Shyam Busireddy
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Belcher Pharmaceuticals, LLC
6911 Bryan Dairy Road
Largo, FL 33777

September 18, 2023

Re: Docket No. FDA-2020-P-1247

Dear Mr. Busireddy:

This letter responds to your citizen petition received on April 2, 2020 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or Agency) take the following actions:

(1) Require the sponsors of tacrolimus oral capsule [abbreviated new drug applications (ANDAs)] which were approved prior to December 2012[1] to test their products according to FDA's December 2012 Draft Guidance on Tacrolimus (2012 [Draft Product-Specific Guidance (2012 Draft PSG)]),[2] which requires both fasting and fed bioequivalence studies designed as single-dose, four-way, fully-replicated crossover studies in vivo.[3]

(2) If such sponsors do not test their products against the current 2012 [Draft PSG] requirements, or if the results of such testing demonstrate that the drugs are not bioequivalent, then FDA should change the therapeutic equivalence [(TE) code] for these ANDAs from AB to BX because they are not bioequivalent to post-December 2012 ANDAs.[4]

We have carefully considered the Petition and comments to the docket.[5] For the reasons described below, your Petition is denied in part and granted in part. Specifically, we deny your

[1] FDA approved six ANDAs before December 2012: (1) ANDA 065461 approved on Aug. 10, 2009; (2) ANDA 090509 approved on May 12, 2010; (3) ANDA 090402 approved on July 1, 2010; (4) ANDA 090596 approved on Sept. 17, 2010; (5) ANDA 091195 approved on Aug. 31, 2011; and (6) ANDA 090802 approved on Sept. 28, 2012.

[2] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a PSG, check the FDA PSG web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

[3] Petition at 1.

[4] Id.

[5] On May 22, 2020, Teva Pharmaceutical Industries, Ltd. (Teva) submitted comments (Comment) to the Petition. Teva's comments are the only comments submitted to this docket. Teva states that it "takes no position on whether, as a scientific matter, abbreviated new drug applications ('ANDAs') for tacrolimus capsule drug products approved prior to December 2012 should fully comply with the bioequivalence recommendations set forth in the [Agency's] December 2012 draft product specific guidance ('PSG') on tacrolimus, [but] Teva does not believe FDA may require compliance with the revised recommendations unless it determines they are essential for demonstrating bioequivalence and the prior recommendations are not capable of making that demonstration.." (Comment at 1). Teva further states that its "comments . . . focus on the legal and policy considerations that should govern FDA's implementation of revised PSGs generally[,]" that it "is particularly concerned that FDA has adopted a general practice of treating revised PSGs as binding requirements that apply retroactively to pending ANDAs only[,]"(Id.) and urges FDA to develop a categorization method for PSGs that includes a category for revisions deemed to be

request to require sponsors of ANDAs for tacrolimus oral capsules approved before December 2012 to demonstrate bioequivalence according to the recommendations in the 2012 Draft PSG. We also deny your request to change the TE code of five of the six ANDAs for tacrolimus oral capsules approved before December 2012 if the ANDA holders do not test their products according to the 2012 Draft PSG. We grant your request to change the TE code for ANDA 091195 from an AB rating to a BX rating. An FDA-contracted bioequivalence study found that bioequivalence between a tacrolimus oral capsule product approved under ANDA 091195 and its reference listed drug (RLD) was not demonstrated and these results along with the Agency's review of the available evidence, provide reason to believe that ANDA 091195 may not be therapeutically equivalent to the RLD.

I. BACKGROUND

A. Tacrolimus Oral Capsules

On April 8, 1994, and August 24, 1998, respectively, FDA approved new drug application (NDA) 050708 for Prograf (tacrolimus) oral capsule, equivalent to (EQ) 1 milligram (mg) and 5 mg, and 0.5 mg, held by Astellas Pharma US Inc. Prograf is a calcineurin-inhibitor immunosuppressant for the prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic liver, kidney, heart or lung transplants, in combination with other immunosuppressants.

The Agency approved six ANDAs for tacrolimus oral capsules before December 2012.[6] Each of these six ANDAs used the bioequivalence testing criteria recommended in the 2009 Guidance on Tacrolimus, which recommended a single-dose, two-treatment, two-period crossover design in healthy human subjects.

B. Narrow Therapeutic Index Drugs

Tacrolimus is considered a narrow therapeutic index (NTI) drug. The specific term *narrow therapeutic index* is not defined in FDA regulations. However, under § 320.33(c) (21 CFR 320.33(c)), a *narrow therapeutic ratio* may be exhibited by evidence that:

essential to demonstrate bioequivalence (Comment at 9). Under 21 CFR 10.30(d), an interested person may support or oppose a petition; however, a request for an alternative or different administrative action must be submitted as a separate petition. Because Teva's comments generally address the legal and policy considerations that should govern the applicability of revised PSGs to pending ANDAs, they seek different relief than the Petition, which, *inter alia*, requests that FDA require sponsors of ANDAs for tacrolimus oral capsules approved prior to December 2012 to demonstrate bioequivalence for their products based on the recommendations in the 2012 Draft PSG. As a result, FDA generally will not address Teva's comments in this petition response. To the extent that Teva's comments request that FDA not require sponsors of ANDAs for tacrolimus oral capsules approved prior to December 2012 to demonstrate bioequivalence of their products again based on the recommendations in the 2012 Draft PSG, we decline to require such sponsors to take such an action for the reasons explained in sections II.A and II.B.1 of this response.

