Nathan A. Beaver
Foley & Lardner, LLP
3000 K Street N.W.
Suite 500
Washington, DC 20007

November 27, 2020

Re: Docket No. FDA-2020-P-0599

Dear Mr. Beaver:

This letter responds to the citizen petition you submitted on behalf of Romark Laboratories, L.C. (Petitioner), received by the Food and Drug Administration (FDA or the Agency) on February 4, 2020 (Petition). Petitioner requests that FDA not approve any abbreviated new drug application (ANDA) that relies on Alinia (nitazoxanide) as the reference listed drug (RLD) unless the applicant conducts:

(1) bioequivalence (BE) studies of both active metabolites, tizoxanide and tizoxanide glucuronide, in plasma under fasted and fed conditions;

(2) BE studies with clinical endpoints (regardless of whether the proposed generic product is quantitatively and qualitatively the same as the RLD); and

(3) two BE studies with clinical endpoints – one in subjects with *G. lamblia* and another in subjects with *C. parvum*.

The Petition also requests that FDA revise the product specific draft guidances on nitazoxanide (tablets and oral suspension) (PSGs) to incorporate the BE criteria requested in the Petition.

We have carefully reviewed the information in the Petition as well as other relevant information. For the reasons set forth below, your Petition is denied.[1]

I. BACKGROUND

A. Alinia (nitazoxanide)

Alinia (nitazoxanide) was approved on November 22, 2002 (NDA 021498), and July 21, 2004 (NDA 021497). Romark Laboratories, L.C. is the application holder for Alinia. Alinia is an antiprotozoal currently indicated for the treatment of diarrhea caused by *Giardia lamblia* (*G. lamblia*) or *Cryptosporidium parvum* (*C. parvum*) and is approved in two dosage forms: tablets (NDA 021497) and oral suspension (NDA 021498). The oral suspension is approved in patients

[1] Today FDA is approving ANDA 213820 for nitazoxanide oral tablets, 500 mg.

one year of age and older. The tablets are approved for patients 12 years of age and older.

Nitazoxanide is a poorly soluble drug substance that acts locally in the gastrointestinal (GI) tract. Nitazoxanide is believed to be effective (i.e., demonstrate antiprotozoal activity) due to its disruption of the pyruvate:ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction, which is essential to anaerobic energy metabolism.[2] Following administration, nitazoxanide is rapidly hydrolyzed to its primary metabolite, tizoxanide. Tizoxanide then undergoes glucuronidation to form the secondary metabolite, tizoxanide glucuronide.[3] Tizoxanide is excreted in urine, bile, and feces while tizoxanide glucuronide is excreted only in urine and bile.[4] After being eliminated in bile and deposited in the duodenum, tizoxanide glucuronide seems to be deconjugated into the more active form, tizoxanide, which may explain why only tizoxanide can be detected in feces.[5] This mechanism of elimination highlights the difficulty in differentiating these two metabolites at the site of action (i.e., the GI tract).

Nitazoxanide is not detected in plasma. Its primary and secondary metabolites, tizoxanide and tizoxanide glucuronide, are detected in plasma, however. The maximum plasma concentration for both metabolites occurs within 1-4 hours after administration, and plasma pharmacokinetic (PK) parameters of tizoxanide and tizoxanide glucuronide are comparable between the two metabolites.[6] Qualitatively, both tizoxanide and tizoxanide glucuronide have been shown to be active against protozoan parasites in vitro. However, from a quantitative standpoint, tizoxanide glucuronide only exhibits 10 percent of *C. parvum* inhibition (sporozoite stage) as compared to 50 percent with tizoxanide and 70 percent with nitazoxanide.[7] Tizoxanide glucuronide is similarly significantly less potent against *G. lamblia* containing trophozoites than nitazoxanide or tizoxanide.[8]

B. Statutory and Regulatory Framework

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to add, among other things, section 505(j) (21 U.S.C. 355(j)), which established an abbreviated

---

[2] Alinia labeling (July 2016), available on FDA's website at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021497s001,021498s004lbl.pdf.

[3] Id.

[4] Id.

[5] Broekhuysen, J., et al. Nitazoxanide: pharmacokinetics and metabolism in man. International journal of clinical pharmacology and therapeutics 38.8 (2000): 387-394.

[6] See Alinia labeling (July 2016), available on FDA's website at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021497s001,021498s004lbl.pdf.

[7] Microbiology Review, Application No.: 021497 & 021498s001, published July 2004 (Part 2, Pages 18-20) available on FDA's website at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-497_Alinia_Microbr_P2.pdf.

[8] See Microbiology Review, Application No.: 021497 & 021498s001, published July 2004 (Part 2, Page 46) available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-497_Alinia_Microbr_P2.pdf.

approval pathway for generic drugs.[9] To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the RLD is safe and effective.[10] The ANDA applicant must identify the listed drug on which it seeks to rely and, with certain limited exceptions, a drug product described in an ANDA must contain the same active ingredient, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.[11]

An ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the RLD.[12] Under section 505(j)(8)(B)(i) of the FD&C Act, a drug is considered bioequivalent to a 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. . . .[13]

Congress also recognized that some drugs do not reach their site of action through absorption into the bloodstream. Thus, section 505(j)(8)(C) states the following:

> 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.

In 21 CFR 314.3(b), FDA defines bioequivalence (BE) (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.

---

[9] For purposes 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.

[10] An *RLD* is the "listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA." 21 CFR 314.3(b). RLDs are identified in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

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

[12] 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 that an ANDA contain information to show that the drug product is bioequivalent to the RLD), and 21 CFR 314.127(a)(6)(i) (stating 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).

