DEPARTMENT OF HEALTH & HUMAN SERVICES

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

FEB 19 2016

Christopher J. Worrell, R. Ph.
Chief Executive Officer
Amedra Pharmaceuticals LLC
2 Walnut Grove Drive, Suite 190
Horsham, PA 19044-7707

Re: Docket No. FDA-2013-P-0766

Dear Mr. Worrell:

This letter responds to your citizen petition received on June 27, 2013 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or Agency) refrain from approving any abbreviated new drug application (ANDA) for a generic version of Albenza (albendazole) tablets unless: (1) the proposed generic product is shown to be bioequivalent to both albendazole and its primary active metabolite, albendazole sulfoxide; (2) the proposed generic product has the same labeling as Albenza; and (3) the ANDA includes simulated use testing or other analyses demonstrating that young children can crush or chew and swallow the proposed generic product with a drink of water without posing an unacceptable choking hazard.

We have carefully considered the information submitted in your Petition and the comments submitted to the public docket for the Petition. For the reasons stated below, your Petition is denied.

I. BACKGROUND

A. Albenza

Albenza is an orally administered broad-spectrum anthelmintic indicated for the treatment of parenchymal neurocysticercosis (NCC) and cystic hydatid disease (HD) of the liver, lung, and peritoneum.[1] It is marketed in the United States as both a non-chewable tablet and chewable tablet under new drug applications (NDAs) 020666 and 207844, respectively. FDA approved NDA 020666 for Albenza tablets, 200 milligrams (mg), on June 11, 1996. FDA approved NDA 207844 for Albenza chewable tablets, 200 mg, on June 11, 2015. Both NDAs are held by Amedra Pharmaceuticals LLC.

The active ingredient in Albenza is albendazole. Albendazole is rapidly converted in the liver to the primary metabolite, albendazole sulfoxide, which is further metabolized to albendazole sulfone and other primary oxidative metabolites that have been identified in human urine.[2]

[1] Albenza labeling approved on June 11, 2015, available online at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020666s009lbl.pdf, at 1.

[2] Id. at 10.

Albendazole has been available in Europe and other international markets as a 200 mg tablet (Zentel) for the treatment of intestinal parasites since 1982. A higher strength 400 mg tablet (Eskazole) became available in Europe in 1992 for the treatment of HD. Albendazole tablets manufactured in France and China were supplied to the United States for the treatment of HD and NCC on a compassionate use basis from 1984 until the NDA for Albenza tablets was approved.

B. Abbreviated Approval Pathway for Generic Drugs (ANDAs)

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.[3] 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 reference listed drug (RLD) is safe and effective.[4] 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, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.[5]

An ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the RLD.[6] 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 . . .[7]

A showing that the active ingredient or therapeutic 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

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[3] In 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.

[4] A *reference listed drug*, or *RLD*, is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluation* (the Orange Book).

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

[6] 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"); 21 CFR 314.94(a)(7) (requiring, as part of an ANDA's content and format, information to show that the drug product is bioequivalent to the RLD); 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).

[7] See also 21 CFR 320.1(e) and 320.23(b).

inactive ingredients) and differences in manufacturing 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.

For drug products whose primary mechanism of action depends on systemic absorption, the determination of bioequivalence generally rests on a comparison of parent drug concentrations and, when appropriate, metabolite concentrations in an accessible biologic fluid after administration of a single dose of each drug product to healthy volunteers.[8] When this methodology is not appropriate, FDA may rely on other in vivo and/or in vitro methods to assess bioequivalence.[9] Section 320.24(b) of our regulations describes the preferred bioequivalence methods in what is generally the descending order of accuracy, sensitivity, and reproducibility. The preferred bioequivalence methods include: (1) in vivo pharmacokinetic studies in whole blood, plasma, serum, or other appropriate biological fluid, or in vitro tests that have been correlated with and are predictive of human in vivo bioavailability data; (2) in vivo studies in which urinary excretion of the active moiety and, when appropriate, its active metabolites, are measured; (3) in vivo pharmacodynamic effect studies; (4) clinical endpoint studies; and (5) in vitro studies acceptable to FDA that ensure human in vivo availability.[10] In addition, consistent with section 505(j)(8)(C) of the FD&C Act, section 320.24(b) states that FDA has the authority to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence."[11]

FDA has wide discretion to determine how the bioequivalence requirement should be met for a given product or class of products, so long as its determination is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion."[12] Courts that have considered FDA's bioequivalence determinations have consistently upheld the

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[8] See section 505(j)(8)(B) of the FD&C Act; Letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to Enrique Carrazana, M.D., Acorda Therapeutics, Inc. re: Docket No. FDA-2014-P-2193 (May 14, 2015) at 4; see also the FDA draft guidance for industry, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*, at 3-7, 12 (Draft ANDA BE Studies Guidance), available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page.

