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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

Amedra Pharmaceuticals LLC ("Amedra"), the sponsor of ALBENZA® (albendazole) Tablets ("ALBENZA"), respectfully submits this Citizen Petition under 21 USC 355 and 21 CFR 10.30, among other provisions of law, to request that the Commissioner of Food and Drugs (the "Commissioner") take the actions described below with respect to any abbreviated new drug application ("ANDA") for a generic version of ALBENZA.

ALBENZA is an orally administered broad-spectrum anthelmintic, first approved by FDA in 1996. The active ingredient, albendazole, is absorbed from the gastrointestinal ("GI") tract into the bloodstream and is converted by the liver to the primary active metabolite, albendazole sulfoxide, before reaching systemic circulation. In December 2012, the Food and Drug Administration ("FDA") published a guidance document in draft form providing product-specific bioequivalence recommendations for generic versions of albendazole oral tablets (the "Draft Guidance").[1]

The Draft Guidance instructs applicants to measure both the parent drug, albendazole, and its active metabolite, albendazole sulfoxide, but recommends that bioequivalence may be demonstrated based on the albendazole data only. Bioequivalence based on albendazole, while necessary, is not in this case sufficient. Because of the nature of the drug –the way it is absorbed into the bloodstream, how it is metabolized, and its mechanism of action – an ANDA referencing ALBENZA must be required to show bioequivalence based upon the active ingredient, albendazole *and* the primary active metabolite, albendazole sulfoxide.

[1] Draft Guidance on Albendazole (Dec. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333003.pdf.

2013-4691

Additionally, in response to safety information regarding a potential choking risk in children, the ALBENZA label was amended to add instructions to enable safe pediatric administration. Specifically, both the Precautions (Information for Patients) section and the Dosage and Administration section of the approved package insert state that for young children, the product should be crushed or chewed and swallowed with a drink of water. A proposed generic drug product referencing ALBENZA must have the same labeling in this regard and must, accordingly, meet appropriate standards, and be subjected to appropriate testing, to ensure that the generic tablet is capable of being crushed and chewed and swallowed by children with a drink of water without posing an unacceptable choking risk.

FDA must therefore refrain from approving any ANDA referencing ALBENZA that fails to meet the criteria below.

ACTION REQUESTED

Amedra respectfully requests that the Commissioner refrain from approving any ANDA referencing ALBENZA unless it includes information showing:

(i) Bioequivalence based on systemic levels of the primary metabolite, albendazole sulfoxide, in addition to the parent drug, albendazole;

(ii) The same labeling, including safety information relevant to the drug product's use in the pediatric population; and

(iii) Simulated use testing or other analyses demonstrating that the drug product can be chewed and crushed, and swallowed by young children with a drink of water without posing an unacceptable choking hazard.

STATEMENT OF GROUNDS

I. BACKGROUND

A. The reference drug product

FDA approved ALBENZA on June 11, 1996, under New Drug Application ("NDA") 020-666, to treat diseases caused by specific forms of parasitic worms (helminthes). Specifically, ALBENZA is indicated for the treatment of parenchymal neurocysticercosis due to active lesions caused by larval forms of pork tapeworm, as well as the treatment of cystic hydatid disease of the liver, lung, and peritoneum, caused by the larval form of dog tapeworm..

Both cystic hydatid disease and parenchymal neurocysticercosis are caused by infection with the larval forms of tapeworm, and occur after tapeworm eggs are ingested.[2] After ingestion, the eggs hatch in the small intestines and release oncospheres (tapeworm embryos) that are absorbed through the intestinal wall. The oncospheres then travel into the liver and either form lesions, or cysts, there, or enter systemic circulation and form cysts elsewhere in the body.[3]

Cystic hydatid disease is caused by the larval form of *Echinococcus granulosus* (dog tapeworm), and occurs when cysts develop in various organs within the body (*e.g.*, liver, lung, and peritoneum).[4] Because the oncospheres travel into the liver before entering systemic circulation, cystic hydatid disease is most commonly found in the liver, representing approximately 75% of cases.[5] Cystic hydatid disease can present clinically as chest pain, allergic reactions, and jaundice or cholangitis.

Parenchymal neurocysticercosis is caused by the larval form of *Taenia solium* (pork tapeworm), and occurs when cysts develop in the parenchyma of the brain.[6] Clinical effects vary, but most commonly include seizures and less commonly headaches and other neurologic abnormalities.[7]

The active ingredient in ALBENZA is albendazole, which is a white to off-white powder. While albendazole is soluble in dimethylsulfoxide, strong acids and bases, it is poorly soluble in water. Due in part to its low aqueous solubility, Albendazole is generally poorly absorbed from the GI tract into the bloodstream. Once absorbed, albendazole is rapidly converted in the liver to the primary active metabolite, albendazole sulfoxide.[8] Albendazole sulfoxide is the predominant systemic metabolite and is believed to be responsible for the systemic anti-parasite (anthelmintic) action of the drug.[9]

ALBENZA is indicated for use by both adults and children. It is supplied as 200 mg tablets and is administered at 400 mg (2 x 200 mg) twice daily for patients 60 kg or greater, and

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[2] *See generally* Zhang, W., *et al.*, *Concepts in immunology and diagnosis of hydatid disease*, Clin. Microbiol. Rev. (2003) 16: 18-36 (attached as Exhibit 1); Pedros, I., *et al.*, *Hydatid Disease: Radiologic and Pathologic Features and Complications*, RadioGraphics (2000) 20: 795-817 (attached as Exhibit 2); Garcia, H.H., *et al.*, *Consensus guidelines for treatment of neurocysticercosis*, Clin. Microbiol. Rev. (2002) 15: 747-756 (attached as Exhibit 3); Baird, R.A., *et al.*, *Evidence-based guideline: Treatment of parenchymal neurocysticercosis (Report of the Guideline Development Subcommittee of the American Academy of Neurology)*, Neurology (2013) 80: 1424-1429 (attached as Exhibit 4).