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

A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of action at a rate and to an extent that is 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) and manufacturing processes between a proposed generic drug and the RLD have an effect on the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

As discussed further below, the statute, regulations, and case law give FDA considerable flexibility in determining how the bioequivalence requirement is met. The testing methods may include in vivo data (data from a study on human subjects), in vitro data (data from laboratory studies), or a combination of in vivo and in vitro data.[14] This flexibility is reflected in FDA's regulations, which describe the types of evidence that may be used to establish bioequivalence:

> 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 . . . . The selection of the method used to meet an *in vivo or in vitro* testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.[15]

Section 320.24(b) (21 CFR 320.24(b)) of FDA's regulations describes acceptable BE methods in general descending order of accuracy, sensitivity, and reproducibility.[16] The BE methods include: (1) in vivo PK studies of the active ingredient, or when appropriate its active metabolites, in whole blood, plasma, 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 as a function of time; (3) in vivo studies measuring acute

---

[14] See section 505(j)(7)(A)(i)(III) of the FD&C Act; see also *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) (noting that this provision "vests the FDA with discretion to determine whether *in vitro* or *in vivo* bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated application process").

[15] § 320.24(a) (emphasis added). In the preamble to the final rule setting forth FDA's regulations for ANDAs, the Agency explained that, depending upon the drug, it 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, April 28, 1992) (emphasis added).

[16] This general descending order of methodologies may not be scientifically appropriate as to many locally acting drug products due to characteristics of those products that differ from most systemically acting drug products.

pharmacodynamic effect;[17] (4) comparative clinical endpoint studies; and (5) in vitro studies acceptable to FDA that ensure human in vivo bioavailability. In addition, consistent with section 505(j)(8)(C) of the FD&C Act, section 320.24(b)(6) of the regulations states that FDA has the authority to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence." The Agency's authority to make BE determinations on a case-by-case basis using in vivo, in vitro, or both types of data enables FDA to effectuate several long-recognized policies that protect the public health: (1) refraining from unnecessary human research when other methods of demonstrating BE meet the statutory and regulatory standards for approval;[18] (2) permitting the Agency to use the latest scientific advances in approving drug products;[19] (3) protecting the public by ensuring only safe and effective generic drugs are approved for marketing;[20] and (4) making more safe and effective generic drugs available.[21]

For most 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 BE 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 or urine, after administration of a single dose or multiple doses of each drug product to healthy volunteers.[22]

---

[17] Whereas a PK study measures the rate and the extent to which the drug is delivered to biological fluids (generally the blood stream), a pharmacodynamic (PD) study measures effects associated with the delivery of the active ingredient to the site of action.

[18] *See* 21 CFR 320.25(a) (stating that a "guiding principle" for the conduct of an in vivo bioavailability study is "that no unnecessary human research should be done"); *Abbreviated New Drug Application Regulations, Proposed Rule,* 54 FR 28872, 28883 (July 10, 1989) (in discussing section 320.22, stating that "[t]he agency does not believe that Congress intended that unnecessary human research be conducted . . . . [I]f the agency concludes that bioequivalence can be demonstrated by in vitro tests, the agency proposes to require only such tests rather than in vivo studies.").

[19] *See Bioavailability and Bioequivalence Requirements: Procedures for Establishing a Bioequivalence Requirement,* 42 FR 1624, 1629 (Jan. 7, 1977) ("As with all new regulations relating to an evolving science, the Commissioner reserves the right to consider other factors that may indicate the need to establish a bioequivalence requirement.").

[20] *See Schering Corp. v. Sullivan,* 782 F. Supp. 645, 650 (D.D.C. 1992) (noting that one underlying policy of the Hatch-Waxman Amendments is to "ensure the safety of these drugs before they are substituted for their name-brand counterparts").

[21] *See id*. (finding that the purposes of Hatch-Waxman Amendments are "to make more inexpensive generic drugs available" and "to ensure the safety of these drugs"); *Fisons Corp. v. Shalala,* 860 F. Supp. 859, 866-67 (D.D.C. 1994) (finding that the BE waiver provision "comports with the structure and broader policy objectives of the Hatch-Waxman Act," including making safe and affordable generic drugs available).

[22] *See* section 505(j)(8)(B) of the FD&C Act; FDA's draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (Dec. 2013), available on FDA's website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. When final, this guidance will represent FDA's current thinking on this topic.

By contrast, a traditional in vivo BE study comparing the rate and extent of absorption of the active ingredient in the blood stream is usually of limited utility for locally acting products. Some locally acting products may not produce measurable concentrations of drug or metabolite in an accessible biologic fluid. For those that do, there may be a lack of evidence of a correlation between the systemic concentrations and concentrations at the site of drug action for the drug or metabolite. For some of these drug products, FDA can review data from pharmacodynamics (PD) effect studies to assess BE.[23] For others, FDA often relies on data from "appropriately designed comparative clinical endpoint BE trials" or from in vitro studies to assess BE.[24]

The choice of appropriate BE 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. Congress intended to grant FDA wide discretion to establish BE standards on a drug-by-drug basis when it enacted the Hatch-Waxman Amendments, and courts have recognized FDA's discretion to determine how the BE requirement should be met for a product or class of products, as long as its determination is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion."[25]

C. Draft Product-Specific Guidances (PSGs) for Nitazoxanide

FDA's guidance for industry *Bioequivalence Recommendations for Specific Products* (June 2010) describes the Agency's process for making available to the public FDA's guidance on the design of bioequivalence studies for specific drug products.[26] FDA periodically publishes

---

[23] *See* 21 CFR § 320.24(b)(3). For example, FDA recommends PD effect BE studies for generic versions of corticosteroids. Studies evaluating blanching or vasoconstriction of the skin microvasculature can provide evidence for the amount of drug entering the skin and thus serve as the basis for comparing drug delivery from two potentially equivalent topical corticosteroid formulations. *See* FDA's guidance for industry on *Topical Dermatologic Corticosteroids: In Vivo Bioequivalence* (June 1995), available on FDA's website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/topical-dermatologic-corticosteroids-vivo-bioequivalence

[24] 21 CFR § 320.24(b)(4)-(5); *see also* FDA's draft guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (Dec. 2013) at 7-8, available on FDA's website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf. When final, this guidance will represent FDA's current thinking on this topic.