[6] ANDAs 065461, 090509, 090402, 090596, 091195, and 090802.

(1) There is less than a two-fold difference in medial lethal dose (LD_{50}) and median effective dose (ED_{50}) values or there is less than a two-fold difference in minimum toxic concentrations and minimum effective concentrations in the blood, and

(2) Safe and effective use of the drug products requires careful titration and patient monitoring.

Definitions of NTI drugs were discussed in FDA advisory committee meetings held in 2010 and 2011.[7] As a result of those discussions, FDA now uses the term narrow therapeutic index and considers NTI drugs to be those drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity.[8]

FDA assesses whether drugs have a narrow therapeutic index on a case-by-case basis, focusing on whether a particular drug has the following characteristics:

- There is little separation between therapeutic and toxic doses (or the associated blood/plasma concentrations),
- Sub-therapeutic concentrations may lead to serious therapeutic failure,
- Patients are subject to therapeutic monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures,
- The drugs have low-to-medium (i.e., no more than 30 percent) within-subject variability (meaning that when the same subject is administered the same dose of the same drug product, no more than a 30 percent difference in the rate and extent of absorption of the drug is observed), and

[7] See, e.g., the meeting materials for the April 13, 2010 Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee (2010 CDER Advisory Committee), available at https://wayback.archive-it.org/7993/20170403224116/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm201700.htm; the Summary Minutes of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, July 26, 2011, available at https://wayback.archive-it.org/7993/20170404155002/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM272111.pdf, at 4–5 (voting 11-0-2 to adopt an NTI definition; voting 12-1-0 to recommend a fully replicate study design for NTI drugs; voting 12-0-1 to adopt the reference-scaled average bioequivalence approach for NTI drugs; and voting 13-0-0 to tighten the assay potency standard for NTI drugs); and the Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, July 26, 2011, Briefing Information, available at https://wayback.archive-it.org/7993/20170405230006/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM263465.pdf, at 9–14 (referencing earlier determination to call this group of products "Narrow Therapeutic Index (NTI) Drugs" and providing background on a proposed NTI definition, current and proposed NTI bioequivalence criteria, current and proposed pharmaceutical quality NTI criteria, and related FDA research).

[8] See the draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021) (2021 PK Endpoints Draft Guidance), at 24. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- In clinical practice, doses are often adjusted in very small increments (less than 20 percent).[9]

The assessment of whether a drug has a narrow therapeutic index generally is reflected in the applicable product-specific recommendations for that drug product.[10]

Doses of NTI drugs often must be adjusted in very small increments because the potential adverse reactions associated with sub- or supra-therapeutic drug concentrations can be serious, even life-threatening. For example, supra-therapeutic levels of warfarin (measured through PD monitoring of prothrombin time and international normalized ratio) can lead to major or fatal bleeding events, and drugs that are indicated for treatment of epilepsy or for immunosuppression can cause severe therapeutic failure at sub-therapeutic concentrations. Accordingly, NTI drugs must be carefully dosed and monitored.

FDA has recommended in general and in product-specific draft guidances that ANDA applicants demonstrate bioequivalence for NTI drugs using a four-way, fully-replicated crossover study design and a comparison of both within-subject[11] and mean variability. Details on how to implement the reference-scaled average bioequivalence (RSABE) approach for NTI drugs are currently described in the draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021) (2021 PK Endpoints Draft Guidance) as well as several draft product-specific guidance recommendations for NTI drugs.[12]

C. Abbreviated Drug Approval Pathways Under the Federal Food, Drug, and Cosmetic Act

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)), which established the ANDA approval pathway for generic drugs.[13] To obtain approval, an ANDA applicant is not required to provide independent

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[9] See the draft PSG for industry on Warfarin Sodium tablets (December 2012) at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm, at 2 (listing these five bases for determining warfarin sodium is an NTI drug). When final this guidance will represent the FDA's current thinking on this topic. See also LX Yu, et al., 2015, Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs, Clin Pharmacol Ther, 97(3):286–291, at 287 (listing five typical characteristics of NTI drugs); FDA BIOEQUIVALENCE STANDARDS, at 14 (similar); and § 320.33(c) (21 CFR 320.33(c)) (similar, for "narrow therapeutic range" drugs). Also see the 2021 PK Endpoints Draft Guidance, at 4, 24 (noting within-subject variability of NTI drugs and risks of sub- and supra-therapeutic concentrations).

[10] See 2021 PK Endpoints Draft Guidance.

[11] Within-subject variability (WSV), also known as intra-subject variability, refers to the variability in a response (such as the plasma drug concentration) within the same subject between the two periods when administrated the same dose of Test (T) or Reference (R) drug products. WSV is usually expressed by the within-subject variance or standard deviation.

