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January 24, 2020

VIA ELECTRONIC SUBMISSION

Dockets Management Branch, HFA-305
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

On behalf of Romark Laboratories, L.C., a Florida limited liability company (hereinafter "Romark")[1], I hereby submit this Citizen Petition under sections 505(b) and 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") (21 U.S.C. §§ 355(b) and (j)), and 21 C.F.R. §§ 10.30 and 10.31 to request that the Commissioner of Food and Drugs not approve any abbreviated new drug application ("ANDA") for any generic version or other pharmaceutical alternative of ALINIA® (nitazoxanide) tablets ("Alinia® Tablets"), for oral use and ALINIA® (nitazoxanide) for oral suspension ("Alinia® Oral Suspension") (collectively "Alinia®") unless and until the applicant satisfies all of the conditions set forth in this petition. Romark is the

[1] Romark, together with its affiliates, is a global pharmaceutical company specializing in the development, production and marketing of proprietary branded pharmaceuticals and is responsible for the development, registration and marketing of Alinia®.

manufacturer and distributor of Alinia®, a treatment for diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*.

I. Actions Requested

Romark respectfully requests FDA not approve any ANDA citing Alinia® as the reference listed drug ("RLD") unless the applicant conducts:

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

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

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

As described in detail below, such requirements are necessary because the product raises complicated and important scientific and legal issues. In addition, Romark requests that FDA revise the Draft Guidance on Nitazoxanide (tablets) and Draft Guidance on Nitazoxanide (oral suspension)[2] (collectively "Draft Guidances") to incorporate the above-listed criteria in order to ensure bioequivalence.

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[2] FDA Guidances entitled Draft Guidance on Nitazoxanide (tablets) and Draft Guidance on Nitazoxanide (oral suspension) are available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Nitazoxanide_Oral%20tablet_NDA%20021497_RV%20Oct%202018.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/psg/Nitazoxanide_Oral%20suspension_NDA%021498_RC%20Oct%202018.pdf.

II. Brief Statement of Grounds

Statutory and Regulatory Requirements

Romark is the manufacturer and NDA holder of FDA-approved drug product Alinia® (nitazoxanide), a treatment for diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*.

Among other things, the FDCA requires that a generic drug be bioequivalent to the listed drug.[3] FDA regulations explain that bioequivalence is "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[4]

These statutory and regulatory standards compel FDA to grant the Actions Requested in this petition because the studies proposed by the Draft Guidances (*in vitro* dissolution of nitazoxanide and tizoxanide and bioequivalence ("BE") of tizoxanide in plasma following oral administration in fed and fasted states) cannot measure comparability of concentrations of active moieties at the site of infection.

III. Complete Statement of Grounds

There is no data to support an assumption that a proposed generic drug with *in vitro* dissolution comparable to the reference drug and BE of tizoxanide in plasma under fed and fasted conditions translates to comparable tizoxanide and tizoxanide glucuronide excretion in bile, and therefore, comparable concentrations of tizoxanide in the lumen and tissues of the

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[3] 21 U.S.C. § 355(j)(a)(8)(B)(i).

[4] 21 C.F.R. § 314.3.

gastrointestinal tract where tizoxanide is active. Failure to provide comparable concentrations of tizoxanide in the gastrointestinal tract could adversely affect the safety and/or efficacy of the drug and present a danger to public health.

The studies proposed by Option 1 of the Draft Guidances (*in vitro* dissolution of nitazoxanide and tizoxanide and *in vivo* BE of tizoxanide in plasma following oral administration in fed and fasted states) make no attempt to directly measure the concentrations of tizoxanide or tizoxanide glucuronide at the site of drug action. They do not even attempt to measure concentrations of the active metabolite, tizoxanide glucuronide, in plasma. Furthermore, the proposed studies cannot provide adequate information to hypothesize (by means of deductive reasoning) BE at the site of drug action because they do not measure biliary excretion of tizoxanide or tizoxanide glucuronide.

The studies proposed by Option 2 of the Draft Guidances (*in vitro* dissolution of nitazoxanide and tizoxanide and *in vivo* BE study with clinical endpoints in subjects with diarrhea caused by *G. lamblia*) do not provide information required to determine BE in subjects with *C. parvum*. The site of infection and disease course are different upon infection with these two organisms, and activity against *G. lamblia* is not indicative of activity against *C. parvum*. This is discussed in further detail below.

Therefore, at a minimum, approval of an ANDA citing Alinia® as the RLD can only be granted pursuant to the Actions Requested, *supra,* which are the only way to definitely establish bioequivalence against *G. lamblia* and *C. parvum* at the site of infection. Failure to do so will likely adversely affect the safety and/or efficacy of the drug and present a danger to public health with respect to individuals who are infected with these organisms.