[3] Exhibit 2, Pedros, *et al.*, at 798; Exhibit 4, Baird, *et al.*, at 1424.

[4] Exhibit 1, Zhang, *et al.*, at 18; Exhibit 2, Pedros, *et al.*, at 804.

[5] Exhibit 2, Pedros, *et al.*, at 798.

[6] Exhibit 4, Baird, *et al.*, at 1424.

[7] *Id.* at 1427.

[8] ALBENZA Package Insert, at Clinical Pharmacology.

[9] *Id.*

at 15 mg/kg/day for patients less than 60 kg.[10] The ALBENZA labeling includes, among other things, specific safety precautions and dosage and administration instructions for use in children. More specifically, the labeling includes the following warning, "[s]ome people, particularly young children, may experience difficulties swallowing the tablets whole."[11] Accordingly, the instruction "[i]n young children, the tablets should be crushed or chewed and swallowed with a drink of water," is found in the "Dosage and Administration" and the "Precautions" sections of the FDA-approved prescribing information.[12]

These warnings and instructions were added to the labeling to increase the safe use of the product. Specifically, in 2007, the then sponsor of ALBENZA, GlaxoSmithKline ("GSK"), submitted a labeling supplement in response to new safety information regarding the administration of albendazole in children. In the labeling supplement, GSK reported that there had been five cases of asphyxia and/or choking related to the administration of albendazole in children.[13] Not all of the cases of asphyxia were well documented or were consistent with albendazole tablets being the cause of the events, but there was sufficient evidence of a potential choking hazard in children to warrant additional labeling precautions.[14]

B. Statutory and Regulatory Standards

1. General standards for generic drug approvals

Under the Federal Food, Drug, and Cosmetic Act ("FDCA"), a generic applicant is permitted to rely on FDA's previous finding of safety and effectiveness for the reference listed drug ("RLD"). In order to rely on FDA's finding with regard to the RLD, the applicant must show, among other things, that the proposed product has the same active ingredients, conditions of use, route of administration, dosage form, strength, and (with certain exceptions) labeling as the RLD, and that it is bioequivalent to the RLD.[15]

An ANDA drug product is not generally required to be "the same" as the RLD in characteristics other than those specified in the statute, including in its formulation and method of manufacture. Because two different manufacturers making the same drug product may use different formulations and components, and different manufacturing processes, the approved RLD and the proposed generic, even if they contain the same amount of active ingredient, have the potential to release or deliver different amounts of drug at different rates to the patient. Thus,

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[10] *Id.*, at Dosage and Administration.

[11] *Id.*, at Precautions.

[12] *Id.*

[13] NDA 20-666/S-004 (attached as Exhibit 5), at 2.

[14] *Id.*

[15] *See* 21 USC 355(j)(2)(A); 21 CFR 314.94(a).

studies are necessary to demonstrate bioequivalence to ensure that patients receive the same treatment whether they are dispensed the RLD or the generic substitute.[16]

2. Bioequivalence

Under the FDCA, a generic drug is considered bioequivalent to the RLD if "the rate and extent of absorption of the [generic] drug do not show a significant difference from the rate and extent of absorption of the [reference] 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]

Under the regulations, "FDA may require *in vivo* or *in vitro* testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products."[18] FDA's regulations describe these methods in descending order of accuracy, sensitivity, and reproducibility. These methods include *in vivo* PK studies, *in vivo* pharmacodynamic effect studies, clinical endpoint studies, and *in vitro* studies.[19] Ultimately, under the statute and regulations, the choice of study design is based on the ability of the design to compare the drug delivered by the two products at the particular site of action of the drug.

The preferred methodology, and what is typically used with drugs that achieve therapeutic effect through systemic absorption, is to perform *in vivo* pharmacokinetic ("PK") studies that measure the rate and extent to which the active ingredient or active moiety is absorbed into the blood over time.[20] FDA's regulations also provide that, when appropriate, it is necessary to also measure the PK of the active metabolite of the drug.[21] Specifically, the regulations state that the applicant should measure "the active ingredient or active moiety, and when appropriate, its active metabolite(s) in whole blood, plasma, serum, or other appropriate biological fluid . . . as a function of time."[22]

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[16] *See generally* 21 CFR 320.24.

[17] 21 USC 355(j)(8)(B)(i).

[18] 21 CFR 320.24(a).

[19] By regulation, FDA has identified the following potential approaches to establishing bioequivalence: (1) *In vivo* PK studies measuring the concentration of the drug in an appropriate biological fluid, such as blood or plasma, or *in vitro* studies that have been correlated with and are predictive of human *in vivo* bioavailability data; (2) *In vivo* studies measuring the urinary excretion of the drug; (3) *In vivo* pharmacodynamic studies measuring effects associated with the delivery of the drug to the site of action; (4) *In vivo* comparative clinical studies that measure the effectiveness of the drug; (5) A currently available *in vitro* test that ensures human *in vivo* bioavailability; (6) Any other approach deemed adequate by FDA to establish bioequivalence. The regulation specifically states that the different methods (1) through (6) are listed "in descending order of accuracy, sensitivity, and reproducibility," and requires applicants to use "the most accurate, sensitive, and reproducible approach available." *See* 21 CFR 320.24(a), (b).

[20] 21 CFR 320.24(b)(1)(i).