[12] See, for example, the draft PSGs containing product-specific recommendations for warfarin sodium, carbamazepine, phenytoin sodium, levothyroxine sodium, and sirolimus. For the most recent version of a PSG, check the FDA PSG webpage at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

[13] For the purpose of this response, the term *generic drug* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act.

evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA's previous finding that the RLD is safe and effective.[14] The ANDA applicant must identify the listed drug on which it seeks to rely, and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.[15]

An ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the RLD.[16] Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the listed drug 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 [17]

In § 314.3(b) (21 CFR 314.3(b)), FDA defines bioequivalence (in pertinent part) as:

> the absence of a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

A showing that the active ingredient in the proposed generic drug reaches the site of drug action at a rate and to an extent not significantly different from that of the RLD, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the RLD. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) between a proposed generic drug and the RLD have an impact on the rate and extent to which the active ingredient becomes available at the site of action.

D. Bioequivalence Study Design

1. General Principles of Bioequivalence

Section 320.24(b) of FDA's regulations (21 CFR 320.24(b)) describes the Agency's preferred bioequivalence methods. They include, in general descending order of accuracy, sensitivity, and reproducibility: (1) in vivo PK studies in whole blood, plasma, serum, or other appropriate

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[14] An RLD is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (21 CFR 314.3(b)). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as the Orange Book, available at http://www.accessdata.fda.gov/scripts/cder/ob/.

[15] Section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act. See also § 314.94(a) (21 CFR 314.94(a)).

[16] See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring "information to show that the new drug is bioequivalent to the listed drug"); § 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the RLD); and 21 CFR 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the RLD referred to in the ANDA).

[17] See also § 314.3(b) and § 320.23(b) (21 CFR 320.23(b)).

biological fluid, or an in vitro test that has been correlated with and is predictive of in vivo bioavailability data; (2) in vivo studies in which urinary excretion of the active moiety, and when appropriate, its active metabolite(s), are measured; (3) in vivo PD effect studies; (4) clinical endpoint studies, and (5) other in vitro studies.[18] In addition, § 320.24(b)(6) states that FDA has the flexibility to accept "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence."

For systemically acting drug products, the rate and extent of systemic absorption of the drug is usually the most sensitive, accurate, and reliable indicator of the rate and extent to which the active ingredient becomes available at the site of drug action. The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption generally rests on a comparison of drug and/or metabolite concentrations in an accessible biological fluid, such as blood, after administration of a single dose or multiple doses of each drug product to healthy volunteers.[19]

For most systemically acting drugs in solid oral dosage forms, FDA recommends conducting a two-period, two-sequence, two-treatment, single-dose crossover study in healthy subjects. In this design, each study subject receives each treatment (i.e., the Test drug and the Reference drug) in random order.[20] Single oral doses of the Test and Reference drugs are administered, and each drug's concentration in the blood or other biological fluid is measured over time. To evaluate the rate and extent of Test drug absorption, the measured plasma concentrations for each subject should be plotted graphically against time of measurement. The graph depicts the plasma sampling time on the horizontal (*x*) axis and corresponding plasma drug concentration on the vertical (*y*) axis. Relevant PK parameters calculated from these data include the area under the plasma concentration versus time curve (AUC), AUC calculated to the last measured concentration time (AUC_{0-t}), and AUC extrapolated to infinity (AUC_{∞}). These parameters represent the extent of absorption (i.e., how much of the drug in the given dose was absorbed). Another relevant PK parameter is the maximum or peak drug concentration (C_{max}), which is used to reflect the rate of absorption.[21] C_{max} and the time at which C_{max} occurs (T_{max}) reflect the rate of absorption. However, typically only C_{max} is statistically evaluated to determine bioequivalence between the Test and Reference drug products.

These PK parameters are analyzed statistically because of the variability inherent in human subjects. This variability means that if a subject receives the *same* drug product on two different occasions, the resulting plasma concentrations will not be exactly the same on each occasion. This inherent variability means that the interpretation of a study of two different products is complex, because the concentrations could differ to some extent even if the products have identical bioavailability. Thus, if a single individual takes two *different* products on separate occasions, and there are some differences in the PK parameters (e.g., AUC and C_{max}), it is not immediately clear whether this difference is the result of a true difference between the products,

[18] See § 320.24(b) (21 CFR 320.24(b)). Whereas a PK study measures the rate and the extent to which the drug is delivered to biological fluids (generally the bloodstream), a PD study measures effects associated with the delivery of the active ingredient to the site of action.

[19] See section 505(j)(8)(B) of the FD&C Act; see also 2021 PK Endpoints Draft Guidance.

[20] 2021 PK Endpoints Draft Guidance at 3–4.

[21] Id. at 6.

the result of differences within the individual, or the result of the inherent variability of the measurements. Thus, FDA recommends that ANDA applicants use statistical analyses to evaluate the similarity or differences in pharmacokinetics that result from the two product formulations. The appropriate statistical approach recommended by the Agency may vary based on the characteristics of the drug product.

When considering the results from bioequivalence studies, it is important to understand what statistical tests are used and how FDA uses the results of these statistical tests to determine whether two products are bioequivalent. To understand the statistical tests for bioequivalence, one must first understand the relevant statistical terms, particularly the definitions of *mean* and *confidence interval*. The statistical term *mean* is frequently used in describing bioequivalence study results. Generally, the mean in this context refers to the average of all the values observed in the small group of study subjects.

