, with the recommendations from its Advisory Committee, FDA made some critical decisions about NTI drug bioequivalence requirements in 2010–11. As a result, the 2012 Tacrolimus Guidance adopted this recommended four-period, fully-replicated crossover study design (as well as the reference-scaled average bioequivalence approach), which was not in place in any of the earlier versions of the document. These are new facts that were not yet available when Astellas filed its citizen petition or sued FDA.

IV. ARGUMENTS

A. All Tacrolimus Oral Drug Products Should Meet Contemporary Bioequivalence Requirements for NTI Drugs

As discussed, there have been substantial changes to FDA's position on bioequivalence testing for NTI drugs in general and tacrolimus oral capsule products in particular. It was not until 2010–11 that FDA began more seriously considering the ramifications of how bioequivalence tests are performed for NTI drugs, leading to the Agency's amendment of the 2009 Tacrolimus Guidance. The 2012 Tacrolimus Guidance, for the first time, recognized the NTI status of tacrolimus and changed the required study design from a two-treatment, two-period crossover to

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[14] 2011 AC Minutes at 5.

[15] Kamal K. Midha, University of Saskatchewan College of Pharmacy and Nutrition, "Narrow Therapeutic Index Drugs: An Approach to Bioequivalence and Interchangeability" (slides presented at July 26, 2011 meeting).

[16] 2011 AC Minutes at 5.

[17] Davit B. and Conner D. *Reference-Scaled Average Bioequivalence Approach*, in Kanfer I. and Shargel L., eds., Generic Drug Product Development – International Regulatory Requirements for Bioequivalence. New York, NY: Informa Healthcare, 2010: 271–72; Davit B.M. *et al.* Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration. THE AAPS JOURNAL 14(4):915–24 (December 2012); Desai J. and Jain P. Reference Scaled Average Bioequivalence: Scaling Approach for the Highly Variable Drugs. INTERNATIONAL J. PHARMACEUTICAL RESEARCH AND INNOVATION 4:20–21 (2011).

[18] Davit 2012 at 921.

[19] Davit 2012 at 920–21 (noting that FDA had fully approved four (and tentatively approved one) highly-variable drugs using the reference-scaled average bioequivalence approach).

6911 Bryan Dairy Road | Largo, FL 33777 | Tel: 727-471-0850 | Fax: 727-471-0858

a four-way, fully-replicated crossover. Moreover, for the first time the 2012 document addressed the use of the reference-scaled average bioequivalence approach for statistical analyses.

These are significant changes in study design that the sponsors of pre-December 2012 products did not have to address. In fact, FDA's decision to change the historical tacrolimus guidance runs contrary to the Agency's previous conclusion in its response to the Astellas petition, where the Agency noted that it "*is confident that it has established sufficient criteria to determine bioequivalence for tacrolimus* whether or not the agency subsequently decides to characterize tacrolimus as a narrow therapeutic range drug product" (emphasis added). FDA's confidence clearly changed following the Advisory Committee's recommendations, or else the guidance modifications would not have been made.

B. If the Products are not Bioequivalent, then Their AB Ratings Should be Replaced with a BX Rating

FDA's Orange Book lists therapeutic equivalence evaluations for multisource prescription drug products approved under FFDCA § 505.[20] FDA bases these determinations on several criteria:[21]

(1) The generic drug is approved as safe and effective; and
(2) The generic drug and RLD are "pharmaceutical equivalents"
    (a) They contain identical amounts of the same active pharmaceutical ingredient, in the same dosage form and route of administration; and
    (b) They meet compendial or other standards of strength, quality, purity, and identity; and
(3) The generic drug and RLD are bioequivalent
    (a) They do not present a bioequivalence problem (known or potential); or
    (b) If they do pose a known or potential problem, they meet an appropriate bioequivalence standard; and
(4) The generic drug is adequately labeled; and
(5) The generic drug is manufactured in accordance with current good manufacturing practices.

