U.S. FOOD & DRUG ADMINISTRATION

DEC 18 2019

Chad A. Landmon
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950 F St. NW
Washington, DC 20004

Re: Docket No. FDA-2019-P-3545

Dear Mr. Landmon:

This letter responds to your citizen petition submitted on behalf of Zydus Pharmaceuticals (USA) Inc. (Zydus) and received on July 24, 2019 (Petition). The Petition requests that the Food and Drug Administration (FDA or the Agency) take the following actions:

(1) Require pending and approved abbreviated new drug applications (ANDAs) for carbamazepine extended release tablets to submit a passing bioequivalence study with a fully replicated crossover design that has scaled bioequivalence limits to the variability of the reference product and compared the within-subject variability of test and reference products, in compliance with the March 2015 Draft Guidance on Carbamazepine (March 2015 Carbamazepine Draft Guidance);[1]

(2) Downgrade the therapeutic equivalence code of any approved ANDA currently listed as "AB" in the *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) to "BX" unless and until such a study has been provided to FDA;

(3) Assess whether the size and shape differences between approved ANDA products and the RLD pose patient safety and compliance issues; and

(4) Downgrade the therapeutic equivalence code of any approved ANDA currently listed as "AB" in the Orange Book to "BX" if FDA concludes that the differences pose safety and compliance issues.

(Petition at 2).

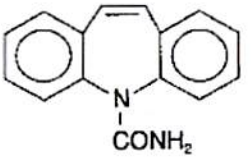
[1] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ default.htm. These draft guidances, when finalized, will represent FDA's current thinking on these topics.

We have carefully considered the Petition.[2] For the reasons described below, your Petition is denied.

I. BACKGROUND

A. Carbamazepine Extended-Release Tablets

On March 25, 1996, FDA approved new drug application (NDA) 020234 for Tegretol-XR (carbamazepine) extended-release tablets, 100 milligrams (mg), 200 mg, and 400 mg. Tegretol-XR is indicated for use as an anticonvulsant drug and for the treatment of pain associated with true trigeminal neuralgia.[3] The Prescribing Information for Tegretol-XR provides that the chemical name of carbamazepine is *5H*-dibenz[*b,f*]azepine-5-carboxamide, and that its structural formula is:



On March 31, 2009, FDA approved ANDA 078115 held by Taro Pharmaceuticals USA, Inc. (Taro) for carbamazepine extended-release tablets, 100 mg, 200 mg, and 400 mg (Taro's carbamazepine product). Taro submitted bioequivalence studies designed as single-dose, randomized, two-treatment, two-sequence, crossover studies in healthy adult subjects.[4]

On February 7, 2019, FDA approved ANDA 205571 held by Zydus for carbamazepine extended-release tablets, 100 mg, 200 mg, and 400 mg. Zydus submitted bioequivalence studies designed as single-dose, two-treatment, two-sequence, four-period, fully replicated crossover studies in healthy adult subjects.

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[2] We received on December 12, 2019 a comment submitted by Lassman Law+Policy on behalf of Teva Pharmaceutical Industries Ltd. The comment did not opine on the specific action requested by the petitioner, but rather raised more general concerns. We are not addressing those general issues in this response.

[3] See Tegretol-XR Prescribing Information, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/016608s115_018281_s058_018927s055_020234_s047.pdf.

[4] See Center for Drug Evaluation and Research, Bioequivalence Reviews, Application Number 078115, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/078115Orig1s000BioeqR.pdf.

B. Narrow Therapeutic Index (NTI) Drugs[5]

Carbamazepine is considered to be a narrow therapeutic index drug. The specific term *narrow therapeutic index* is not defined in FDA regulations. However, under 21 CFR 320.33, a *narrow therapeutic ratio* may be exhibited by evidence that:

(1) There is less than a two-fold difference in median 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 at FDA advisory committee meetings held in 2010 and 2011.[6] 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.[7]

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: (1) there is little separation between therapeutic and toxic doses (or the associated blood/plasma

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[5] Other terms have been used synonymously with *narrow therapeutic index*. These terms include *narrow therapeutic range*, *narrow therapeutic ratio*, *narrow therapeutic window*, and *critical-dose drugs*.