[21] *Id.*

[22] *Id.*

To demonstrate bioequivalence based on PK data, FDA generally requires that the 90% confidence interval surrounding the ratios of the test drug to the RLD for C_{max}, AUC_{0-t}, and AUC_{0-inf} fit entirely within boundaries of 80% to 125% (the "confidence interval approach"). Under this general approach, C_{max} serves as a surrogate for the rate of absorption, and AUC as a surrogate for the extent of absorption.

3. Moieties to be measured

In demonstrating bioequivalence through an *in vivo* PK study, FDA generally recommends measurement of the parent drug released from the dosage form, rather than the metabolite. The rationale for this recommendation is that the PK profile of the parent drug is a more direct form of measurement and is generally more sensitive to changes in formulation than a metabolite. The PK profile of a metabolite reflects the rate and extent of biochemical conversion (metabolite formation, distribution, and elimination) in addition to absorption. It is therefore a less direct means of measuring the rate and extent of absorption of the drug.[23]

However, FDA's regulations provide that the active metabolite(s) should be measured in addition to the parent drug or active moiety when appropriate.[24] For example, FDA's general guidance on bioavailability and bioequivalence studies for orally administered drugs indicates that measurement of a metabolite may be required when parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum.[25] In such cases FDA will generally recommend that bioequivalence be based on the metabolite data obtained from these studies. If, however, the concentration and activity of the parent drug are relevant to the efficacy or safety of the drug product, the agency may also require that the parent drug be measured and analyzed statistically in addition to the metabolite.[26]

Similarly, if a metabolite is formed as a result of gut wall or other pre-systemic metabolism, and if the metabolite contributes meaningfully to the safety and/or efficacy of the drug product, FDA will recommend that both the metabolite and the parent drug be measured.[27] In such cases the agency will generally recommend that the parent drug be analyzed using the confidence interval approach and that the metabolite data be used to provide supportive evidence of comparable therapeutic outcome.[28] Again, however, if there are clinical concerns relating to

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[23] FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations at 18 (March 2003) ("BA/BE Guidance"), *available at* http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070124.pdf.

[24] 21 CFR 320.24(b)(1)(i).

[25] BA/BE Guidance at 18.

[26] *Id.*

[27] *Id.*

[28] *Id.*

concentration and activity, relevant to both the parent drug and the metabolite, FDA may require that both are subject to the confidence interval approach. [29]

In the alternative, a comparative clinical endpoint study may be required to show that the proposed generic product is bioequivalent to the RLD.

4. Comparative clinical endpoint studies

Bioequivalence for locally-acting topical products presents unique challenges because the bioavailability of locally-acting drugs generally cannot be assessed through assaying the concentration of the active moiety in the bloodstream. The regulations therefore provide that bioequivalence may be shown by an appropriately designed comparative clinical study, designed not to assess PK but to assess the clinical effect of the drug.[30]

The regulations also recognize that a comparative clinical endpoint study may be necessary to show bioequivalence for drugs that are systemically acting in cases where analytical methods cannot be developed to permit use of one of the other approaches that are described under the regulations.[31]

5. Same labeling

Under section 505(j) of the FDCA, an ANDA applicant must submit "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug."[32] However, the statute narrowly permits the labeling to include certain limited changes. Namely, "changes required because of differences approved under a [suitability] petition[33] or because the new drug and the listed drug are produced or distributed by different manufacturers" may be permitted.[34]

To accommodate the fact that the RLD and the generic are not manufactured by the same company, FDA's rules implementing section 505(j) state that labeling changes are permitted to

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[29] *See id.*

[30] 21 CFR 320.24(b)(4); *see also* 21 USC 355(j)(8)(C) ("For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.")

[31] 21 CFR 320.24(b)(4).

[32] 21 USC 355(j)(2)(A)(v).

[33] Under certain circumstances not at issue here, the FDCA permits an ANDA applicant to petition the agency (a suitability petition) for permission to submit an ANDA for a drug with a different active ingredient, or different route of administration, dosage form, or strength than that of the RLD. 21 USC 355(j)(2)(C). The proposed modification must not affect the safety or effectiveness of the product.

[34] 21 USC 355(j)(2)(A)(v).

reflect "differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance."[35]

FDA's rules also provide that when "aspects of the listed drug's labeling are protected by patent, or by exclusivity," an ANDA may be approved with different labeling so long as "such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."[36] In practice, this has meant that aspects of the labeling and the labeled use may be omitted where they remain exclusive to the RLD to enable the generic to come to market, so long as the product remains safe and effective for the remaining uses.

In other respects, however, a product approved under an ANDA must have the same labeling as the RLD. Indeed, one of the key differences separating products approved under section 505(b)(2) of the FDCA and those approved under section 505(j) of the FDCA is that the later must have the same labeling.

6. *Other features of the drug product*

As indicated above, in most cases generic products are not required to be exactly the same as their reference products in characteristics other than those specified in the statute, including aspects of their formulation, method of manufacture, size, shape, container closure systems, or package configurations.

Under the FDCA, however, FDA must ensure that all drug products marketed in the United States are safe and effective, and not misbranded or adulterated.[37] A generic drug product is not relieved of this requirement.

For example, if the proposed generic product includes a different inactive ingredient, the agency must conclude that the different inactive ingredient will not alter the safety or efficacy of the product.[38] Similarly, to the extent the manufacturing process or other factors may affect the safety or effectiveness of the product, these must be evaluated. A generic product, like

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[35] 21 CFR 314.94(a)(8)(iv).