[9] See 21 CFR 320.24(a). In the preamble to the final rule setting forth FDA's regulations for ANDAs, we explained that, depending upon the drug, we would determine the appropriate bioequivalence methodology on a case-by-case basis:

> Bioequivalence can be established by pharmacodynamic measurement as well as by in vitro techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence . . . *is determined on a case-by-case basis*, depending on the drug under study.

"Abbreviated New Drug Application Regulations" final rule, 57 FR 17950, 17972 (Apr. 28, 1992) (emphasis added).

[10] 21 CFR 320.24(b).

[11] 21 CFR 320.24(b)(6); see also *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 20 (D.D.C. 2009) (quoting 21 CFR 320.24(b) in upholding FDA's sameness determination of a generic drug product).

[12] *Schering Corp. v. Sullivan,* 782 F. Supp. 645, 651 (D.D.C. 1992); see also *Fisons Corp. v. Shalala,* 860 F. Supp. 859, 866-67 (D.D.C. 1994) ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion.").

Agency's implementation of the FD&C Act's bioequivalence requirements.[13]

C. Requirements Related to Generic Drug (ANDA) Labeling

The FD&C Act requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers."[14] Our regulations contain the following parallel requirement:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 [21 CFR 314.93] or because the drug product and the reference listed drug are produced or distributed by different manufacturers.[15]

Section 314.94(a)(8)(iv) of our regulations sets forth examples of permissible differences in labeling that may result because the generic drug product and the RLD are produced or distributed by different manufacturers. These permissible differences include the following:

> differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the [FD&C A]ct.[16]

Our regulations further provide that to approve an ANDA containing proposed labeling that is different from the labeling approved for the RLD, we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use."[17]

D. Draft Albendazole BE Guidance

FDA issued a draft guidance on bioequivalence testing for albendazole tablets (Draft Albendazole BE Guidance) on December 12, 2012.[18] The draft guidance recommends that ANDA applicants conduct two single-dose, two-way crossover in vivo studies with a 400 mg dose (2 x 200 mg tablets) in normal, healthy males and in nonpregnant females—one under fasting conditions and the other under fed conditions. It further recommends that applicants

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[13] See, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 397-400 (3d Cir. 1995); *Fisons Corp.*, supra note 12, at 867.

[14] Section 505(j)(2)(A)(v) of the FD&C Act; see also section 505(j)(4)(G).

[15] 21 CFR 314.94(a)(8)(iv).

[16] 21 CFR 314.94(a)(8)(iv); see also 21 CFR 314.127(a)(7).

[17] 21 CFR 314.127(a)(7).

[18] See "Draft and Revised Draft Guidances for Industry Describing Product-Specific Bioequivalence Recommendations" 77 FR 74669 (Dec. 17, 2012) (announcing the availability of draft product-specific bioequivalence recommendations for albendazole and several other drug products).

measure both albendazole and its active metabolite, albendazole sulfoxide, in plasma for each study, and that the applicants conduct comparative dissolution testing with the proposed generic drug and the RLD.

The Draft Albendazole BE Guidance advises ANDA applicants that they should demonstrate bioequivalence to albendazole based on the 90% confidence intervals (CIs) for the standard pharmacokinetic measures of area under the plasma concentration-time curve (AUC) and peak drug concentration (C_{max}).[19] Applicants are also advised to submit the AUC and C_{max} data for albendazole sulfoxide as supportive evidence of a comparable therapeutic outcome. If an ANDA applicant can demonstrate that it is not possible to measure albendazole in plasma accurately and reliably, the draft guidance recommends that the applicant demonstrate bioequivalence to the active metabolite, albendazole sulfoxide, using the 90% CI approach.