[6] U.S. Food and Drug Administration, April 13, 2010, Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee: Topic 1, revising the Bioequivalence approaches for critical-dose drugs, https://wayback.archive-it.org/7993/20170403224116/https:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm201700.htm (2010) (2010 Advisory Committee); U.S. Food and Drug Administration, July 26, 2011, Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee: bioequivalence issues and quality standards relative to narrow therapeutic index (NTI) drug products, https://wayback.archive-it.org/7993/20170403224114/https:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm240583.htm (2011) (2011 Advisory Committee).

[7] See FDA, Fiscal Year 2015 Regulatory Science Research Report: Narrow Therapeutic Index Drugs, available at https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2015-regulatory-science-research-report-narrow-therapeutic-index-drugs; see also 2011 Advisory Committee meeting. https://wayback.archive-it.org/7993/20170403224114/https:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm240583.htm (2011); L.X. Yu et al., "Novel bioequivalence approach for narrow therapeutic index drugs," *Clin Pharmacol Ther*, 2015, 97(3):286-291.

concentrations), (2) sub-therapeutic concentrations may lead to serious therapeutic failure, (3) patients are subject to therapeutic monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures, (4) 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 (5) in clinical practice, doses are often adjusted in very small increments (less than 20 percent).[8] The assessment of whether a drug has a narrow therapeutic index generally is reflected in the applicable product-specific recommendation for that drug product.[9]

For several NTI drugs, FDA has recommended in draft guidances that one acceptable method for establishing the bioequivalence is a four-way, fully-replicated crossover study design that permits both variability comparison and mean comparison. Details on how to implement the reference-scaled average bioequivalence approach are described in these draft guidances containing product specific recommendations for certain NTI drugs.[10]

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.[11] To obtain approval, an ANDA applicant is not required to provide independent 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.[12] The ANDA applicant must identify the listed drug on which

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[8] See L.X. Yu et al.; see also draft guidance containing product specific recommendations for *Warfarin Sodium* (Dec. 2012) (warfarin sodium guidance), draft guidance containing product specific recommendations for *Digoxin* (Aug 2017) (2017 digoxin guidance).

[9] See draft guidance, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) ("FDA recommends that applicants consult this general guidance in conjunction with any relevant product-specific guidance when considering the appropriate [bioequivalence] study for a proposed product.) See e.g., warfarin sodium guidance; 2017 digoxin guidance. Guidances containing product specific recommendations for generic drug development can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[10] See, e.g., draft guidances containing product-specific recommendations for tacrolimus, warfarin sodium, carbamazepine, phenytoin sodium, levothyroxine sodium, and sirolimus. See also guidance for industry, *Statistical Approaches to Establishing Bioequivalence* (Jan. 2001); see also L.X. Yu et al. at 288 *citing* Westlake, W.J. Bioavailability and Bioequivalence of Pharmaceutical Formulations. *Pharmaceutical Statistics for Drug Development* (Marcell Dekker, New York, 1988) at 329-352.

[11] 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.

[12] 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*

it seeks to rely, and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.[13]

An ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the RLD.[14] 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 . . . .[15]

In 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,

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Products with Therapeutic Equivalence Evaluations, generally known as the Orange Book, available at http://www.accessdata.fda.gov/scripts/cder/ob/.

[13] 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)).

[14] 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); § 314.127(a)(6)(i) (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).

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

serum, or other appropriate 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.[16] 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.[17]

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.[18] 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. The relevant pharmacokinetic 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). The other relevant pharmacokinetic parameter is the maximum or peak drug concentration (C_{max}), which is used to reflect the rate of absorption.[19] 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.

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[16] See § 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.

[17] See Section 505(j)(8)(B) of the FD&C Act; FDA draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (Dec. 2013).

[18] FDA draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) at 3.

[19] See FDA draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) at 5, 20.

These pharmacokinetic 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 pharmacokinetic 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, 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 RLD should fall entirely within an 80 percent to 125 percent acceptance interval (0.8

- 1.25).[20] 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 Recommendations

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 Congress assigned this decision to FDA. It is well accepted that 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."[21]

FDA publishes product-specific recommendations describing the Agency's current thinking and expectations regarding the development of generic drug products that are therapeutically equivalent to specific RLDs.[22] 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.[23] Applicants may confer with the Agency on use of alternative approaches for establishing bioequivalence.