[36] 21 CFR 314.127(a)(7) ("FDA will refuse to approve an abbreviated application for a new drug under section 505(j) of the act [if i]nformation submitted in the abbreviated new drug application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the abbreviated new drug application except for changes required because of differences approved in a [suitability] petition . . . or because the drug product and the reference listed drug are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use."); *see also* 21 CFR 314.94(a)(8)(iv).

[37] 21 USC 355(d); 21 USC 355(j)(2), (4); 21 USC 331(a); 21 USC 352.

[38] 21 CFR 314.94(a)(9)(ii).

the innovator product, must be safe and effective as labeled, and not misbranded or adulterated. Within limits the agency has recognized it is proper for a generic manufacturer to be required to address these issues independently. To that end, the agency has broad discretion to determine the kinds of data it needs to make the expert assessment it is entrusted to make.[39]

7. Special considerations for pediatric use of oral dosage forms

To ensure that the pediatric population receives safe and effective medications, it is necessary that drug products for pediatric use are appropriately formulated and configured. In 2009, the National Institutes of Health ("NIH") and FDA entered into an inter-agency agreement – the Pediatric Formulations Platform – aimed at developing appropriate pediatric formulations.[40] While FDA has yet to publish comprehensive standards regarding the formulation and configuration of drug products for pediatric use, it has issued guidance regarding nonclinical and clinical studies in the pediatric population.[41] In addition, international bodies such as the World Health Organization and the European Medicines Authority have begun to develop appropriate standards specific to the development of pediatric formulations. The Consumer Product Safety Commission ("CPSC") has also developed standards relating to the risk of injuries and deaths resulting from young children choking on small objects. The factors considered by FDA and these international bodies, as well as by the CPSC, are all relevant to the development of an oral tablet that can be safely used in children.[42]

In formulating and designing the specifications for a drug product whose use includes the pediatric population, it is essential to take steps to ensure that children are not exposed to unnecessary safety risks. In particular, among children, choking is one of the leading causes of mortality and morbidity.[43] Children can choke on a variety of different items, including items that are intended to be placed in the mouth, such as food and drug products, as well as items that are not intended to be placed in the mouth, such as toys. For that reason, manufacturers of products with a potential choking risk for children should, and do, conduct simulated use testing to evaluate the choking hazard posed by a product, and design the product to minimize this

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[39] *See, e.g., Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998); *sanofi-aventis v. FDA et al.*, 842 F. Supp. 2d 195, 203-04, 207-11 (D.D.C. 2012).

[40] National Institutes of Health, *Pediatric Formulations Platform* (last modified Feb. 15, 2012), *available at* http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/index.cfm (attached as Exhibit 6).

[41] FDA Guidance for Industry: Nonclinical Safety Evaluation of Pediatric Drug Products (Feb. 2006); FDA Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population (Dec. 2000).

[42] There is a precedent for collaboration between FDA and the CPSC. In 2002, FDA seized Konjac candy from a New Choice Food's Irwindale, California facility because the agency had determined that the candy posed a serious choking hazard. In making its determination, FDA consulted with experts on choking from the CPSC. CFSAN, *Enforcement Story Archive – Konjac Candy* (2002), *available at* http://www.fda.gov/ICECI/EnforcementActions/EnforcementStory/EnforcementStoryArchive/ucm105953.htm.

[43] American Academy of Pediatrics, *Policy Statement—Prevention of Choking Among Children*, Pediatrics (2010) 125: 601-607, 601 (attached as Exhibit 7).

risk.[44] Simulated use testing is conducted throughout the product design process and may involve computer modeling approaches as well as collecting data from participants using the product in realistic situations.[45] This type of testing provides insight into whether the intended consumer can safely use the product as designed, or whether there are common errors in using the product.[46] This information enables a manufacturer to identify design failures, take corrective action, and design a final product that minimizes previously identified risks.

The palatability of a drug product intended to be placed in the mouth also plays an important role in a child complying with the instructions of use. In particular, drug substances are generally bitter tasting, and taste plays a key role in the overall acceptance of the drug product in the pediatric population. Children tend to prefer sweet flavors, and there may be a need to add a sweetener to the formulation to increase the probability that a child will take the tablet as instructed.[47] Compliance is particularly important when an oral tablet is labeled to be chewed based on a risk of choking. An oral tablet with a bitter taste is less likely to be chewed immediately by a child, which lengthens the time an intact tablet remains in the mouth. This may increase the probability that a child will accidentally swallow and choke on the tablet. At the same time, however, an oral tablet should not be formulated to contain too much sweetener because it risks being too attractive to children. An oral tablet that tastes too similar to candy runs the risk of children overdosing, thereby increasing the risk of accidental poisoning.[48]

II. ARGUMENT

A. Proposed generics to ALBENZA should be required to demonstrate bioequivalence based on systemic levels of the primary metabolite, albendazole sulfoxide, in addition to the parent drug, albendazole

When demonstrating bioequivalence using an *in vivo* PK study, FDA's regulations state that, when appropriate, the active metabolite of the drug product should be measured in addition

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[44] *See id.* at 604 (stating that "Manufacturers of foods that are frequently consumed by children should, to the extent possible, design these products to minimize choking risk to those in that age group."). In addition, manufacturers of consumer products are required to conduct product testing that simulates use and abuse by children to ensure that small parts will not break off and pose a choking hazard in young children. 16 CFR 1501.

[45] FDA Draft Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors, at 14 (Dec. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf.

[46] *Id.*

[47] World Health Organization, *Development of Paediatric Medicines: Points to Consider in Formulation*, WHO Technical Report Series No. 970, Annex 5, 197 at 209 (2012) (attached as Exhibit 8); European Medicines Agency, Committee for Medicinal Products for Human Use, Paediatric Committee, *Guideline on pharmaceutical development of medicines for paediatric use draft*, EMA/CHMP/QWP/805880/2012 Rev. 1 at 19-21 (Jan. 2013) (attached as Exhibit 9).