A *confidence interval* is used to address the factor of variability. The confidence interval describes where the results can be expected to lie based on the mean values and the variability seen. The confidence interval's width specifies the location within which the true mean value can be expected to lie.

In analyzing in vivo bioequivalence studies, FDA generally uses a 90 percent confidence interval. For example, the ratio of the mean AUC values for a small study (reflecting the average difference between the Test and Reference products for all of the study subjects) could be 99 percent. Furthermore, a statistical analysis of the data could determine that the 90 percent confidence interval for this small study is a range of 94 to 112 percent for the ratio of PK values. The 90 percent confidence interval means, generally, if a similar study was carried out many times, and the same procedure was used to construct this interval, 90% of the resulting intervals would contain the true ratio of the AUC of the two products. If the study had used a greater number of subjects to more accurately reflect the general population's results, then the 90 percent confidence interval would likely be smaller (i.e., a smaller range of the possible pharmacokinetic values in the general population, such as 96 to 110 percent).

Generally, to establish bioequivalence, the calculated 90 percent confidence interval for the ratio of the geometric mean for AUC and C_{max} values of the generic Test product and the Reference product should fall entirely within an 80 percent to 125 percent acceptance interval (0.8 - 1.25).[22] The use of an 80 to 125 percent acceptance interval to compare two products with the same active ingredient, dosage form, route of administration, and strength is a scientific judgment about the best statistical practices for bioequivalence determinations and reflects decades of scientific data on the variability of product characteristics within and between batches, as well as biological variability in patients.

2. Product Specific Guidance for Bioequivalence Study Recommendation

The choice of appropriate bioequivalence study design is based on the ability of the study to compare the drug delivered by the two products at the particular site of action of the drug, and

[22] See the draft guidance for industry *Statistical Approaches to Establishing Bioequivalence* (December 2022). To pass a confidence interval limit of 80 to 125 percent, the value would be at least 80.00 percent and not more than 125.00 percent. See also 2021 PK Endpoints Draft Guidance.

Congress assigned this decision to FDA. FDA has considerable discretion in determining how a bioequivalence requirement is met, and this discretion extends to FDA's determination of how a bioequivalence requirement should be met for a given product or class of products, as long as the determination is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion."[23]

FDA publishes product-specific guidances describing the Agency's current thinking and expectations regarding the development of generic drug products that are therapeutically equivalent to specific RLDs.[24] While FDA publishes product-specific recommendations in guidance documents, these guidance documents do not establish legally enforceable responsibilities. Instead, guidances, once finalized, describe the Agency's current thinking on a topic and should be viewed as recommendations, unless specific regulatory or statutory requirements are cited.[25] Applicants may use an alternate approach if the approach satisfies the applicable statutory and regulatory requirements for establishing bioequivalence. Applicants may confer with the Agency on use of such alternative approaches.

In 2009, FDA issued a final guidance on tacrolimus oral capsules (2009 PSG).[26] In the 2009 PSG, FDA's recommendations include a fasting and fed in vivo study for tacrolimus oral capsules, with each study performed as a single-dose, two-treatment, two-period, crossover in vivo study in healthy males and nonpregnant females from the general population. The recommendations further provided for conducting comparative dissolution testing on 12 dosage units of all strengths of the Test and Reference drug products.

In 2011, the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology recommended the use of a two-treatment, four-period, fully replicated crossover design with a RSABE approach and narrower assayed potency standards for NTI drugs.[27] As part of its efforts to implement the advisory committee's recommendation, FDA issued a revised draft guidance in December 2012 (2012 Draft PSG) addressing bioequivalence study recommendations for tacrolimus oral capsules.

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[23] *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 865 (D.D.C. 1994) (quoting *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 651 (D.D.C. 1992), *vacated as moot*, 955 F.2d 1103, 1106 (D.C. Cir. 1993)). See also *Fisons*, 860 F. Supp. at 866–67 ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion."); *Schering Corp. v. FDA*, 51 F.3d 390, 397–400 (3d Cir. 1995).

[24] See the Product-Specific Guidances for Generic Drug Development web page, *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[25] FDA's process for making product-specific bioequivalence guidance available to the public is explained in the guidance for industry *Bioequivalence Recommendations for Specific Products* (June 2010).

[26] See the *Federal Register* document published Dec. 1, 2009 (74 FR 62793). FDA published Draft [Product-Specific] Guidance[s] on Tacrolimus [Oral Capsule] in July 2006 and May 2007. The 2009 PSG finalized the previous draft recommendations.

[27] See the CDER Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (July 26, 2011), Summary Minutes, https://wayback.archive-it.org/7993/20170404155002/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM272111.pdf, and Briefing Information, https://wayback.archive-it.org/7993/20170405230006/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM263465.pdf.