In February 2008, FDA issued draft guidance on Carbamazepine (February 2008 Carbamazepine Draft Guidance). In the February 2008 Carbamazepine Draft Guidance, FDA's recommendations include a fasting and a fed study for carbamazepine extended

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[20] See guidance for industry *Statistical Approaches to Establishing Bioequivalence* (Jan. 2001). 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 draft guidance for industry, *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application* (Dec. 2013).

[21] *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).

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

[23] Our 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).

release tablets, 400 mg,[24] with each study performed as a single-dose, two-treatment, two-period crossover in vivo study. The recommendations further provided for conducting comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the method outlined by USP-NF.[25] In addition, dissolution profiles in at least three pH dissolution media were recommended to be generated for each of the test and reference products for modified-release products.

In 2011, the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology recommended the use of a reference scaled average bioequivalence approach and narrower assayed potency standards for NTI drugs.[26] As part of its efforts to implement the advisory committee's recommendation, FDA issued revised draft guidance in March 2015 addressing bioequivalence study recommendations for carbamazepine extended release tablets.

In the March 2015 Carbamazepine Draft Guidance, FDA's recommendations include a fasting and a fed study for carbamazepine extended release tablets, 400 mg,[27] with each study performed as a single-dose, two-treatment, two-sequence, four-period, fully replicated crossover in vivo study and statistical analysis of the data generated by this study using the reference-scaled average bioequivalence approach for NTI drugs detailed by the Agency in a Draft Guidance on Warfarin Sodium.[28] Other aspects of the March 2015 Draft Carbamazepine Guidance, e.g., study dose, study population, analytes to measure, and in vitro release studies recommendations remain the same.

The study design and statistical analysis recommended in the March 2015 Draft Carbamazepine Guidance allows for scaling bioequivalence limits to the within-subject variability of the reference product and comparing test and reference products' within-subject variability in PK parameters. Because both the test and reference NTI products are given twice in each subject, the four-way crossover, fully-replicated study design recommended in the March 2015 Carbamazepine Draft Guidance enables the determination of the variability in PK parameters in the same individual, i.e., "within-

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[24] The February 2008 Carbamazepine Draft Guidance states that in vivo BE studies for the 100 mg and 200 mg strengths may be waived based on (i) acceptable BE studies for the 400 mg strength, (ii) proportional similarity of the formulations, and (iii) acceptable in vitro dissolution testing of all strengths.

[25] Product-specific dissolution methods are listed at http://www.accessdata.fda.gov/scripts/cder/dissolution/.

[26] See 2011 Advisory Committee meeting, https://wayback.archive-it.org/7993/20170403224114/https:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm240583.htm (2011).

[27] The March 2015 Carbamazepine Draft Guidance states that in vivo BE studies for the 100 mg and 200 mg strengths may not be needed based on (i) acceptable BE studies for the 400 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

[28] Draft Guidance on Warfarin Sodium (Dec 2012), https://www.accessdata.fda.gov/drugsatfda_docs/psg/Warfarin_Sodium_tab_09218_RC12-12.pdf

subject" variability, when administered the same dose of test or reference NTI drug product. By applying the reference-scaled average bioequivalence approach, the variability of reference product is accounted for when the means of the PK parameters are compared between test and reference product, i.e., limits are scaled based on the within-subject variability of the reference NTI product. FDA's recommended approach for NTI drugs is to use reference-scaled average bioequivalence limits (capped at the conventional bioequivalence limits of 80 to 125 percent) and to perform variability testing. The four-way, crossover, fully-replicated study design permits the comparison of within-subject variability in the test and reference products to confirm that their variances do not differ significantly.[29] If the generic NTI product has a significantly different within-subject variability than the reference NTI product, the two products would not be considered bioequivalent.