[25] *Fisons*, 860 F. Supp. at 865 (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).

[26] See FDA's guidance for industry *Bioequivalence Recommendations for Specific Products* (June 2010) available on FDA's website at: https://www.fda.gov/media/71401/download. This guidance states that the Agency intends to develop bioequivalence recommendations based on its understanding of the characteristics of the listed drug, information derived from published literature, and Agency research and consultations within different offices in FDA's Center for Drug Evaluation and Research (CDER) as needed based on the novelty or complexity of the bioequivalence considerations. Specific product recommendations may contain differing amounts of detail and background information depending on the product and will be revised as appropriate to ensure that the most up-to-date bioequivalence information is available to the public. Id. at 2-3.

notices in the *Federal Register* announcing the availability of draft, revised draft, and final versions of product-specific guidances. These documents are available on FDA's website.[27]

FDA considers comments received on PSGs when developing its final guidances. As with Agency guidance in general, these PSGs describe the Agency's current thinking and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. Applicants following our PSGs have an expectation that FDA will agree that their approach to establishing bioequivalence is appropriate. However, applicants may confer with the Agency on using a different approach for establishing bioequivalence. Recommendations made in a draft or final guidance do not bind the Agency or the public. Further, even in the absence of a PSG, FDA has the authority to approve a product supported by bioequivalence data that meet the applicable statutory and regulatory requirements.

In October 2011, FDA published an initial draft PSG for nitazoxanide tablets. This PSG recommended that ANDA applicants conduct three types of studies to establish bioequivalence: in vivo BE studies with PK endpoints under fasting and fed conditions; an in vivo BE study with clinical endpoints in patients with diarrhea caused by *G. lamblia*; and in vitro comparative dissolution testing in multiple biorelevant media.

Following the receipt of several controlled correspondence requesting revisions to the initial draft PSG, in November 2018 FDA published a revised draft PSG that recommended that ANDA applicants establish bioequivalence using one of two separate options.[28] The first option is a recommendation if the proposed ANDA product formulation is qualitatively and quantitatively (Q1/Q2)[29] the same as the RLD. This first option recommends that ANDA applicants conduct fasting and fed in vivo BE studies with PK endpoints along with in vitro dissolution studies. Under this option applicants should conduct a single-dose, two-treatment, two-period crossover study with PK endpoints obtained from healthy males and nonlactating, non-pregnant females from the general population using a 500 milligram (mg) tablet. The PSG recommends that applicants measure tizoxanide in plasma and that bioequivalence should be established based on the 90-percent confidence interval. The PSG also recommends a panel of comparative dissolution studies under multiple biorelevant conditions (i.e., biorelevant media representing different GI regions under fed or fasting conditions) and different pH levels (i.e., buffer solutions at pH levels between 6.8 and 7.5 with varying surfactant levels to discriminate formulation differences).

---

[27] Product-Specific Guidances for Generic Drug Development are available on FDA's website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[28] Draft nitazoxanide tablet Product Specific Guidance (PSG) available on FDA's website at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Nitazoxanide_Oral%20tablet_NDA%20021497_RV%20Oct%202018.pdf., When final, this guidance will represent FDA's current thinking on this topic.

[29] Q1 (qualitative sameness) means that the Test product uses the same ingredient(s) as the reference product. Q2 (quantitative sameness) means that the concentrations of the ingredient(s) used in the Test product are within ±5% of those used in the reference product. Because all ANDAs must have the same active ingredient and the same strength as the RLD, an analysis of whether an ANDA and its RLD are Q1/Q2 the same focuses on whether the products have the same inactive ingredients in the same concentrations.

The second option, for situations where a proposed ANDA product formulation is not Q1/Q2 the same as the RLD, recommends that ANDA applicants conduct an in vivo BE study with clinical endpoints, in vivo BE studies with PK endpoints, and in vitro comparative dissolution testing. The recommended in vivo BE studies with PK endpoints and in vitro dissolution studies are the same as those recommended under the first option. Under the second option, the study design for the clinical endpoint study should be a randomized, double blind, parallel, placebo-controlled study with samples obtained from immunocompetent subjects with diarrhea caused by *G. lamblia* using a 500 mg nitazoxanide tablet.

In November 2018, FDA also published a draft PSG for nitazoxanide oral suspension. The recommendations for establishing BE in this PSG are identical to those found in the PSG for nitazoxanide tablets except the recommended dosage for the in vivo bioequivalence studies is 100 mg / 5 milliliters (mL) (Dose: 500 mg).[30]

As explained in section I.B, the purpose of a BE study is to determine whether differences in formulation have an effect on the rate and extent to which the active ingredient or active moiety becomes available at the site of action. The recommendations in the PSGs for assessing bioequivalence of nitazoxanide products are designed to make such a determination, based on the nature of the product and nitazoxanide's site of action in the body. Because nitazoxanide is locally acting in the GI tract, it is difficult to directly measure the rate and extent to which the active ingredient or active moiety becomes available in the GI tract. No single test is adequate to determine BE, but the recommended tests together are adequate for FDA to determine whether BE has been demonstrated.

Nitazoxanide becomes available for both local action in the GI tract and systemic absorption following its release from the drug product after administration. After its release in the GI tract, and also after its absorption, nitazoxanide is hydrolyzed to tizoxanide. Given the significance of nitazoxanide's release in the GI tract and the differing conditions for drug release in the different regions of the GI tract, the dissolution studies recommended in the PSGs seek to ensure that there are no significant differences between the test and reference product in the rate and extent of drug release from those formulations in different regions of the GI tract that would affect the rate and extent to which the active moiety reaches the relevant regions of the GI tract. The biorelevant media recommended for in vitro dissolution studies in the PSGs are expected to simulate those physiological conditions relevant for different regions of the GI tract with or without the presence of food.