In the 2012 Draft PSG, FDA's recommendations include a fasting and fed in vivo study for tacrolimus oral capsules, with each study performed as a single-dose, four-way, fully replicated crossover in vivo study in healthy males and nonpregnant females from the general population. In a four-way, fully replicate study design, each subject receives the same dose of the Test product (i.e., proposed generic drug product) and Reference product (e.g., the reference standard) twice over the course of the study. FDA considers the default (baseline) bioequivalence limits for NTI drugs to be 90.00% to 111.11% and these limits are scaled based on the within-subject variability of the Reference product: when the Reference variability is <10%, the implied bioequivalence limits on the ratio of geometric means will be narrower than 90.00% to 111.11%; conversely, when the reference variability is >10%, the implied bioequivalence limits will be wider than 90.00% to 111.11%—but always capped at the unscaled average bioequivalence limits of 80.00% to 125.00%.[28]

The 2012 Draft PSG also recommends a statistical analysis using the RSABE approach for NTI drugs[29] as also detailed by the Agency in the Draft Guidance on Warfarin Sodium[30] and since detailed in the 2021 PK Endpoints Draft Guidance. A fully replicate study design with an RSABE approach for NTI drugs enables the scaling of the acceptance bioequivalence limit to the within-subject variability of the Reference product.[31] For more information on the current recommended statistical analyses, see the 2021 PK Endpoints Draft Guidance, Appendix C.

In addition to scaling, a fully replicate study with the RSABE approach for NTI drugs—unlike a two-way crossover study—also allows for a comparison of the within-subject variability of the Test and Reference drug products.[32] Within-subject variability (also known as "intra-subject variability") refers to whether and by how much PK parameters differed in a given subject between the two periods when administrated the same dose of the Test or Reference drug products. Within-subject variability is of particular importance for NTI drugs because "variations in plasma concentrations may have serious consequences. If an NTI Test drug product has much higher within-subject variability than the reference drug product in a bioequivalence study, the larger variation in blood concentration may result in higher likelihood of serious therapeutic failures and/or adverse reactions."[33] The RSABE approach for NTI drugs

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[28] See FDA, CDER Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (July 26, 2011) (2011 CDER Advisory Committee), Briefing Information, available at https://wayback.archiveit.org/7993/20170114020315/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM263465.pdf, at 13; see also FDA BIOEQUIVALENCE STANDARDS, at 202; LX Yu, et al., 2015, Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs at 289–290.

[29] Other aspects of the 2012 Draft PSG, e.g., study dose, study population, analytes to measure, and in vitro release recommendations remain the same as in the 2009 PSG.

[30] Draft Guidance on Warfarin Sodium (Dec. 2012), https://www.accessdata.fda.gov%2Fdrugsatfda_docs%2Fpsg%2FWarfarin_Sodium_tab_09218_RC12-12.pdf.

[31] See LX Yu, et al., 2015, Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs at 288; FDA BIOEQUIVALENCE STANDARDS at 202; see also, e.g., 2012 Warfarin Draft PSG at 2; see generally FDA BIOEQUIVALENCE STANDARDS at 14, 191–216.

[32] See, e.g., 2012 Warfarin Draft PSG at 2 (explaining basis for fully replicate study on NTI drug).

[33] FDA BIOEQUIVALENCE STANDARDS, at 203; see also 2011 CDER Advisory Committee Briefing Information, at 13 ("For NTI drugs, small changes in the dose could cause serious or life-threatening adverse results.").

tightens bioequivalence limits and is designed to prevent the possibility of approving a generic Test product with a large mean difference from its Reference drug product.[34]

As with other FDA guidances containing product specific recommendations, the 2012 Draft PSG is not binding.[35] Regulated parties can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.[36]

E. Therapeutic Equivalence

1. General Discussion of Therapeutic Equivalence

Drug products that meet the approval requirements under section 505(j) of the FD&C Act and are both bioequivalent and pharmaceutically equivalent[37] to the RLD are considered by FDA to be therapeutically equivalent to the RLD. Therapeutically equivalent drugs generally may be substituted for each other with the expectation that the substituted product will produce the same clinical effect and safety profile when used according to the labeling.[38]

Drug products are considered therapeutically equivalent only if they are pharmaceutical equivalents for which bioequivalence has been demonstrated and can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[39] 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; (3) they are bioequivalent in that they do not present a known or potential bioequivalence problem and they meet an acceptable in vitro standard, or if they do present a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with current good manufacturing practices (CGMP) regulations.[40] An AB therapeutic equivalence code (TE code) generally means a multisource drug product is considered to be therapeutically equivalent to the RLD because the drug product has the identical active ingredients(s), dosage form, route(s) of administration, and strength and has submitted adequate data and information demonstrating bioequivalence.[41] A BX code means that a drug product is not considered

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[34] FDA BIOEQUIVALENCE STANDARDS, at 15, 204.

[35] See § 10.115(d) (21 CFR 10.115(d)) ("Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA").

[36] See § 10.115(d)(2).

[37] Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; 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. § 314.3(b); the *Orange Book*, Preface, at vii.

[38] See the *Orange Book*, Preface, at vii.

[39] § 314.3(b).

[40] *Orange Book*, Preface, at vii; see also § 314.3(b).