[48] Exhibit 8, World Health Organization, *Development of Paediatric Medicines: Points to Consider in Pharmaceutical Development*, at 202.

to the parent drug or active moiety.[49] For example, if a metabolite is formed as a result of gut wall or other pre-systemic metabolism, and if the metabolite contributes meaningfully to the safety and/or efficacy of the drug product, FDA will recommend that both the metabolite and the parent drug be measured.[50] In such cases, FDA may require that the parent drug, the metabolite, or both, be subject to statistical analysis and that one or the other, or both meet the requirements for demonstrating bioequivalence using the confidence interval approach.[51] FDA's BA/BE Guidance specifically indicates that if the concentration and activity of the parent drug and the metabolite are both significant to the safety and/or effectiveness of the drug product, statistical analysis of both may be required to show bioequivalence.[52]

The Draft Guidance for ALBENZA recommends that sponsors perform two *in vivo* PK studies: a single dose (400 mg dose, 2 x 200 mg tablets), two-way crossover, fasting study in normal healthy volunteers (healthy male and non-pregnant females); and an identical study in normal health volunteers in the fed state. For both studies, the Guidance provides that both the parent drug, albendazole, and its active metabolite, albendazole sulfoxide, are to be measured. However, the Draft Guidance then recommends that bioequivalence be based only on the albendazole data. Specifically, the Draft Guidance advises that while PK data for albendazole sulfoxide should be collected, this data will only be used as "supportive evidence of comparable therapeutic outcome." In other words, the data for albendazole sulfoxide will not necessarily be required to meet the formal test for bioequivalence. Thus, even if the data for albendazole sulfoxide falls outside the usual limits, FDA may still consider the proposed generic product to be bioequivalent to ALBENZA.

Under the Draft Guidance, it is only on condition that the applicant demonstrates that it is not possible to measure the parent drug albendazole "accurately and reliably," that bioequivalence may be demonstrated based *solely* on the PK data for albendazole sulfoxide.[53] In other words, PK data for albendazole sulfoxide is dispositive in demonstrating bioequivalence if albendazole cannot be measured, but such evidence is merely supportive if albendazole can be measured.

Amedra agrees that bioequivalence must be established based on the parent drug. While albendazole exhibits generally low bioavailability orally, a 400 mg (2 x 200 mg) dose of ALBENZA results in levels of albendazole in plasma that can be reliably measured.[54] As such, it should not be a conditional requirement. Consistent with the statute and implementing regulations, FDA must not approve any ANDA referencing ALBENZA unless bioequivalence is

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[49] 21 CFR 320.24(b)(1)(i).

[50] *See* BA/BE Guidance at 18.

[51] *See* 21 CFR 320.24(b)(1)(i); BA/BE Guidance at 18.

[52] *See* BA/BE Guidance at 18.

[53] Draft Guidance.

[54] When administered at 400 mg (2 x 200 mg), albendazole is readily measureable in plasma. *See* Exhibit 10.

shown at the 90% confidence interval based on the *in vivo* PK data for the parent drug, albendazole.

Amedra further agrees that both fasting and fed studies using a 400 mg (2 x 200 mg) dose is an appropriate recommendation. Oral administration of albendazole with food is widely reported to have marked effect on bioavailability, and the administration of albendazole with a high fat content meal is known to increase bioavailability significantly.[55] Enhanced bioavailability when administered with food is thought to be due to lower pH caused be stimulation of gastric acid, and by increased residence time in the stomach.[56] Thus, bioequivalence based on direct measurement and analysis of the active ingredient, in both fed and fasting studies, should be a necessary condition of ANDA approval.

However, analysis of albendazole is not in itself sufficient. In this case, as opposed to merely providing supportive evidence of comparable therapeutic outcome, PK data for the primary active metabolite must be required to meet the statistical test for bioequivalence. The primary active metabolite, albendazole sulfoxide, is the predominant systemic moiety, and it is also well-established that systemic anthelmintic activity can be attributed to circulating levels of albendazole sulfoxide.

Specifically, after absorption into the bloodstream, the liver converts albendazole into a racemic mixture (R(+) and S(-) enantiomers) of albendazole sulfoxide.[57] Formation of R(+) albendazole sulfoxide is catalyzed by microsomal flavin mono-oxidase, and the formation of the S(-) enantiomer by cytochrome P450 enzymes. In addition to hepatic metabolism, available evidence suggests that albendazole is also metabolized presystemically by CYP3A4 enzymes in the intestinal mucosa.[58]

This so-called first pass metabolism is highly efficient, resulting in systemic levels of albendazole sulfoxide that far exceed those of albendazole. The systemic anthelmintic activity of the drug is therefore thought to be largely attributable to albendazole sulfoxide.[59] Thus, the concentration and systemic activity of albendazole sulfoxide are critical to the safety and

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[55] ALBENZA Package Insert, at Clinical Pharmacology; *see also* Rigter, I.M., *Relative bioavailability of three newly developed albendazole formulations: a randomized crossover study with healthy volunteers*, Antimicrobial Agents and Chemotherapy (2004) 48: 1051-1054, 1051 (attached as Exhibit 11); Nagy, J., *et al.*, *Effect of grapefruit juice or cimetidine coadministration on albendazole bioavailability*, Am. J. Trop. Med. Hyg. (2002) 66: 260-263, 260 (attached as Exhibit 12).