The PSGs also recommend fasting and fed in vivo PK endpoint BE studies, which measure the systemic concentration of tizoxanide. The rationale for the PK endpoint studies is that they are sensitive to detect differences in the rate and extent of release of nitazoxanide from different formulations. The release from a formulation determines the amount of drug that is available for both local action and systemic absorption. However, nitazoxanide is not detected and therefore cannot be measured in plasma because it is rapidly converted to tizoxanide. In this way,

[30] Draft nitazoxanide for oral suspension Product Specific Guidance (PSG) available on FDA's website at: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Nitazoxanide_Oral%20suspension_NDA%20021498_RC%20Oct%202018.pdf. When final, this guidance will represent FDA's current thinking on this topic.

tizoxanide plasma concentrations can serve as a surrogate for the amount of nitazoxanide released in the GI tract (i.e., local availability).[31] Accordingly, the recommended in vivo PK BE studies provide additional evidence to distinguish between two different formulations with potentially different in vivo release rates.

The same in vitro dissolution and in vivo PK studies are recommended regardless of whether a test product formulation is Q1/Q2 the same as the reference product. However, the PSGs differ as to their recommendations for a comparative clinical endpoint BE study depending on whether a test product formulation is Q1/Q2 the same. If product formulations are Q1/Q2 the same, then the formulations have virtually identical concentrations of identical inactive ingredients. Therefore, we are not concerned about the potential for differences in inactive ingredients between the ANDA product and RLD to affect the rate and extent to which the active moiety reaches the site of action. If the test formulation is Q1/Q2 the same, the recommended in vitro dissolution testing is normally sufficiently sensitive to discriminate between two nitazoxanide formulations with different in vivo drug release rates. This is because the recommended in vitro dissolution studies are expected to simulate the physiological conditions in different regions of the GI tract, where the drug is primarily released. The in vivo PK studies provide an additional means of detecting differences in in vivo drug release rates. In combination, the similarities between Q1/Q2 the same formulations, the recommended in vitro dissolution testing, and the recommended in vivo PK studies can permit a finding of equivalence in the rate and extent to which the active ingredient becomes available at the local site of action, and thus a finding of bioequivalence.

If the test formulation is not Q1/Q2 the same as the reference formulation, however, there are additional factors that may affect the rate and extent to which the active moiety becomes available in the GI tract. Impacts of different excipients and excipient levels may not be adequately assessed through in vitro dissolution testing and in vivo PK studies. For example, excipients may affect gastric and intestinal motility and interact with transporters and metabolizing enzymes in the gut. Although comparative clinical endpoint BE studies are generally not considered as sensitive as other BE studies, the PSGs recommend that a comparative clinical endpoint BE study be conducted to serve as an additional assessment to reduce residual uncertainty associated with the possible impact of different excipients and further ensure that any formulation differences between the test and reference product formulations do not result in differences in clinical effect. For non-Q1/Q2 formulations, the results of all three studies permit FDA to conclude that there are no significant differences in the rate and extent to which the active moiety becomes available at the site of action.

II. DISCUSSION

Petitioner requests that FDA refrain from approving an ANDA referencing Alinia as the listed drug unless the applicant conducts: (1) BE studies of both active metabolites, tizoxanide and tizoxanide glucuronide, in plasma under fasted and fed conditions; (2) BE studies with clinical

[31] See also Study 198.613 in NDA 021497 (nitazoxanide) (supporting that plasma concentrations of tizoxanide are correlated with on the amount of drug in the GI tract by showing that the area under the curve (AUC) and peak concentration (C_{max}) increase with doses between 1-4 grams under both fed and fasting conditions).

endpoints (regardless of whether the proposed generic product is quantitatively and qualitatively the same as the RLD); and (3) two BE studies with clinical endpoints – one in subjects with *G. lamblia* infection and another in subjects with *C. parvum* infection. Petitioner also requests that FDA revise its nitazoxanide PSGs accordingly.

A. Conducting BE Studies on Both Tizoxanide and Tizoxanide Glucuronide

Petitioner requests that FDA not approve any ANDA referencing Alinia as the RLD that does not conduct BE studies with PK endpoints that measure both metabolites of nitazoxanide, tizoxanide and tizoxanide glucuronide. According to Petitioner, because tizoxanide glucuronide has been shown to have therapeutic effect, it should be assayed directly to estimate its contribution to the "disposition of nitazoxanide" (Petition at 7-8). Petitioner contends that because the recommended studies in the PSGs do not account for tizoxanide glucuronide, those studies cannot measure comparability of concentrations of the active moieties[32] after the administration of nitazoxanide in vivo.

We disagree. For purposes of establishing BE, including detection of possible formulation impacts on a drug, FDA generally recommends measuring a parent drug rather than a metabolite. The concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a concentration-time profile of the metabolite, which is more reflective of metabolite formation, distribution, and elimination.[33] However, if a parent drug's concentration is too low and cannot be accurately and reliably measured in blood, plasma, or serum for an adequate length of time, FDA recommends measuring its primary active metabolite for a BE study with PK endpoints.[34] If the primary active metabolite can be accurately and reliably measured, FDA does not generally recommend collecting data on secondary metabolites because their concentrations are governed by the formation of the primary metabolites and do not normally reflect formulation differences of the parent drug during the absorption process.