When final, the Draft Albendazole BE Guidance will describe FDA's current thinking and should be viewed only as recommendations.[20] Neither the Agency nor the public is bound by the recommendations in a draft guidance.[21] Thus, FDA has discretion to approve a generic product supported by bioequivalence data that otherwise meet the statutory and regulatory requirements described above.[22]

II. DISCUSSION

In the Petition, you request that FDA refrain from approving any ANDA for albendazole tablets that references Albenza as the RLD unless: (1) the ANDA includes information showing bioequivalence based on systemic levels of the primary metabolite, albendazole sulfoxide, in addition to the parent drug, albendazole; (2) the proposed generic product has the same labeling as Albenza, including safety information relevant to the drug product's use in the pediatric population; and (3) the ANDA includes simulated use testing or other analyses demonstrating that young children can crush or chew and swallow the proposed generic product with a drink of water without posing an unacceptable choking hazard.[23] We address your claims in support of this request below.

A. Demonstrating Bioequivalence to Albenza

You state that FDA should require ANDA applicants to demonstrate bioequivalence to Albenza based on both the systemic levels of the primary active metabolite, albendazole sulfoxide, and

[19] FDA generally considers products to be bioequivalent when the 90% CIs for the mean AUC and C_{max} measurements of the applicant's proposed generic product (e.g., albendazole) are entirely within 80% to 125% of the mean AUC and C_{max} measurements of the RLD (e.g., Albenza). See the FDA guidance for industry, *Statistical Approaches to Establishing Bioequivalence*, available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[20] See 21 CFR 10.115(d)(3).

[21] See 21 CFR 10.115(d)(1).

[22] See 21 CFR 10.115(d)(2).

[23] Petition at 2.

the parent drug, albendazole.[24] You argue that albendazole sulfoxide is the predominant systemic moiety and that the concentration and systemic activity of albendazole sulfoxide "are critical" to the safety and effectiveness of Albenza.[25] You also argue that it is well established that systemic anthelmintic activity can be attributed to circulating levels of albendazole sulfoxide.[26] Thus, you conclude that albendazole sulfoxide levels in plasma must be measured and be subject to the statistical analysis using the 90% CI approach.[27] You further state that this approach would be consistent with FDA precedent. Specifically, you note that FDA has recommended that bioequivalence be based on both the parent and its active component for at least four drugs: Colazal (balsalazide disodium), Ditropan XL (oxybutynin chloride), Dipentum (olsalazine sodium), and Azulfidine (sulfasalazine).[28] Lastly, you argue, in the alternative, that a generic version of albendazole must undergo comparative clinical endpoint testing in order to establish bioequivalence. We disagree.

As explained above, a proposed generic product must deliver the active ingredient to the site of drug action at a rate and to an extent not significantly different from those of the RLD to be considered bioequivalent to the RLD. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) and manufacturing processes 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.

For systemically acting drug products with active metabolites,[29] we generally recommend that ANDA applicants demonstrate bioequivalence based on a comparison of parent drug concentrations in an accessible biologic fluid.[30] The concentration-time profile of the parent drug reflects how fast the drug product releases the drug substance into the body, whereas the concentration-time profile of a metabolite is more reflective of how the body processes the parent drug *after it has been released* from the drug substance. Consequently, the concentration-time profile of the parent drug is a better indicator of differences in formulation and manufacturing between a proposed generic drug and the RLD.

Based on the above considerations, we have concluded that a statistical comparison of albendazole's concentration-time profile data (i.e., AUC and C_{max}) under the 90% CI approach is the most sensitive, accurate, and reproducible method for demonstrating that a proposed generic albendazole tablet product is bioequivalent to Albenza. As the parent drug, albendazole is

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[24] Id. at 10-12.

[25] Id. at 13.

[26] Id. at 12.

[27] Id. at 13.

[28] Id. at 14.

[29] In this response, the term *active metabolite* refers to a primary metabolite that is formed directly and substantially from the parent compound through presystemic metabolism (i.e., first-pass, gut wall, or gut lumen metabolism) and contributes significantly to the safety and efficacy of the drug product.