As with other FDA guidances containing product specific recommendations, the March 2015 Draft Carbamazepine Guidance is not binding.[30] Regulated parties can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.[31]

E. Size and Shape of Generic Drug Products

FDA recommends that ANDA applicants design and develop generic drug products with a similar size and shape to the RLD, and we have acknowledged that differences in physical characteristics (e.g., size and shape of the tablet or capsule) may affect patient compliance and acceptability of medication regimens or could lead to medication errors. We believe these patient safety concerns are important, and we have recommended in the *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* Guidance, issued June 2015, that generic drug manufacturers consider physical attributes when they develop quality target product profiles for their generic product candidates.

The recommendations contained in the *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* Guidance do not apply to approved ANDAs that were already on the market at the time of the guidance issuance in June 2015.[32] If a safety issue is reported about a marketed generic drug, we will investigate the issue, and if it is found to be related to the physical characteristics of the product, we may require changes, regardless of when the product was approved.

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[29] L.X. Yu et al., "Novel bioequivalence approach for narrow therapeutic index drugs," *Clin Pharmacol Ther*, 2015, 97(3):286-291.

[30] 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").

[31] See § 10.115(d)(2).

[32] See *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* Guidance (June 2015) at 1.

F. 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[33] 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.[34]

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.[35] 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.[36] An "AB" therapeutic equivalence code (TE code) means a drug product is considered to be therapeutically equivalent to the RLD because the drug product meets necessary bioequivalence requirements.[37] A "BX" code means that a drug product is not considered therapeutically equivalent to an RLD because there are insufficient data to determine therapeutic equivalence.[38]

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[33] 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. 21 CFR 314.3(b); the *Orange Book*, Introduction at p. vii.

[34] See the *Orange Book*, Introduction at p. vii.

[35] 21 CFR 314.3(b).

[36] Orange Book at vii.

[37] See id. at xvi.

[38] 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. . . .").

2. Approved ANDAs for Carbamazepine

FDA previously found Taro's carbamazepine drug product approved under ANDA 078115 and Zydus's carbamazepine drug product approved under ANDA 205571 to be therapeutically equivalent to Tegretol-XR (NDA 020234). These products are currently assigned an "AB" TE code in the Orange Book.

II. DISCUSSION

A. Application of March 2015 Draft Carbamazepine Guidance to Any Pending and Approved ANDAs

In your Petition, you assert that FDA should ensure that any pending and approved ANDAs for carbamazepine extended release tablets comply with the study design requirements set out in the March 2015 Draft Carbamazepine Guidance (Petition at 8). You state that absent a showing of bioequivalence using the "standards" from the March 2015 Carbamazepine Draft Guidance, there is no assurance that the reference listed drug (RLD) and ANDA product are bioequivalent or that they share the same clinical profile (Petition at 8).

To support your argument that that older bioequivalence studies are inadequate, you assert that: (1) older bioequivalence studies that do not comply with the updated parameters set out in the March 2015 Draft Carbamazepine Guidance will not be able to detect clinically significant differences in the PK profiles of the generic product and the RLD (NDA 020234) (Petition at 7); (2) ANDAs approved on the basis of older bioequivalence studies that do not comply with the updated parameters set out in the March 2015 Draft Carbamazepine Guidance could create risks for switching between generic products, if one of those generic products is not therapeutically equivalent to the RLD (Petition at 7); and (3) changes to the bioequivalence methodology for Wellbutrin XL are an example of a case in which FDA determined approved ANDAs were not bioequivalent and required holders of approved ANDAs to conduct additional studies (see Petition at 8). We discuss these arguments below.

As an initial matter, it is well accepted that FDA has considerable discretion in determining how a bioequivalence requirement is met, and we would expect all ANDAs approved after the revision of the March 2015 Draft Carbamazepine Guidance to rely upon data from bioequivalence studies that use a study design and statistical analysis that are consistent with the recommendations in the March 2015 Carbamazepine Draft Guidance or provide an acceptable alternative approach to demonstrating bioequivalence.[39] Additionally, we disagree with your assertion that the March 2015

[39] As with all of our product-specific bioequivalence guidances, the March 2015 Draft Carbamazepine Guidance 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 March 2015 Carbamazepine Draft Guidance.

Draft Carbamazepine Guidance changed the parameters for establishing bioequivalence. The March 2015 Draft Carbamazepine Guidance offers study design and statistical analysis recommendations to assist applicants in generating the evidence needed to meet the bioequivalence requirements of section 505(j)(2)(A)(iv) and (j)(4)(F) of the FD&C Act and FDA's regulations.