In the case of nitazoxanide, the parent drug cannot be reliably and accurately measured in plasma, but its primary metabolite, tizoxanide, can be measured. FDA therefore recommends measuring tizoxanide in PK BE studies. Tizoxanide glucuronide is a secondary metabolite of nitazoxanide that is formed from the primary metabolite, tizoxanide. Concentrations of tizoxanide glucuronide are governed by the formation of tizoxanide. Thus, tizoxanide glucuronide is believed to be less sensitive than tizoxanide to detect differences in formulation performance, and separately measuring tizoxanide glucuronide in addition to tizoxanide likely

[32] Petitioner appears to characterize tizoxanide and tizoxanide glucuronide as "active moieties" because they have been shown to be active against protozoan parasites in vitro (Petition at 7). However, we refer to tizoxanide and tizoxanide glucuronide as active metabolites of nitazoxanide.

[33] See FDA draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (Dec. 2013) at 12, available on FDA's website at: https://www.fda.gov/media/87219/download. When final, this guidance will represent FDA's current thinking on this topic.

[34] Id.

would add little information of significance to the bioequivalence analysis.[35] Moreover, as noted in section I.A, tizoxanide glucuronide is significantly less potent than tizoxanide and nitazoxanide against the sporozoite stage of *C. parvum* and the trophozoite stage of *G. lamblia*.[36] For these reasons, FDA does not recommend measuring tizoxanide glucuronide in PK BE studies.[37]

In sum, the BE recommendations for option 1 outlined in the PSGs are consistent with FDA's general approach to BE testing that we believe accurately assesses the comparative BE of Alinia and a potential generic product. Additionally, Petitioner has failed to provide persuasive data or evidence indicating the need for tizoxanide glucuronide, a secondary metabolite of nitazoxanide, to be separately assayed. We believe that only PK BE studies on the primary metabolite (tizoxanide), in combination with the other recommended studies, are sufficient to support bioequivalence of a nitazoxanide ANDA, and we decline to recommend additional BE testing with PK endpoints for tizoxanide glucuronide for nitazoxanide generic products as Petitioner requests.

B. Conducting BE Studies with Clinical Endpoints Regardless of Whether Proposed Generic Is Q1/Q2 the Same

Petitioner argues that even if plasma concentrations of tizoxanide and tizoxanide glucuronide are accounted for, the studies described in option 1 of the PSGs do not adequately assess BE because they fail to measure the comparability of concentrations of the active moiety at the site of drug action. Petitioner claims those studies are deficient because, even if the proposed generic is Q1/Q2 the same: (1) plasma concentration of active moieties may not be indicative of concentrations of the active moiety at the site of drug action; (2) in vitro dissolution studies are incapable of meaningfully comparing the BE of the test and reference products at the site of drug action; and (3) quantitative and qualitative composition of the drug product fails to take into account differences in manufacturing processes (Petition at 8-12).

For the reasons discussed in section I.C, FDA believes that, collectively, the studies recommended under option 1 of the PSGs are sufficient to demonstrate BE for a proposed generic product that is Q1/Q2 the same as the RLD. Q1/Q2 sameness ensures that the proposed generic and RLD formulations, in addition to having the same active ingredient, have virtually

---

[35] Petitioner cites the inclusion of PK information for tizoxanide glucuronide in the Alinia labeling in support of its claim that tizoxanide glucuronide should be assayed directly (Petition at 8 & n.18 (citing Alinia labeling, section 12.3)). However, the inclusion of PK information for a secondary metabolite in labeling for the RLD does not mean that it is necessary or appropriate to measure that secondary metabolite to establish bioequivalence.

[36] See Microbiology Review, Application No.: 021497 & 021498s001, published July 2004 (Part 2, Pages 18-20 & 46) available on FDA's website at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-497_Alinia_Microbr_P2.pdf.

[37] We also note that studies submitted in the original marketing application for Alinia assessed the PK parameters of tizoxanide in lieu of nitazoxanide or tizoxanide glucuronide to determine the relative bioavailability between the tablet and oral suspension formulations (see Clinical Pharmacology and Biopharmaceutics Review, Application No.: 021497 & 021498s001, at page 16 (document page 16; pdf page 31 of 35), available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-497_Alinia_BioPharmr.pdf).

identical concentrations of identical inactive ingredients, thus alleviating the potential concern that different excipients and excipient levels in the generic product may affect the rate and extent to which the active moiety reaches the site of action. We acknowledge that manufacturing differences may impact formulation release rates. However, the recommended studies and applications' review process are adequately sensitive to detect these differences. The different biorelevant conditions and pH levels recommended for the in vitro dissolution studies in the PSGs are expected to simulate the relevant physiological conditions in different regions of the GI tract, such that these studies can detect differences between the proposed generic and RLD in the rate and extent of drug release in the different regions of the GI tract. The recommended in vivo PK BE studies, under both fasting and fed conditions, provide additional sensitive studies that can detect potential differences in release rates between formulations.

1. Measurement of Concentrations at the Site of Drug Action

We disagree with Petitioner's contention that the recommendations in the PSGs for Q1/Q2 the same formulations are not sufficient to establish comparability of local concentrations at the site of action. Although it is not possible to directly measure and compare drug concentrations at the local site of action in the GI tract, for the reasons discussed above, the formulation controls and in vitro and in vivo testing recommended under option 1 of the PSGs can nevertheless ensure comparability in the rate and extent to which the drug reaches the site of action.