[30] See Letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to Kevin Barber, PhD, Watson Laboratories, Inc. re: Docket No. FDA-2013-P-0574 (Oct. 3, 2013) at 5; see also Draft ANDA BE Studies Guidance, supra note 8, at 12.

inherently more sensitive to formulation and manufacturing differences than albendazole sulfoxide. Albendazole is thus an inherently more accurate and reliable indicator of bioequivalence than albendazole sulfoxide. Nonetheless, if an ANDA applicant were to show that it is not possible to measure albendazole accurately or reliably in plasma as you claim,[31] we would consider a statistical comparison of albendazole sulfoxide's concentration-time profile data under the 90% CI approach as the basis for a demonstration of bioequivalence. Otherwise, we recommend that ANDA applicants submit the concentration-time profile data for albendazole sulfoxide as supportive evidence of a comparable therapeutic outcome.

The recommendation that ANDA applicants demonstrate bioequivalence based on a statistical comparison of albendazole's concentration-time profile data, if possible, is consistent with the approach recommended in the bioequivalence guidance for Ditropan XL (oxybutynin chloride).[32] Although the draft bioequivalence guidance for oxybutynin chloride extended-release tablets previously recommended that ANDA applicants demonstrate bioequivalence based on both the parent drug and its active component, the draft guidance was revised in November 2013 to recommend that only the parent drug (oxybutynin) be evaluated for bioequivalence using the 90 % CI approach.

Our recommended bioequivalence approach for albendazole is not inconsistent with the bioequivalence approaches that we have recommended for Colazal (balsalazide disodium), Dipentum (olsalazine sodium), and Azulfidine (sulfasalazine). Contrary to your assertion, Colazal, Dipentum, and Azulfidine are not similarly situated to Albenza.[33] All three products are prodrugs (i.e., drugs where the metabolite is the active moiety) that act *locally* in the gastrointestinal (GI) tract, whereas albendazole tablets act *systemically* to eradicate HD and NCC. This difference in the site of action (i.e., local versus systemic) explains why our bioequivalence guidances for Colazal, Dipentum, and Azulfidine recommend that both the parent drug and the active metabolite be measured and evaluated for bioequivalence under the 90% CI approach. For these specific locally acting prodrugs, it is appropriate to evaluate both the parent and the metabolite compounds to infer the local availability of the active metabolite in the GI tract. Because albendazole acts systemically, it is not necessary to evaluate the local availability of the metabolite.

Finally, the Agency does not agree that comparative clinical endpoint studies would be an appropriate alternative bioequivalence method here.[34] Clinical endpoint studies are less sensitive than pharmacokinetic studies at detecting differences in formulation performance.[35] In particular, comparative clinical endpoint studies measure formulation differences indirectly, rather than directly; may be limited by confounding variables such as different severities of

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[31] According to Amedra, albendazole is readily measurable in plasma. Petition at 11.

[32] Product-specific bioequivalence recommendation guidances are available on FDA's Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm075207.htm.

[33] Petition at 14.

[34] Id.

[35] 21 CFR 320.24(b)(4) (stating that comparative clinical endpoint studies are "the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence").

disease; may have variability in the definition of the instrument used to measure efficacy (i.e., what is being used for the primary endpoint); and may have difficulty in assessing dose response. We acknowledge that comparative clinical endpoint studies are sometimes appropriate,[36] but they are not generally appropriate where, as here, the nature of the drug product permits a more direct evaluation of bioequivalence through pharmacokinetic methods.

B. Labeling of Generic Albendazole Tablet Products

You assert that a generic albendazole drug product must have the same labeling as Albenza, which includes information related to the drug product's safe use in pediatric populations.[37] You note that the PRECAUTIONS section of Albenza's labeling states that "[s]ome people, particularly young children, may experience difficulties swallowing the tablets whole."[38] You also note that the DOSAGE AND ADMINISTRATION and PRECAUTIONS sections include the instruction, "[i]n young children, the tablets should be crushed or chewed and swallowed with a drink of water."[39] You contend that these "pediatric instructions" can neither be carved out of nor otherwise changed in a generic albendazole drug product's labeling under the limited exceptions to the statutory requirement that a generic have "the same" labeling as the RLD.[40] We disagree.