[56] *See* Exhibit 12, Nagy, *et al.*, at 263. Bioavailability of albendazole is believed to be pH dependent. *Id.*

[57] *See* Moroni, P., *et al.*, *Chiral sulfoxidation of albendazole by the flavin adenine dinucleotide-containing and cytochrome P450-dependent monooxygenases from rat liver microsomes*, Drug Metab. Dispos. (1995) 23: 160-165 (attached as Exhibit 13); Delatour, P. *et al.*, *Comparative enantioselectivity in sulphoxidation of albendazole in man, dogs and rats*, Xenobiotica (1991) 21: 217-221 (attached as Exhibit 14).

[58] *See* Exhibit 12, Nagy, *et al.*, at 260, 262-63.

[59] *See* ALBENZA Package Insert, at Clinical Pharmacology.

effectiveness of ALBENZA. It is therefore essential that albendazole sulfoxide levels in plasma be measured and subject to statistical analysis using the confidence interval approach.

This must be required in addition to, not instead of, measurement and statistical analysis of the parent drug.[60] FDA has recognized that the PK profile of metabolic derivatives is indirect evidence of bioequivalence relative to the active ingredient, and that it can reflect metabolic variation. The pathway by which albendazole is metabolized after absorption is not precisely understood. The extent to which the flavin mono-oxidase and P450 enzyme systems contribute to sulfoxidation of albendazole varies among species and has not been well characterized in humans.[61] Metabolic variation may therefore be a significant consideration.

Furthermore, the extent to which albendazole may be absorbed without being metabolized, and therefore contribute directly to systemic anthelmintic activity, is not fully understood. It is well established that albendazole in its native, un-metabolized form is a potent anthelmintic agent.[62] Published studies report the use of albendazole in the effective treatment of a wide range of helmintic infections of the human GI tract.[63] In treating gastrointestinal parasites, albendazole acts directly (locally) within the GI tract and has potent anthelmintic effect upon both larval and adult forms of the parasite. In other words, it has potent anthelmintic and cysticidal activity in its native state. Thus, albendazole and albendazole sulfoxide are both pharmacologically active and both may contribute significantly to the clinical efficacy of the drug product.

The extent to which albendazole may exhibit anthelmintic action directly (presystemically) on hydatid cysts in the liver is not well understood. After absorption, albendazole passes from the gastrointestinal tract into the liver through the portal vein. It is not known the extent to which albendazole acts directly to treat hydatid cysts in the liver prior to being metabolized. Given the known anthelmintic activity of albendazole in the GI tract, the therapeutic effect of albendazole in the liver may be due, in part, to the parent molecule.

In the case of mebendazole, a closely related anthelmintic drug substance, FDA has held that bioequivalence must be shown using comparative clinical endpoint studies in addition to PK

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[60] BA/BE Guidance, at 18 (stating that the "concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination.").

[61] *See* Exhibit 12, Nagy, *et al.*, at 260.

[62] *See* Horton, J., *Albendazole: A broad spectrum anthelmintic for treatment of individuals and populations*, Curr. Opin. Infect. Dis. (2002) 15: 599-608 (attached as Exhibit 15); Horton, J., *Albendazole*, in Kucer's the Use of Antibiotics § 193: 2225-2237 (attached as Exhibit 16); CDC, *Intestinal Parasite Guidelines for Domestic Medical Examination for Newly Arrived Refugees* (April 16, 2012) (attached as Exhibit 17); Grove, D.I., *et al.*, *Efficacy of albendazole against Strongyloides ratti and S. stercoralis in vitro, in mice, and in normal and immunosuppressed dogs*, J. Antimicrob. Chemother. (1988) 21, 75-84 (attached at Exhibit 18).

[63] *See* Exhibit 15, Horton, at 599-603; Exhibit 16, Horton, at 2226, 2229-33.

studies.[64] Like albendazole, mebendazole is poorly absorbed from the gastrointestinal tract and undergoes extensive first-pass hepatic metabolism, but nonetheless is extremely effective in treating helmintic infections within the GI tract.[65] Because mebendazole is used to treat intestinal parasites and is locally acting in the GI tract, a comparative clinical endpoint study is the only way to ensure equivalence in bioavailability at the local site of action.[66]

Unlike mebendazole, albendazole is not approved to treat helmintic disease caused by adult worms residing in the GI tract. However in treating cystic hydatid disease in particular, a pre-systemic mechanism of action may exist. Furthermore, both moieties, albendazole and albendazole sulfoxide, are pharmacologically active, and both are present systemically. Thus, to establish bioequivalence in the treatment of cystic hydatid disease and neurocysticercosis, it is essential that PK data for both albendazole and albendazole sulfoxide are statistically analyzed using the confidence interval approach.

In the alternative, given the lack of complete understanding of the relative contributions of albendazole and albendazole sulfoxide to the pharmacological action of the drug product, and whether there is a systemic and local effect, a proposed generic version of ALBENZA must, like mebendazole, undergo comparative clinical endpoint testing in order to establish that it is bioequivalent to the RLD. Short of this, because albendazole has a direct anthelmintic and cysticidal effect unrelated to the concentration and activity of albendazole sulfoxide, it is essential that albendazole be measured and subject to statistical analysis at the 90% confidence interval.

This approach is consistent with FDA precedent. FDA has recommended that bioequivalence be based on both the parent drug and its active component for at least four similarly situated drug products: Colazal® (balsalazide disodium),[67] Ditropan XL® (oxybutynin chloride),[68] Dipentum® (olsalazine sodium),[69] and Azulfidine® (sulfasalazine).[70] For Colazal,

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[64] Draft Guidance on Mebendazole (Feb. 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm088648.pdf; FDA Citizen Petition Response (Vermox), Docket No. 88P-0369/CP & PSA (attached as Exhibit 19).