Petitioner appears to place particular emphasis on the notion that comparable plasma concentrations do not establish comparable local concentrations at the site of action (see Petition at 9-10). But the function of the recommended in vivo PK BE studies is not to measure local concentrations of the drug directly. Rather, given that both local action and systemic absorption of nitazoxanide follow from nitazoxanide's release from the product formulation, and that nitazoxanide is rapidly hydrolyzed to tizoxanide in plasma such that nitazoxanide cannot be detected, tizoxanide plasma concentrations serve as a surrogate for local drug release of nitazoxanide at the site of action.[38] Thus, the recommended PK BE studies provide an additional means of detecting differences in in vivo drug release rates. Notably, results from studies submitted to NDA 021497 (Study B099597 and Study RM01-3011), which separately compared the systemic bioavailability of the tablet and oral suspension formulations of Alinia and compared clinical efficacy between the two formulations, suggest that BE studies of nitazoxanide with PK endpoints are more sensitive to formulation differences than comparative clinical endpoint BE studies.[39] Based on the PK study, the tablet and oral suspension formulations were not bioequivalent, but no significant difference in efficacy between the two

[38] Petitioner also suggests that the measurement of tizoxanide and tizoxanide glucuronide in bile may reflect the local availability of tizoxanide (see Petition at 6-7, 9). Again, this argument misunderstands the purpose of the recommended PK BE studies. The measurement of tizoxanide in plasma is not intended to directly reflect the amount of tizoxanide at the relevant site of action. It is intended to be a sensitive test to detect differences between the proposed generic drug product and the RLD that would affect release rates of the active ingredient from the drug product. The actual quantities of tizoxanide and tizoxanide glucuronide at the site of action are a function of both the formulation of the drug product and an individual's metabolic processes.

[39] See medical review part 1, NDA 021497 & 021498s001, available on FDA's website at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-497_Alinia_Medr_P1.pdf; clinical pharmacology and biopharmaceutics review, NDA 021497 & 021498, available on FDA's website at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-497_Alinia_BioPharmr.pdf.

formulations was shown in the comparative clinical endpoint study. Because we believe that formulation controls (i.e., Q1/Q2), in vitro dissolution testing, and in vivo PK BE studies can provide adequate information to conclude that a generic product that is Q1/Q2 the same as its RLD is also bioequivalent to the RLD, we do not recommend comparative clinical endpoint BE studies for such products. Such clinical endpoint BE studies would expose patients to unnecessary human research.

2. Sufficiency of Dissolution Studies to Compare Test and Reference Products

The in vitro dissolution testing recommended in the PSGs is expected to be sufficiently sensitive to discriminate between two nitazoxanide formulations that are Q1/Q2 the same with potentially different in vivo drug release rates.[40] As noted, nitazoxanide is a poorly soluble drug that becomes available and acts locally in the GI tract after its release from the drug product. The PSGs recommend a panel of comparative dissolution studies under multiple biorelevant conditions and different pH levels, which are expected to simulate the relevant physiological conditions in different regions of the GI tract. These studies can therefore ensure that there are no significant differences between the test and reference products in formulations and release mechanisms in different regions of the GI tract, and thus provide meaningful information to demonstrate bioequivalence.

To further address the assertions in this Petition, FDA developed a physiologically-based PK (PBPK) model for nitazoxanide. The PBPK model characterizes the PK of both nitazoxanide and its primary and secondary metabolites, tizoxanide and tizoxanide glucuronide, respectively. FDA conducted simulations evaluating multiple pH and other biorelevant conditions for in vitro dissolution testing in conjunction with in vivo PK studies for BE evaluation. Absorption profiles of nitazoxanide in different regions in the GI tract demonstrate that the absorption of nitazoxanide occurs throughout the GI tract with differing degrees of absorption occurring in each GI tract segment. FDA believes that this evidence supports the need to test comparative drug release and dissolution under different pH and other media conditions that are reflective of the lumen conditions in different GI regions. The evidence FDA obtained from these simulations also provides further support that the recommended in vitro comparative dissolution testing at multiple pH and media conditions can detect formulation-dependent dissolution differences, which may result in differences in local exposure in different GI regions. In sum, the in vitro dissolution studies recommended in the PSGs (along with the recommended in vivo PK BE studies) for proposed generic nitazoxanide products that are Q1/Q2 the same as the RLD are sufficiently capable of evaluating BE.

3. Quantitative and Qualitative Composition of Drug Product and Differences in Manufacturing Processes That May Impact BE

Finally, Petitioner argues that the mere fact that a generic product is Q1/Q2 the same as Alinia

[40] If present, differences in in vivo drug release rates may also be determined by systemic concentration measurements using in vivo PK endpoint BE studies.

does not ensure comparability of the active moiety at the site of action because the analysis of the drug product fails to take into account differences in manufacturing processes, which may have a significant impact on concentrations of the metabolites at the site of action. We do not disagree that differences in manufacturing processes may impact formulation release rates even between product formulations that are Q1/Q2 the same. However, we believe that the in vitro dissolution and in vivo PK studies recommended in option 1 of the PSGs are sufficiently sensitive to detect such differences.

Initially, we note that because the concentrations of the active ingredient or active moiety at the site of action cannot be measured for nitazoxanide, the impact of differences in manufacturing processes on the concentrations of the active moiety at the site of action also cannot be determined directly. It is possible that two nitazoxanide drug products could exhibit different release rates even when these drug products are considered qualitatively and quantitatively the same (i.e., Q1/Q2 the same). Nitazoxanide is practically insoluble in water and its formulation is relatively simple in composition.[41] Differences in the nitazoxanide drug substance manufacturing process may potentially affect the physicochemical properties of nitazoxanide (e.g., particle size, polymorphism), which in turn may contribute to differences in the release rate of nitazoxanide from the drug product formulation. Also, differences in the drug product manufacturing process (e.g., granulation, blending, drying, tableting, and coating) may potentially contribute to differences in the release rate of nitazoxanide from the drug product formulation.

Although differences in manufacturing processes may contribute to differences in drug release even where two nitazoxanide formulations are Q1/Q2 the same, FDA believes, for the reasons discussed above, that the in vitro dissolution and in vivo PK studies recommended in the PSGs are sufficient to detect such differences in drug release and thus demonstrate bioequivalence. Notably, PK studies measuring tizoxanide in plasma following administration of two different batches of Alinia tablets, each manufactured with nitazoxanide drug substance of different particle sizes, showed significantly different PK profiles of tizoxanide between the two batches.[42] These studies provide evidence that in vivo PK studies measuring tizoxanide in plasma, as recommended in the PSGs, may in fact detect differences in manufacturing processes even where two product formulations are Q1/Q2 the same.