At the outset, we note that the labeling for Albenza has been changed since the Petition was submitted and that it no longer includes the exact pediatric instructions described above. Instead, the DOSAGE AND ADMINISTRATION section of the labeling for both the non-chewable tablet product and the recently approved chewable tablet product now contains the following information for children and other individuals who may have difficulty swallowing tablets whole: "ALBENZA tablets may be crushed or chewed and swallowed with a drink of water. ALBENZA chewable tablets are also available for children and patients who may experience swallowing difficulties."[41] Similarly, the PATIENT COUNSELING INFORMATION section of both products' labeling states the following: "Some people, particularly children, may experience difficulties swallowing ALBENZA tablets whole. ALBENZA chewable tablet is available for children and patients who may be unable to swallow a tablet."[42]

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[36] As you note, the draft bioequivalence guidance for mebendazole tablets recommends that ANDA applicants conduct a comparative clinical endpoint study. Petition at 13-14. This recommendation reflects the fact that mebendazole acts locally in the GI tract. Because of this local activity, a pharmacokinetic study of systemic mebendazole concentrations alone is not sufficient to ensure bioequivalence. Local activity is not a concern here. It is scientifically accepted that albendazole tablets eradicate HD and NCC primarily through systemic activity. Thus, a pharmacokinetic study of systemic albendazole concentrations alone is sufficient to ensure the bioequivalence of a proposed generic product to Albenza.

[37] Petition at 15.

[38] Id. at 16.

[39] Id.

[40] Id. at 15 (citing 21 U.S.C. 355(j)(2)(A)(v), (j)(4)(G)).

[41] Albenza labeling, supra note 1, at 2.

[42] Id. at 11.

In light of these changes, your assertion that the labeling for a generic albendazole tablet product must include the same pediatric instructions described in the Petition is a moot point. Because the approved labeling for the Albenza products no longer includes the pediatric instructions described in the Petition, the labeling for a proposed generic albendazole tablet product is not required to include them either.

As for the pediatric instructions that exist in the currently approved labeling for Albenza products, we decline to opine on whether an exception to the statutory requirement that a generic have the same labeling as the RLD could apply to one or more proposed generic albendazole tablet products, as such a request would need to be evaluated during the ANDA review process for a particular ANDA. As explained above, the labeling for a generic drug generally must be the same as the labeling approved for the RLD.[43] Consequently, an ANDA for a generic albendazole tablet product that references an Albenza product as the RLD generally must propose labeling that is the same as the labeling approved for Albenza. The labeling for a generic albendazole drug product may differ from the currently approved labeling for Albenza if changes are necessary either: (1) because of differences approved under a petition filed under section 505(j)(2)(C) of the FD&C Act (i.e., a suitability petition); or (2) because the generic product and the RLD are produced or distributed by different manufacturers. This latter exception contemplates, among other changes, the omission of an indication or other aspect of labeling protected by patent or exclusivity and changes to reflect permissible differences in the drug products (such as permissible differences in inactive ingredients). We would evaluate whether changes to the pediatric instructions in the currently approved labeling for Albenza could qualify for one of these exceptions during the review of an individual ANDA that proposes to make such changes to the labeling. Accordingly, we do not conclude at this time that the labeling for a proposed generic to Albenza must always contain the same pediatric instructions that are in the approved labeling for Albenza.

C. Crushability and Chewability of Generic Albendazole Tablet Products

In the Petition, you request that FDA require ANDA applicants to conduct simulated use testing or other analyses demonstrating that young children can crush or chew and swallow the proposed generic product with a drink of water without posing an unacceptable choking hazard.[44] You claim that because generic albendazole tablet products must have the same labeling as Albenza, an ANDA applicant must demonstrate that its proposed generic product is capable of being crushed or chewed to avoid having a false or misleading label (i.e., avoid being misbranded).[45] You also claim that the palatability, chewability, crushability, and usability of a finished generic product must be evaluated because there is a known risk of choking associated with the administration of albendazole in children.[46] You contend that requiring ANDA applicants to demonstrate that a proposed generic albendazole tablet product is capable of being crushed or

[43] See Section I.C.

[44] Petition at 2.

[45] Id. at 16.

[46] Id. at 17.

chewed would be consistent with the Agency's past recommendations concerning the testing of drugs that present a medication error risk (e.g., Lazanda and Arcapta Neohaler).[47]

As an initial matter, we note that there is little evidence that a 200 mg albendazole tablet poses a significant choking hazard for children. The pediatric instructions were added to Albenza's labeling in 2007 based on choking events involving the higher strength 400 mg albendazole tablet that is not marketed in the United States. You have not provided any evidence of choking events involving the smaller 200 mg albendazole tablet.