As the Orange Book notes, "FDA believes that products classified as therapeutically equivalent can be substituted with the *full expectation that the substituted product can be expected to have the same clinical effect and safety profile* as the prescribed product when administered to patients under the conditions specified in the labeling."[22] The Agency has rated tacrolimus oral capsules as "AB," indicating that the drugs have "actual or potential bioequivalence problems" that have been addressed with adequate evidence (*in vivo* or *in vitro*) that supports a finding of

[20] Orange Book, 40th Edition (2020), *available at* https://www.fda.gov/media/71474/download, at iv.

[21] Orange Book at vii.

[22] Orange Book at viii (emphasis added).

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bioequivalence.[23] According to FDA, these products are therapeutically interchangeable. On the other hand, drugs rated "BX" are those drugs for which there is insufficient data to determine therapeutic equivalence "under the policies stated in this document [the Orange Book]."[24] Demonstrating a *lack* of safety or effectiveness is not required.

Making changes to therapeutic equivalence codes is not unprecedented, and the Orange Book provides that FDA can make changes to a therapeutic equivalence code for either a single drug product or an entire category of drugs. For example, FDA will change a code for a single product from AB to BX if, for example, there is "new information raising a significant question as to bioequivalence."[25] Furthermore, FDA can change the code for an entire category of drug products "when the Agency becomes aware of new scientific information affecting the therapeutic equivalence of an entire category of multisource drug products in the Orange Book."[26]

In November 2014, FDA changed the rating for methylphenidate hydrochloride extended release tablets from AB to BX, providing the generic drug sponsors (Mallinckrodt and Kudco Ireland) with an opportunity to confirm their products' bioequivalence within six months using a revised product-specific bioequivalence guidance document.[27] Mallinckrodt immediately filed a complaint for declaratory and injunctive relief in the U.S. District Court for the District of Maryland,[28] arguing that the coding change would cause pharmacists to not use the company's product to fill prescriptions written for the RLD. As Mallinckrodt argued, "FDA classification action effectively takes Mallinckrodt's methylphenidate ER tablets off the market."[29]

FDA countered by noting an increase in adverse event reporting after Mallinckrodt's ANDA approval as well as other evidence, which caused the Agency to re-evaluate the rating. FDA argued that its decision did not impact the ability of the drugs to continue to be marketed, as no adverse determination about safety or efficacy had been made. As a result, "[d]iminished marketplace availability does not equate to withdrawal of a drug approval."[30] The court found in FDA's favor.

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[23] Orange Book at xiii.

[24] Orange Book at xx.

[25] Orange Boo at xxiv.

[26] Orange Book at xxiii.

[27] FDA Press Release, "FDA Concerns about Therapeutic Equivalence with Two Generic Versions of Concerta Tablets (Methylphenidate Hydrochloride Extended Release)" (November 13, 2014), *available at* http://www.fda.gov/drugs/drugsafety/ucm422568.htm.

[28] Mallinckrodt v. FDA, Case 8:14-cv-03607, Complaint for Declaratory and Injunctive Relief, U.S. Dist. Ct. Md. (filed November 17, 2014) (hereinafter "Mallinckrodt Complaint").

[29] Mallinckrodt Complaint at ¶ 30.

[30] FDA Opposition Memorandum at 12.

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If current sponsors of tacrolimus oral capsule ANDAs cannot demonstrate that their products are bioequivalent to the RLD under the more rigorous and contemporary 2012 Tacrolimus Guidance, then FDA would be encouraged to re-evaluate the therapeutic equivalence codes of these other generic products (perhaps changing from AB to BX). This will ensure that patients, physicians, and pharmacists are fully aware of which products may be substituted for others without fear that the patient will suffer an adverse consequence when using this NTI drug.

C. Environmental Impact

A claim for categorical exclusion is made under 21 C.F.R. § 25.31.

D. Economic Impact

An economic impact determination will be made at the request of the Commissioner.

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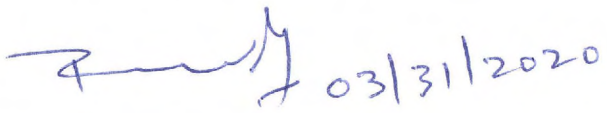
E. CERTIFICATION

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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