[41] See *Orange Book*, Preface, at xv.

therapeutically equivalent to its RLD because there are insufficient data to determine therapeutic equivalence.[42]

2. Approved ANDAs for Tacrolimus Oral Capsules

FDA previously found six ANDAs for tacrolimus oral capsule drug products approved before December 2012 to be therapeutically equivalent to Prograf (NDA 050708).[43] These drug products, with the exception of ANDA 090402,[44] will maintain a TE code of AB in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the Orange Book). As previously mentioned and further discussed below, FDA will be changing the TE code of ANDA 091195 from an AB to a BX.

II. DISCUSSION

In the Petition, you state that as the sponsor of ANDA 206651, which was approved on November 30, 2017, you have "an interest in ensuring that all generic tacrolimus oral capsule drug product sponsors adhere to the same NTI drug bioequivalence testing standards that [Belcher Pharmaceuticals] followed."[45] Specifically, you request the Agency to require all approved ANDAs for tacrolimus oral capsules approved before December 2012 to retest their products in accordance with the recommendations in the 2012 Draft PSG to demonstrate bioequivalence, and if these sponsors do not retest their ANDAs or if the results of retesting demonstrate that the ANDA is not bioequivalent, you request that those pre-December 2012 ANDAs have their TE code changed from an AB to a BX.[46]

Based on the most relevant information available to the Agency, we deny your request to require sponsors of ANDAs for tacrolimus oral capsules approved before December 2012 to demonstrate bioequivalence according to the recommendations in the 2012 Draft PSG. We also deny your request to change the TE code of five of the six ANDAs for tacrolimus oral capsules approved before December 2012 if the ANDA holders do not test their products according to the 2012 Draft PSG. An FDA-contracted study conducted using the four-way, fully-replicated crossover design for NTI drugs recommended in the 2012 Draft PSG found that bioequivalence was not demonstrated between a tacrolimus capsule product approved under ANDA 091195 and its RLD. The Agency is changing the TE code of ANDA 091195 from an AB to a BX and grants that

[42] Id. at xxi ("The code BX is assigned to specific drug products for which the data that have been reviewed by the Agency are insufficient to determine therapeutic equivalence. .....[Such] drug products are presumed to be therapeutically inequivalent until the Agency has determined that there is adequate information to make a full evaluation of therapeutic equivalence.").

[43] ANDA 065461 approved on Aug. 10, 2009; ANDA 090509 approved on May 12, 2010; ANDA 090402 approved on July 1, 2010; ANDA 090596 approved on Sept. 17, 2010; ANDA 091195 approved on Aug. 31, 2011; and ANDA 090802 approved on Sept. 28, 2012.

[44] Drug products placed in the Discontinued Drug Product List of the Orange Book do not have TE Codes. See *Frequently Asked Questions on the Orange Book*, available at https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book; see also the draft guidance for industry *Evaluation of Therapeutic Equivalence* (July 2022) at 8 (When final, this guidance will represent the FDA's current thinking on this topic.). As ANDA 090402 is currently listed in the Discontinued Drug Product List, it does not currently have a TE code.

[45] Petition at 2.

[46] Petition at 1–2.

aspect of your request. We discuss the requests made in the Petition and our response in detail below.

A. Application of 2012 Draft Tacrolimus PSG to ANDAs Approved Before December 2012

In the Petition, you request that the FDA "require the sponsors of tacrolimus oral capsule ANDAs which were approved prior to December 2012 to test their products according to FDA's [2012 Draft PSG], which requires both fasting and fed bioequivalence studies designed as single-dose, four way, fully-replicated crossover studies in vivo."[47] You state that there have been substantial changes to the Agency's position on bioequivalence testing for NTI drugs for tacrolimus oral capsule products and that the Agency changed its study design recommendation from a single dose, two-treatment, two-period crossover design in vivo in the 2009 PSG to a single dose, four-way, fully-replicated crossover design in vivo in the updated 2012 Draft PSG, which notes that the study should be a fully replicated crossover design in order to scale bioequivalence limits to the variability of the reference product and to compare Test and Reference product within-subject variability.[48] You state that "[t]hese are significant changes in study design that the sponsors of pre-December 2012 products did not have to address" and these products should meet the standards in the 2012 Draft PSG.[49]

As an initial matter, FDA has considerable discretion in determining how a bioequivalence requirement is met,[50] and we generally expect ANDAs approved after the revisions to the product-specific guidance on tacrolimus oral capsules to rely upon data from bioequivalence studies that use a study design and statistical analysis that are consistent with the recommendations in the 2012 Draft PSG[51] or provide an alternative approach to demonstrating bioequivalence. The Agency's authority to make bioequivalence determinations on a case-by-case basis using specific types of data enables FDA to effectuate several long-recognized policies that protect the public health, including: (1) permitting the Agency to utilize the latest scientific advances in approving drug products;[52] (2) protecting the public by ensuring only safe

[47] Petition at 1.

[48] Petition at 5–6.

[49] Id.

[50] *See Schering Corp.*, 51 F.3d at 398; *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 217-218 (D.D.C. Mar. 25, 1996).

[51] As with all of our product-specific bioequivalence guidances, the 2012 Draft PSG is not binding on FDA or ANDA applicants. An ANDA applicant may use an alternative approach to demonstrate bioequivalence if the approach satisfies the requirements of the applicable statutes and regulations. FDA will not refuse to approve an ANDA solely because an applicant uses an acceptable alternative approach to what is recommended in the 2012 Draft PSG.