[65] Horton, J., *Mebendazole*, in Kucer's the Use of Antibiotics § 194: 2238-2243 (attached as Exhibit 20).

[66] FDA has recommended an *in vivo* clinical endpoint study in order to establish bioequivalence for other oral drug products that are locally acting within the gastrointestinal tract. Most recently in 2012, FDA issued a bioequivalence recommendation for generic versions of Xifaxan (rifaximin) oral tablets, which is an antibiotic used to treat traveler's diarrhea. FDA recommended a clinical endpoint study and *in vivo* PK studies. Draft Guidance on Rifaximin (Feb. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291392.pdf.

[67] Guidance on Balsalazide Disodium (Jan. 2008), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm082854.pdf.

[68] Draft Guidance on Oxybutynin Chloride (Oct. 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm118381.pdf.

[69] Guidance on Olsalazine Sodium (May 2008), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm089229.pdf.

FDA determined that the parent drug (balsalazide) should be measured because "plasma concentrations of a parent drug are sensitive to changes in formulation performance," and that the active component (mesalamine) should be measured as well because mesalamine is "formed presystemically and contributes meaningfully to efficacy."[71] Further, FDA determined that to demonstrate bioequivalence, mesalamine data should be evaluated using the confidence interval approach, as opposed to merely providing supportive evidence. The agency made this determination because it "ensures us [FDA] that balsalazide disodium reaches the colon and is converted to mesalamine at an equivalent rate for both the generic formulation and the reference listed drug."[72] In a similar fashion, albendazole sulfoxide, the active component of albendazole, is formed presystemically and contributes meaningfully to efficacy.[73] Moreover, it is important that albendazole sulfoxide data are used to evaluate bioequivalence, as opposed to merely providing supportive evidence, because doing so ensures that albendazole reaches the liver and is converted to albendazole sulfoxide at an equivalent rate for both the generic formulation and ALBENZA. FDA must likewise require that bioequivalence for a generic drug product that references ALBENZA be based on both albendazole and albendazole sulfoxide.

Accordingly, bioequivalence of a generic albendazole drug product must be established based on both albendazole and albendazole sulfoxide in plasma. In other words, the 90% confidence interval surrounding the ratios of the test generic drug to the RLD with respect to C_{max}, AUC_{0-t}, and AUC_{0-inf} for albendazole and albendazole sulfoxide must fit entirely within boundaries of 80% to 125%.

B. Proposed generics to ALBENZA must have the same labeling, including safety information relevant to the drug product's use in the pediatric population

A generic albendazole drug product must have the same labeling as ALBENZA.[74] The ALBENZA labeling includes safety information highly relevant to the drug product's safe use in the pediatric population. Physicians rely on this information in order to make prescribing decisions. There are limited exceptions to the statutory requirement that a generic have "the same" labeling as the RLD. None apply to these pediatric instructions.

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[70] Draft Guidance on Sulfasalazine (Feb. 2010), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199674.pdf.

[71] FDA Citizen Petition Response (Colazal), Docket No. 2005P-0146, at 10; *see also* Guidance on Balsalazide Disodium (Jan. 2008), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm082854.pdf.

[72] FDA Citizen Petition Response at 10 (Colazal), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2005-P-0314-0004.

[73] As previously mentioned, albendazole is metabolized by the liver into albendazole sulfoxide prior to reaching systemic circulation.

[74] 21 USC 355(j)(2)(A)(v), 355(j)(4)(G); 21 CFR 314.94(a)(8)(iv). FDA must refuse to approve any ANDA unless it includes "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug." 21 USC 355(j)(2)(A)(v).

Specifically, the Precautions section of the FDA approved package insert includes a warning that "[s]ome people, particularly young children, may experience difficulties swallowing the tablets whole."[75] Further, the "Dosage and Administration" and the "Precautions" sections of the labeling contain the instruction "[i]n young children, the tablets should be crushed or chewed and swallowed with a drink of water."[76] The previous sponsor, GSK, proposed to add this safety information in response to reports of asphyxia and/or choking associated with the administration of albendazole in children. The adverse event reporting relating to the potential choking hazard in young children was a significant-enough safety signal that FDA permitted adding these precautions to the labeling.

This safety information is essential to the safe use of the drug in the pediatric population. Accordingly, a proposed generic to ALBENZA must be labeled identically in this regard.

C. Proposed generics to ALBENZA must conduct simulated use testing to ensure that the drug product is crushable and chewable, and does not pose an unacceptable safety risk in children

As indicated above, adverse event reporting relating to a potential choking hazard in young children necessitates that proposed generics to ALBENZA include safety instructions in their labeling. Two further requirements flow from this. First, since a generic that references ALBENZA must contain these instructions, it must also be capable of being crushed and chewed in order to avoid having a false and misleading label. A generic that contains these instructions but lacks these characteristics is misbranded.[77] As such, a generic that references ALBENZA must demonstrate that the proposed generic tablet is capable of being crushed and chewed, and that the proposed generic tablet conforms to compendial, quality control, and other standards consistent with a product labeled to be crushed or chewed for pediatric administration.

Formulation, manufacturing and packaging can all be critical to the development of a chewable product. Factors that must be considered include taste-masking, mouth feel, grittiness, and tooth packing (the tendency of the substance to lodge and adhere to interdental spaces and the surface of teeth).[78] Oral tablets that are chewable typically contain specific excipients that help maintain a softer, more pliable product. However, it is important that the tablets are not so

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[75] ALBENZA Package Insert, at Precautions.

[76] *Id.*, at Precautions, Dosage and Administration.

[77] 21 USC 352. A drug is deemed misbranded if its labeling is false or misleading in any particular.