In addition, the impact of different manufacturing processes on the release rate for a particular drug product can be significantly diminished by establishing: (1) sufficient in-process controls for the manufacturing processes; and (2) adequate specifications for the active pharmaceutical ingredient and for the final dosage form of the drug product. Normally, both manufacturing

[41] The tablet formulation for Alinia (NDA 021497) contains the following inactive ingredients: maize starch, pregelatinized corn starch, hydroxypropyl methylcellulose, sucrose, sodium starch glycollate, talc, magnesium stearate, soy lecithin, polyvinyl alcohol, xanthan gum, titanium dioxide, FD&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, and FD&C Blue No. 2 Aluminum Lake. See current labeling for Alinia (NDA 021497) (July 2016), available on FDA's website at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021497s001,021498s004lbl.pdf.

[42] See chemistry review, NDA 021497.

controls and specifications are reviewed and approved through the NDA and ANDA review process. With adequate manufacturing controls and specifications for generic products and RLDs, batch-to-batch consistency of each individual drug product can be ensured, and thus the reliability of comparisons between products to determine BE, as shown by the in vitro and in vivo studies recommended in the PSGs, can also be ensured.[43]

C. Conducting Two BE Studies – One in Subjects with *G. lamblia* and One in Subjects with *C. parvum*

Petitioner argues that the BE studies described in the PSGs are insufficient to ensure public safety because they do not require a BE study with clinical endpoints in patients with *C. parvum*. According to the Petitioner, because the sites of action for *C. parvum* and *G. lamblia* are different, a single BE study with clinical endpoints in patients with *G. lamblia* does not support a conclusion that the same drug product would be successful in treating *C. parvum* infections (Petition at 12-14). We disagree.

To approve a generic drug, FDA requires studies that demonstrate bioequivalence to a drug already proven safe and effective. Under § 320.24(a), different types of evidence may be used to establish BE for pharmaceutically equivalent drug products, including in vivo or in vitro testing, or a combination of both. The selection of the method used to demonstrate BE depends upon the purpose of the study, the analytical methods available, and the nature of the drug product.[44] For drug products whose active moiety(ies) or active metabolite(s) are not systemically available in biological fluid or for which PK measurements are less meaningful, FDA may request comparative clinical endpoint BE studies.[45] Comparative clinical endpoint BE studies are not the same as the pivotal safety and efficacy studies that support an NDA approval. The purpose of a comparative clinical endpoint BE study is to detect formulation differences between the test product and the RLD that may impact the safety or therapeutic effect of the proposed generic drug when substituted for the RLD. These studies are not a study of therapeutic efficacy, but are instead a quantitative comparison of the clinical (therapeutic) effect of a test and reference product.

FDA recommends only those studies necessary to assess bioequivalence. Therefore, if BE for all indications can be shown for a multi-indication drug with a comparative clinical trial in just one indication, the other indications do not need to be studied. For a drug product such as

---

[43] We note that FDA's recommendations for the evaluation of BE of generic nitazoxanide products are consistent with our recommendations for evaluating BE in other poorly-soluble GI locally-acting products. See citizen petition responses for rifaximin (FDA-2016-P-3418) and lubiprostone (FDA-2014-P-0144) and their respective PSGs (available on FDA's website at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Rifaximin_oral%20tablet_NDA%20022554%20and%20021361_RV03-17.pdf https://www.accessdata.fda.gov/drugsatfda_docs/psg/Lubiprostone_draft_Oral%20cap_RLD%2021908_RC07-15.pdf).

[44] See § 320.24(a).

[45] See § 320.24(b)(4).

nitazoxanide, one aspect of determining appropriate BE study design is determining which indication or indication(s) to study to use the most sensitive, accurate, and reproducible approach available. Additionally, if the site of action is the same for all indications of a multi-indication drug, there generally is no need to conduct a comparative clinical endpoint BE study in more than one indication and expose humans to unnecessary clinical studies.

G. lamblia and *C. parvum* are intestinal protozoa responsible for outbreaks associated with water or foodborne transmission. The clinical symptoms caused by these protozoa in immunocompetent patients are similar: a self-limited illness characterized by diarrhea, abdominal cramps, bloating, weight loss, and malabsorption.[46] Unlike giardiasis,[47] the epidemiology for cryptosporidiosis[48] is affected by the host-immune status; there is a higher prevalence in immunocompromised individuals, particularly those with AIDS and low White Blood Cell (CD4) counts. In immunocompromised individuals, *C. parvum* can cause a life-threatening infection with profuse, watery, cholera-like diarrhea.[49]

Following ingestion, the *Cryptosporidium* oocytes or *Giardia* cysts pass through the stomach to the small intestine where they excyst to give rise to *Cryptosporidium* sporozoites or *Giardia* trophozoites. The *Cryptosporidium* sporozoites or *Giardia* trophozoites adhere to the small intestine epithelial cells where they replicate and/or reproduce. *Giardia* trophozoites remain on the mucosal surface of the epithelial cell, but the *Cryptosporidium* sporozoites invade the epithelial cells and change to merozoites before replication. The *Cryptosporidium* oocytes or *Giardia* cysts are then excreted into the feces. Thus, the sites of action for nitazoxanide's two indications are closely related. As noted in section I.A, nitazoxanide's antiprotozoal activity is believed to be due to interference with the PFOR enzyme-dependent electron transfer reaction. The PFOR protein sequence of *G. lamblia* appears similar to that of *C. parvum*.[50]

FDA considered a number of factors in developing the nitazoxanide PSGs including: whether a showing of BE in one indication would be sufficient to show BE in the other indication; and in which of the two indications studies would be more sensitive for detecting differences between drug products, provide more reproducible results, and be most feasible to conduct.