[52] Bioavailability and Bioequivalence Requirements: Procedures for Establishing a Bioequivalence Requirement, 42 Fed. Reg. 1624, 1629 (Jan. 7, 1977) (in promulgating final bioequivalence regulations, FDA noted that "[a]s with all new regulations relating to an evolving science, the Commissioner reserves the right to consider other factors that may indicate the need to establish a bioequivalence requirement").

and effective generic drugs are approved for marketing;[53] and (3) making more safe and effective generic drugs available.[54]

With respect to pre-December 2012 approved ANDAs for tacrolimus oral capsules that are the subject of your requests in the Petition, FDA made a determination at the time of approval that those ANDAs were bioequivalent and therapeutically equivalent to the RLD. The Agency generally does not expect application holders of approved ANDAs to re-demonstrate bioequivalence according to bioequivalence recommendations revised after approval of that ANDA unless the Agency becomes aware of evidence indicating that the ANDA drug product(s) may not be therapeutically equivalent to the respective RLD or an application-holder proposes to make a change to the approved drug product(s) that necessitates new bioequivalence studies to support approval of the change. Your Petition does not provide evidence indicating that the pre-December 2012 ANDAs are not bioequivalent or therapeutically equivalent to the RLD. Furthermore, based on our review of the evidence available to FDA – with the exception of ANDA 091195, which we discuss below – we are not currently aware of persuasive evidence of bioinequivalence or postmarketing issues regarding safety or efficacy that indicate that the pre-December 2012 ANDAs may not be therapeutically equivalent to the RLD. If FDA finds evidence of a problem regarding therapeutic equivalence in the future, we will evaluate what, if any, action is needed.

B. TE Code Assessment

In the Petition, you suggest that FDA does not have sufficient information to confirm that ANDAs for tacrolimus oral capsules approved prior to December 2012 are therapeutically equivalent to the RLD (NDA 050708), and request FDA to change the TE code of these products from an AB to a BX unless the ANDA holders test their products according to the 2012 Draft PSG. You claim that this action is necessary because FDA made significant testing changes in the 2012 Draft PSG to acknowledge tacrolimus as an NTI drug product.

1. Pre-December 2012 Approved ANDAs: ANDAs 065461, 090509, 090402, 090596, 090802, and 091195

As noted, your Petition does not provide evidence indicating that ANDAs for tacrolimus oral capsules approved prior to 2012 are not bioequivalent or therapeutically equivalent to the RLD.

Based on our own review of the available evidence, we have not identified any postmarketing issues that would suggest ANDAs 065461, 090509, 090596, and 090802 are not therapeutically equivalent to the RLD or that ANDA 090402 is not bioequivalent to the RLD.[55] In an August

[53] *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 650 (D.D.C. Jan. 16, 1992) (citing one underlying policy of the Hatch-Waxman Amendments as "ensur[ing] the safety of these drugs before they are substituted for their name-brand counterparts").

[54] Id. (purposes of the Hatch-Waxman Amendments are "to make more inexpensive generic drugs available" and "to ensure the safety of these drugs"); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 866 (D.D.C. May 5, 1994) (bioequivalence waiver provision "comports with the structure and broader policy objectives of the Hatch-Waxman Act" including making safe and affordable generic drugs available).

[55] As ANDA090402 is currently listed in the Discontinued Drug Product List, it does not currently have a TE code. See note 44.

2011 review of the formulation, dissolution, bioequivalence studies, and safety profiles of then-approved and then-pending ANDAs for tacrolimus oral capsules, and in a February 2012 review of the dissolution data and specifications of then-approved and then-pending ANDAs for tacrolimus oral capsules, FDA did not identify any bioequivalence problems with ANDAs 065461, 090402, 090509, 090596, 090802, or 091195. From October 2019 through January 2020, FDA conducted an independent-focused FDA Adverse Event Reporting System (FAERS) analyses relating to tacrolimus oral capsule products. In a high-level analysis, FDA did not identify a disproportionate number of reports associated with any single manufacturer with any of 25 product quality-related "preferred terms" relating to therapeutic effect or drug toxicity. In a case-level analysis, FDA did not identify any new safety concerns relating to product substitution when switching between the RLD and ANDAs 065461, 090509, 090596, 090802, or 091195, or when switching between ANDAs 065461, 090509, 090596, 090802, and 091195.

Additionally, based on studies known to the Agency conducted from 2013 to the present, FDA has not identified persuasive evidence indicating bioequivalence problems with marketed ANDAs approved prior to December 2012 other than Accord's ANDA 091195—i.e., ANDAs 065461, 090509, 090596, and 090802.