[78] *See* Strickley, R.G., *et al.*, *Pediatric drugs – a review of commercially available oral formulations*, J. Pharmaceut. Sci. (2008) 97: 1731-1774, 1761-1762 (attached as Exhibit 21).

soft that they are unable to withstand the stresses inherent in shipping and handling.[79] Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and mouth feel.[80] Various grades of microcrystalline cellulose are available that help provide a smoother mouth feel, eliminate grittiness, and reduce tooth packing.[81] Quality-by-design with regard to these factors can help with direct compression formulations to produce comparably softer tablets that are less friable and disintegrate rapidly, resulting in a tablet that is effectively chewable.

Taste-masking for a chewable/crushable tablet is critically important to patient acceptability, particularly for children. Also, particularly relevant in this case, taste-masking maximizes the likelihood that a child will correctly chew the tablet, decreasing the risk that the tablet will be swallowed intact, causing a potential choking event. A sensory-directed formulation development process has been advanced from decades of experience in the food industry where taste is paramount and is being applied to the development of palatable drug products. The process consists of three steps: (a) taste assessment of the drug substance to quantify the taste-masking challenge (b) base and flavor system development to develop a palatable formulation and (c) testing to verify patient acceptability.[82] Quantitative taste assessment by trained evaluators should be used to guide formulation development.

Thus, for ANDA approval, the proposed finished product attributes must be evaluated using validated tests to ensure that the product specifications are compatible with the labeling to ensure that it is not misbranded.[83]

Second, given the existence of this known safety risk, FDA must require that proposed generics to ALBENZA conduct simulated use testing to evaluate the choking hazard posed by the finished drug product. This evaluation must consider tablet features such as palatability, chewability, crushability, and usability, in order to ensure that the drug product does not pose an unacceptable choking risk in young children. The concept of conducting simulated use testing and identifying risk factors in drug products is not new. FDA has recommended that sponsors

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[79] Friability and hardness are two in-process specifications that are used to evaluate the ability for a tablet to resist the stresses inherent during shipping and handling. *See* USP 36, ch. 1216 (Tablet Friability) (2013), at 973 (attached as Exhibit 22); USP 36, ch. 1217 (Tablet Breaking Force) (2013), at 974 (attached as Exhibit 23).

[80] Exhibit 21, Strickley, *et al.*, at 1761.

[81] *Id.*

[82] *Id.* at 1756.

[83] *See, e.g.*, Clinical Pharmacology and Biopharmaceutics Review (NDA 203-045) (stating that the "chewable tablets are taste-masked and its chewability, as assessed by its mean crush strength and tablet hardness, is suitable for the target patient population. Tablet hardness is based on breakability characteristics as well as the intended chewability characteristics for the 2 to 12 year old children. Tablet hardness boundaries are within those required for acceptable chewability of the tablets.").

perform proactive risk assessments in the development of a drug product.[84] Proactive risk assessment is important because it evaluates and ensures that design modifications minimize use errors and unintended consequences, such as choking. In addition, the Division of Medication Error Prevention and Analysis ("DMEPA") conducts failure mode and effects analysis ("FMEA") and simulated use testing (i.e. human factors or usability or use testing). DMEPA has recommended that sponsors conduct human factors and clinical usability testing for drugs that presented a risk for medication errors.[85]

Proposed generics to ALBENZA must therefore conduct simulated use testing to ensure that the oral tablet can be crushed and chewed, and does not pose an unacceptable safety risk in children. This will permit FDA to evaluate the potential choking hazard of the generic drug product, and whether steps need to be taken to prevent an unacceptable safety risk.

III. CONCLUSION

For the above stated reasons, FDA must refrain from approving any ANDA referencing ALBENZA unless the application demonstrates (1) bioequivalence based on systemic levels of the primary metabolite, albendazole sulfoxide, in addition to the parent drug, albendazole; (2) that the generic drug will have the same labeling, including safety information relevant to the drug product's use in the pediatric population; and (3) that the drug product can be crushed and chewed, and swallowed by children with a drink of water, without exposing children to unnecessary safety risks.

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[84] FDA Draft Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors (Dec. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf.

[85] *See, e.g.*, Memorandum from Loretta Holmes, Safety Evaluator, Division of Medication Error Prevention and Analysis to Bob Rappaport, Division of Anesthesia and Analgesia Products re: LAZANDA® (fentanyl) Nasal Spray, NDA 22-569, at 2 (page 37 of the .pdf) (Mar. 4, 2011) (concluding that the instructions for use were lengthy and complex and recommending that the applicant conduct a usability study to determine if drug could be administered safely and effectively by patients and caretakers and to identify any vulnerabilities that could lead to medications errors), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022569Orig1s000OtherR.pdf; *see also* Memorandum from Anne Crandall Tobenkin, Safety Evaluator, Division of Medication Error Prevention and Analysis to Badrul Chowdhury, Director, Division of Pulmonary, Allergy, and Rheumatology Products re: ARCAPTA™ NEOHALER™ (indacaterol inhalation powder), NDA 22-383, at 1-4 (page 52 of the .pdf) (Feb. 3, 2011) (noting that the Division of Pulmonary, Allergy, and Rheumatology Products raised concerns regarding the risk of medication errors and that the applicant proposed conducting a usability study to address this risk), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022383Orig1s000OtherR.pdf.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 CFR § 25.31.

ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.[86]

Respectfully submitted,

Christopher J. Worrell, R. Ph.
Chief Executive Officer
Amedra Pharmaceuticals LLC

Enclosures

[86] Amedra is not aware of any ANDA or 505(b)(2) applications referencing ALBENZA that are pending before FDA, and thus is providing certification under 21 CFR 10.30.