Nonetheless, we acknowledge that differences in physical characteristics (e.g., size and shape) of generic and RLD tablet products could increase the risk of adverse events such as choking. The Agency recently issued a guidance for industry, *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* (Physical Attributes Guidance),[48] which addresses this issue. The guidance advises ANDA applicants that they should consider the effect that physical attributes (e.g., tablet coating, weight, surface area, disintegration time, and propensity for swelling) have on factors that contribute to patient acceptance (e.g., palatability and smell) and to ease of swallowing when developing a quality target product profile (QTTP) for generic tablet products.[49] It also recommends that generic oral tablets be of a similar shape as the RLD and that differences in size between therapeutically equivalent tablets not exceed certain limits for comparable ease of swallowing.[50] ANDA applicants are advised to consult with the Agency before establishing the QTTP if a generic tablet product intended to be swallowed intact differs from the criteria recommended in the Physical Attributes Guidance.[51]

We would expect a generic albendazole tablet product that satisfies the criteria in the Physical Attributes Guidance's recommendations to present no greater risk of choking than Albenza. Accordingly, we disagree with the proposition that simulated use testing should be required for every ANDA that references Albenza as its RLD. The need for any additional testing of a proposed generic albendazole tablet product will be determined during the ANDA review process following a detailed examination of the proposed product's physical attributes.

We also disagree with the notion that requiring simulated use testing would be consistent with our recommendations that the sponsors of Lazanda and Arcapta Neohaler conduct usability studies. Those recommendations related to specific safety and efficacy concerns that arose during the review of the Lazanda and Arcapta Neohaler NDAs—not ANDAs—thus your reliance on them is misplaced. As discussed in the legal and regulatory background section of this response, the requirements for an NDA differ from the requirements for an ANDA. An NDA applicant must demonstrate that its drug product is safe and effective. In connection with this requirement, FDA will sometimes ask an NDA applicant for a usability study demonstrating

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[47] Id. at 18.

[48] The Physical Attributes Guidance is available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[49] Physical Attributes Guidance at 4-6.

[50] Id.

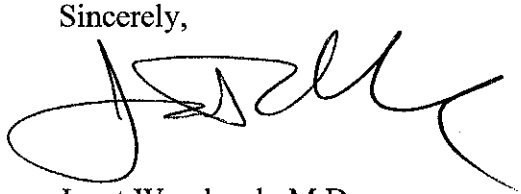
[51] Id. at 4.

that the drug product is safe and effective when used in real-world conditions. Once an NDA drug product is found to be safe and effective, however, an ANDA applicant may rely on that finding and need not independently demonstrate the safety and effectiveness of a proposed generic version of the NDA drug product. To rely on the Agency's finding of safety and effectiveness for an NDA drug product, an ANDA applicant must cite the NDA drug product as the RLD in its application; demonstrate that its proposed generic drug product is bioequivalent to the NDA drug product; and, with limited exceptions, show that its proposed generic drug product has the same active ingredient, conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) as the NDA drug product. Furthermore, as noted above, ANDA applicants would be expected to follow the recommendations in the Physical Attributes Guidance regarding differences in physical characteristics of generic and RLD tablet products.

III. CONCLUSION

For the reasons discussed in this response, your Petition is denied. We are not persuaded that ANDA applicants for generic albendazole tablet products should be required to demonstrate bioequivalence to albendazole sulfoxide using a 90% CI approach. We therefore will not revise the Draft Albendazole BE Guidance to include such a recommendation. We also do not agree that a generic albendazole tablet product must necessarily have the identical labeling describing the drug product's use in the pediatric population as Albenza. Some changes to the "pediatric instructions" in the Albenza labeling might be appropriate under the exceptions to the statutory requirement that a generic product have the same labeling as the RLD, but a determination in this regard will only be made in the context of review of a particular ANDA. Finally, we will not require ANDA applicants to conduct simulated use testing or other analyses showing that their proposed generic albendazole tablet product can be administered to young children with a drink of water without an unacceptable risk of choking. We expect ANDA applicants to follow the recommendations in the Physical Attributes Guidance, which are intended to help ensure that a generic oral tablet product is comparable to or better than the RLD in terms of ease of swallowing.

Sincerely,



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