Although FDA agrees that your reference to methylphenidate hydrochloride (ANDA 202608 and ANDA 091695)[56] is an example of FDA exercising its authority to change (lower) a TE code of approved ANDA products, to the extent your petition contends that those cases are analogous to all ANDAs for tacrolimus oral capsules approved prior to December 2012, FDA disagrees. For methylphenidate hydrochloride, FDA received numerous FAERS reports about insufficient therapeutic effect of the drug products approved under two ANDAs, which prompted the Agency to initiate a Tracked Safety Issue (TSI) and conduct an extensive multi-disciplinary review. The TSI determined that the ANDAs may not be bioequivalent or therapeutically equivalent to the RLD and FDA changed the TE codes for the drug products approved under ANDA 202608 and ANDA 091695 from an AB to a BX. In contrast, here, FDA's review of the FAERS reports related to generic tacrolimus oral capsule products did not identify new safety concerns related to product substitution or sufficient information to suggest therapeutic inequivalence with respect to a specific generic manufacturer of tacrolimus oral capsules, nor is FDA aware of other persuasive information raising a significant question regarding the therapeutic equivalence of ANDAs 065461, 090509, 090596, or 090802, or the bioequivalence of ANDA 090402.

Therefore, at this time, we decline to change the TE codes for drug products approved under ANDAs 065461, 090509, 090596, or 090802.[57] FDA considers ANDAs 065461, 090509,

[56] Petition at 7.

[57] As stated above (see notes 44 and 55), because ANDA 090402 is currently listed in the Discontinued Drug Product List of the Orange Book, it does not currently have a TE code.

090596, and 090802 bioequivalent to and therapeutically equivalent to the equivalent strengths of the RLD, Prograf, NDA 050708.[58]

2. Accord Healthcare's ANDA 091195

As previously mentioned, drug products are considered therapeutically equivalent only if they are pharmaceutical equivalents for which bioequivalence has been demonstrated and can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[59] As detailed below, FDA has evidence that Accord Healthcare's ANDA 091195 may not be bioequivalent to the RLD and that therefore provides reason to believe that ANDA 091195 may not be therapeutically equivalent to the RLD.

Since the launch of generic tacrolimus oral capsules, FDA has closely monitored safety data and investigated questions from the transplant community on the substitution of generic versions of tacrolimus oral capsules for the RLD. Informed in part by these considerations, FDA conducted internal Agency reviews and explored the stability, pharmacokinetics, and bioequivalence of generic tacrolimus oral capsules through FDA-funded studies. Certain studies regarding tacrolimus[60] raised some concerns about the bioequivalence of Accord Healthcare's ANDA 091195 to the RLD and led us to further investigate.

In March 2020, to address the outstanding concerns from the previous studies, the Agency awarded a contract to BioPharma Services USA (BioPharma) to conduct a new study. The study, titled *A Single Dose, Open-Label, Randomized, Four-Way Crossover, Fully Replicate, Bioequivalence Study of Generic Tacrolimus Capsules and Prograf Capsules in Healthy Volunteers Under Fasting Conditions*,[61] followed the 2012 Draft PSG's recommendations to use a four-way, fully-replicated crossover design to scale bioequivalence limits to the variability of the Reference product and compare the within-subject variability of the Test and Reference products. The study tested Prograf (tacrolimus) 1 mg oral capsule (Reference) and Accord Healthcare's 1 mg tacrolimus oral capsule (Test). Data from 62 subjects who provided sufficient samples for PK parameter estimation for at least two study periods and were included in the PK/statistical analysis. Bioequivalence was assessed using the unscaled average bioequivalence approach and the RSABE approach for NTI drugs in accordance with the recommendations in the 2012 Draft PSG and the 2021 PK Endpoints Draft Guidance.

The data from this study shows that the tested Accord Healthcare's ANDA 091195 product had a higher rate of absorption (C_{max}) compared to the RLD, Prograf. The study found that the Accord Healthcare's product exceeded the acceptable criterion for C_{max} despite an acceptable AUC. In the BioPharma study, bioequivalence between the Prograf 1 mg capsule and Accord Healthcare's ANDA 091195 1 mg capsule was not demonstrated in healthy male and female volunteers under fasting conditions, using either the unscaled average bioequivalence approach or the RSABE

[58] Should FDA find evidence in the future of a problem regarding therapeutic equivalence, we will evaluate what, if any, action is needed for that product.
[59] § 314.3(b).
[60] See Clinical Trials.gov, https://clinicaltrials.gov/study/NCT02014103, https://clinicaltrials.gov/study/NCT02341274.
[61] See ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT04725682.

approach for NTI drugs. FDA has identified no study conduct or data concerns with the FDA-contracted BioPharma study, and FDA has confirmed the study results.

As a result of the findings of the FDA-contracted BioPharma study and the Agency's review of other available evidence, we no longer have sufficient data to determine that the drug products approved under ANDA 091195 are bioequivalent and therapeutically equivalent to the respective strengths of the RLD. Consequently, FDA is changing the TE codes for all drug products (i.e., the 0.5 mg, 1 mg, and 5 mg strengths) approved under ANDA 091195 from an AB to a BX.

III. CONCLUSION

For the reasons described in this response, the Petition is granted in part with respect to changing the TE codes of the drug products approved under ANDA 091195 from an AB to a BX based on new evidence available to the Agency that demonstrates that ANDA 091195 may not be therapeutically equivalent to the RLD. The Petition is denied in part with respect to the remaining tacrolimus oral capsule ANDAs approved prior to December 2012.

Sincerely,

On behalf of Dr. Cavazzoni

Jacqueline A. Corrigan-curay -S

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