Considering the nature of the nitazoxanide drug product, including its site and mechanism of action, FDA concluded that the results of a clinical endpoint study showing BE in one

---

[46] Painter JE, Gargano JW, Collier SA, et al. Giardiasis Surveillance – United States, 2011-2012. *MMWR Suppl* 2015; 64(3): 15-25; Painter JE, Hlavsa MC, Collier SA, et al. Cryptosporidiosis Surveillance – United States, 2011-2012. *MMWR Suppl* 2015; 64(3): 1-14.

[47] Giardiasis is a diarrheal disease caused by the microscopic parasite *Giardia*. See Centers for Disease Control and Prevention (CDC) website, available at https://www.cdc.gov/parasites/giardia/index.html.

[48] Cryptosporidiosis is a diarrheal disease caused by the parasite *Cryptosporidium*. See CDC website, available at https://www.cdc.gov/parasites/crypto/index.html.

[49] Huang DB, White AC. An Updated Review on *Cryptosporidium* and *Giardia*. *Gastroenterol Clin N Am* 35(2006):291-314.

[50] Alinia labeling (NDA 021497) (July 2016), available on FDA's website at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021497s001,021498s004lbl.pdf.

indication can be extrapolated to show BE in the other indication. Specifically, because of the similarity in the site of action between the two indications and the similarity in the PFOR protein sequence between *G. lamblia* and *C. parvum*, FDA expects that a drug that reaches the site of action for *G. lamblia* (the small intestine epithelial cells) and demonstrates antiprotozoal activity against *G. lamblia* would also reach the site of action for *C. parvum* (i.e., penetrate the epithelial cells) and act against *C. parvum*. Accordingly, FDA believes that a comparative clinical endpoint BE study showing BE in patients with *G. lamblia* infection, along with the other studies recommended in the PSGs, would provide sufficient evidence to demonstrate comparable therapeutic effect in patients with *C. parvum* infection.[51]

In selecting the indication in which to recommend a clinical endpoint BE study, FDA sought to determine which studies would be most sensitive, accurate, and reproducible. Given that the treatment effect of the study indication may impact the study sensitivity, treatment effect observed in the pivotal RLD clinical studies were considered. FDA determined that the nitazoxanide treatment effect appears similar between the two indications and therefore that a BE study enrolling patients for either indication would not impact the study sensitivity. The reproducibility and accuracy of the BE study results also affected the selected indication. Unlike *G. lamblia*¸ the treatment effect of nitazoxanide on *C. parvum* appears to depend on the nutritional and immune status of the host. In clinical studies of the RLD, pediatric patients who were malnourished had a lower treatment effect (33%) to nitazoxanide treatment than pediatric patients of normal nutritional status (50%). Nitazoxanide was also not shown to be superior to placebo for the treatment of diarrhea caused by *C. parvum* in immunocompromised patients.[52] This variability in the treatment effect due to patient characteristics makes a clinical endpoint BE study in patients with *C. parvum* less accurate and reproducible. Additionally, study enrollment for *G. lamblia* infection is less challenging than for *C. parvum* infection because there are *G. lamblia* endemic areas that can be targeted while *C. parvum* is more dependent on an infection outbreak. In sum, the PSGs' recommendation for a single clinical endpoint BE study conducted in patients with diarrhea caused by *G. lamblia* is consistent with FDA's

[51] Petitioner argues that "clinical trials supporting efficacy" should be conducted in both indications, and asserts as support for this argument that FDA asked for at least two adequate and well-controlled trials in each indication to support the efficacy of each of Alinia's approved dosage forms (the tablets and oral suspension) (Petition at 14). But the purpose of comparative clinical endpoint BE studies is different from that of efficacy and safety studies conducted to support an NDA approval. In addition, ANDAs are designed to have the same properties as the RLD, including the same dosage form. Although multiple clinical trials were conducted to demonstrate Alinia's efficacy and safety in the first instance, FDA has concluded that a comparative clinical endpoint BE study in only one indication can suffice to achieve the purpose of that type of study – to detect formulation differences between a proposed generic product and the RLD – and (together with the other studies recommended in the PSGs) demonstrate bioequivalence of a non-Q1/Q2 generic product.

[52] That Alinia has "not been shown to be superior to placebo for the treatment of diarrhea caused by *C. parvum* in HIV-infected or immunodeficient patients" (see Alinia labeling, section 8.7) undercuts Petitioner's argument that, if a clinical endpoint BE study is conducted in only one indication, it should be in *C. parvum* infection. Petitioner argues that this is because *C. parvum* infection can be fatal, particularly in children and immunosuppressed persons (Petition at 12-14). The Alinia labeling has a limitation of use for treatment of diarrhea caused by *C. parvum* in HIV-infected or immunodeficient patients. Thus, any clinical endpoint BE study would not include patients in these categories and testing in an approved patient population with *C. parvum* infection would not be more sensitive for distinguishing formulations.

approach to its recommended BE study design and a second clinical endpoint BE study in patients with diarrhea caused by *C. parvum* is not recommended.

III. CONCLUSION

As explained above, we have carefully reviewed the information in the Petition. Based on our review of the available scientific and medical information, the Agency believes that its current approach to BE study design for nitazoxanide as reflected in the PSGs is appropriate. Therefore, we do not agree that the draft PSGs need to be revised to change these recommendations. We note, however, that we will continue to examine our recommendations in light of any new scientific information that becomes available to the Agency and will update the PSGs as appropriate. Accordingly, the Petition is denied.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002411843, cn=Patrizia A. Cavazzoni -S
Date: 2020.11.27 13:13:06 -05'00'

Patrizia Cavazzoni, M.D.
Acting Director
Center for Drug Evaluation and Research