With respect to the approved ANDA that is the subject of your concerns in the Petition (Taro's ANDA 078115), FDA made a determination at the time of its approval in 2009 that Taro's carbamazepine product was bioequivalent and therapeutically equivalent to the RLD. The Agency generally does not expect application holders of approved ANDAs to demonstrate bioequivalence according to the recommendations revised after approval of that ANDA, unless the Agency becomes aware of evidence indicating that the product may not be therapeutically equivalent to its RLD. Your Petition does not provide evidence that would cause us to be concerned that Taro's carbamazepine product is not bioequivalent or therapeutically equivalent to the RLD.[40] For instance, your Petition cites to literature questioning the differences between carbamazepine brand name and generic products;[41] however, this literature does not persuade us that Taro's carbamazepine product is not bioequivalent or therapeutically equivalent to the RLD. Furthermore, based on our review, we are not currently aware of postmarketing issues regarding safety or efficacy which may indicate that Taro's carbamazepine product is not 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.

We also disagree with your statement that older bioequivalence studies were not be able to detect clinically significant differences in the PK profiles of the generic product and the RLD (NDA 020234) (Petition at 7). The March 2015 Draft Carbamazepine Guidance contains study design and statistical analysis recommendations for carbamazepine extended-release tablets. FDA has not deviated from its practice of evaluating PK parameters like AUC and C_{max} to determine if an ANDA is bioequivalent to its RLD. Although we believe the March 2015 Draft Carbamazepine Guidance contains the most accurate, sensitive, and reproducible approach for demonstrating bioequivalence for this drug, it does not imply that bioequivalence studies conducted before publication of the March 2015 Draft Carbamazepine Guidance that did not use the same study methodology and statistical analysis could not detect clinically significant differences in the PK profiles of the generic product and the RLD. Rather, such bioequivalence studies (e.g., those using a two-way crossover study) are capable of detecting differences in PK parameters (e.g., AUC and C_{max}) and evaluating the 90% confidence interval of these

[40] Thus, this situation is different from that of methylphenidate, cited in your petition (see Petition at 8 n.34). There, based on an extensive analysis prompted by post-marketing signals that two generic products did not produce the same effects as the reference product, FDA had significant concerns about whether the generic drugs at issue would be found to be bioequivalent if evaluated using the partial AUC criteria set out in the revised guidance for that drug and thus asked that they be retested utilizing the methods and criteria set out in that guidance. Here, FDA does not have reason to believe that the Taro product would fail to be shown to be bioequivalent if it were tested using the methodology recommended in the 2015 guidance.

[41] See Petition at 4; Petition Exhibit D.

geometric mean ratios to be within recommended bioequivalence limits, even though these studies may not reflect our current recommendations for the most accurate, sensitive, and reproducible bioequivalence approach for this drug.

Further, with respect to your assertion that bioequivalence studies that do not apply the recommendations set out in the March 2015 Draft Carbamazepine Guidance could create risks for switching between generic products if one of those products is not therapeutically equivalent to the RLD (Petition at 7), we disagree because we are not aware of evidence that would cause us to be concerned suggesting that ANDA 078115 is not therapeutically equivalent to its RLD.

Lastly, we do not find your analogy to the example of Wellbutrin XL to be compelling, as it is not an appropriate standard of comparison for carbamazepine extended release tablets. In the case of Wellbutrin XL, changes to a product specific guidance were initiated because of postmarketing adverse event reporting and determination of bio-inequivalence of certain ANDAs.[42] In contrast, as it pertains to carbamazepine extended release tablets, we have not noted postmarketing signals indicating that Taro's carbamazepine extended release tablets are not therapeutically equivalent to its RLD.

B. Size and Shape of Generic Drug Product

In the Petition, you assert that there are differences in shape and size between Tegretol-XR (carbamazepine), approved under NDA 020234, and Taro's carbamazepine product, approved under ANDA 078115, and that these differences are significant and pose safety and patient compliance issues (Petition at 1, 6). You state that a comparison of Tegretol-XR with Taro's carbamazepine product demonstrates that Taro's tablet size is significantly larger than that of Tegretol-XR for the 400 mg strength (Petition at 6).

FDA recommends that ANDA applicants design and develop generic drug products with a similar size and shape to the RLD. However, a drug product described in an ANDA may have a size and/or shape that is somewhat different from the RLD. We have recommended in the *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* Guidance, issued June 2015, that generic drug manufacturers consider physical attributes when they develop quality target product profiles for their generic product candidates. The recommendations in the *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* Guidance do not apply to approved ANDAs that were already on the market at the time of the guidance issuance in June 2015.[43] Because Taro's carbamazepine product was approved in 2009 (before the time of the *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* Guidance issuance), the recommendations contained in the guidance do not apply to Taro's carbamazepine

[42] See FDA, *Update: Bupropion Hydrochloride Extended-Release 300 mg Bioequivalence* Studies, *available at* https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/update-bupropion-hydrochloride-extended-release-300-mg-bioequivalence-studies (last accessed Dec. 13, 2019).

[43] See *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* Guidance (June 2015) at 1.

product approved under ANDA 078115. If a safety issue is reported about a marketed generic drug, we will investigate the issue, and if it is found to be related to the physical characteristics of the product, we may require changes, regardless of when the product was approved.

We acknowledge that there is a difference in shape and size between the 400 mg strength of Tegretol-XR, and the 400 mg strength of Taro's carbamazepine product. Tegretol-XR 100 mg, 200 mg and 400 mg tablets are round with a largest dimension of 8 mm, 10 mm and 12 mm, respectively. The 100 mg and 200 mg strengths of Taro's carbamazepine product are also round with a largest dimension of 7 mm and 9 mm, respectively. However, the 400 mg strength of Taro's carbamazepine product tablets is capsule-shaped with a largest dimension of 17 mm.

While there is an easily observable difference in shape and size between the 400 mg strength of Tegretol-XR, and the 400 mg strength Taro's carbamazepine product, we have determined that the difference in size and shape of the generic 400 mg strength alone do not present a risk in the swallowability or safety and patient compliance. In the course of our review of this issue, we searched the Drug Quality Reporting System, and we located no Field Alert Reports or MedWatch Reports related to the size or shape of Taro's carbamazepine product marketed under ANDA 078115. Based on our review and information available to the Agency, a difference in shape and size between the 400 mg strength of Tegretol-XR and the 400 mg strength of Taro's carbamazepine product do not present a risk to public health. Therefore, we do not agree with your assertion that differences in shape and size between Tegretol-XR and Taro's carbamazepine product are significant and pose safety and patient compliance issues.

C. Therapeutic Equivalence Code

In the Petition, you suggest that FDA does not have sufficient information to confirm that Taro's carbamazepine product is therapeutically equivalent for the RLD (NDA 020234) (Petition at 6), and you state that FDA should downgrade the TE code to "BX" of any approved ANDA product to the RLD, until the ANDA applicant has proven bioequivalence according to the March 2015 Draft Carbamazepine Guidance (Petition at 8). You further assert that if FDA agrees that a difference in shape and size between the RLD and Taro's carbamazepine product poses safety and compliance issues, FDA should downgrade the TE code from "AB" to "BX" (see Petition at 2).

While you suggest that FDA should downgrade the TE code of Taro's carbamazepine product, you have not provided evidence that would cause us to be concerned demonstrating that Taro's carbamazepine product is not therapeutically equivalent to the RLD. 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.[44] As previously noted, FDA made a determination at the time of the approval that Taro's carbamazepine product was bioequivalent to the RLD, and your Petition does not provide evidence that causes FDA concern regarding the bioequivalence of the Taro product. Taro's carbamazepine product is therapeutically equivalent to the RLD; that is, they are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[45] Additionally, we disagree with your position that a difference in shape and size between Taro's carbamazepine product and the RLD poses safety and compliance issues, and we do not believe that the TE code for Taro's carbamazepine product should be downgraded on the basis of a difference in shape and size. Therefore, at this time, we decline to change the TE code for Taro's carbamazepine product.

III. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,

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

[44] 21 CFR 314.3(b).

[45] See Id.