A. Background

Alinia® is approved in two forms: tablets, for oral use and oral suspension. Romark is the manufacturer and distributor of Alinia®, a treatment for diarrhea caused by *G. lamblia* or *C. parvum*.[5]

C. parvum and *G. lamblia* are both waterborne protozoan parasites. Despite this similarity, there are important differences in the nature of disease caused by these organisms, their life cycles and sites of infection.

In the case of *C. parvum*, oocysts are ingested, then undergo excystation, then release four sporozoites, which invade epithelial cells of the intestinal tract, primarily in the ileum. Epithelial cell infection consists of two sequential steps: (1) attachment of sporozoites to the plasma membrane of epithelial cells, and (2) invasion of sporozoites into host cells via invagination of the host cell plasma membrane, resulting in the formation of a parasitophorous vacuole where the parasite remains intracellular, but extracytoplasmic.[6]

In the case of *G. lamblia*, ingested cysts release trophozoites that colonize and replicate in the small intestine of the host. *G. lamblia* trophozoites do not invade the epithelial or deeper layers of the mucosa, but rather attach to the mucosal tissues of the duodenum and upper jejunum. Propagation occurs on the epithelial surface.[7] Both *C. parvum* and *G. lamblia* can

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[5] Alinia® Prescribing Information §§ 1, 3.1, 3.2 (Rev. 04/2017) (hereinafter "Alinia® PI")

[6] O'Hara SP, Chen X-M. "The cell biology of *Cryptosporidium* infection" *Microbes and Infect*ion 13.8-9 (2011): 721-730.

[7] Solaymani-Mohammadi S., et al. "A meta-analysis of the effectiveness of albendazole compared with metronidazole as treatments for infections with *Giardia duodenalis*" *PLoS Neglected Tropical Diseases* 4.5 (2010): e682

enter the bile ducts causing biliary infection.[8,9] Notably, the administration of nitazoxanide has been reported to be effective in reducing biliary infection by *C. parvum* in immunosuppressed gerbils.[10]

The active ingredient in Alinia® is nitazoxanide. However, following oral administration in humans, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide.[11] Tizoxanide then undergoes conjugation, primarily by glucuronidation. Both tizoxanide and tizoxanide glucuronide have been shown to be active against protozoan parasites *in vitro*, although the concentrations required for tizoxanide glucuronide are much higher than for tizoxanide.[12]

Tizoxanide is >99.9% bound to proteins (primarily albumin) in plasma, and is excreted in urine, bile and feces.[13] On the other hand, tizoxanide glucuronide is cleared more slowly from the plasma than the free form, and it is excreted in urine and bile, but not in feces.[14]

Concentrations of tizoxanide and tizoxanide glucuronide in bile have been measured at approximately ten-fold those observed in plasma. After being eliminated in bile and deposited in

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[8] Chen X-M, LaRusso N. "Human intestinal and biliary cryptosporidiosis" *World journal of gastroenterology.* 5.5 (1999): 424-429.

[9] Hiromichi A et al. "Acute acalculous cholecystitis caused by *Giardia lamblia*" *Internal medicine (Tokyo, Japan)* 56.13 (2017):1657-1662.

[10] Baishanbo, Gargala, et al. "Efficacy of nitazoxanide and paromomycin in biliary tract cryptosporidiosis in an immunosuppressed gerbil model." *Journal Antimicrobial Chemotherapy* 57.2 (2006):353-5.

[11] Alinia® PI § 12.3.

[12] Gargala, Gilles, et al. "Efficacy of nitazoxanide, tizoxanide and tizoxanide glucuronide against Cryptosporidium parvum development in sporozoite-infected HCT-8 enterocytic cells." *Journal of Antimicrobial Chemotherapy* 46.1 (2000): 57-60.

[13] Alinia® PI § 12.3.

[14] Stockis A., et al. "Nitazoxanide pharmacokinetics and tolerability in man after single ascending oral doses" *International Journal of Clinical Pharmacology and Therapeutics* 40.5 (2002):213-220.

the duodenum, tizoxanide glucuronide is deconjugated, so that only tizoxanide can be recovered in feces.[15]

Therefore, the activity of nitazoxanide and tizoxanide against *C. parvum* and *G. lamblia* in the intestinal tract is at least partially attributed to tizoxanide glucuronide, which is eliminated in bile, deconjugated and passes through the intestinal tract from the duodenum through the rectum. Approximately two-thirds of an oral dose of nitazoxanide is eliminated in feces as tizoxanide.

B. FDA Should Not and Cannot Approve Any ANDA Citing Alinia® As The RLD Unless The ANDA Applicant Has Conducted Bioequivalence Studies Of Tizoxanide And Tizoxanide Glucuronide In Plasma In Fasted And Fed Conditions.

As noted *supra*, the FDCA requires a generic to be *bioequivalent* to the RLD, and this bioequivalence should focus on the availability of the *active moiety* at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. 21 C.F.R. § 320.1(e).

The active metabolites of Alinia® include both tizoxanide and tizoxanide glucuronide, which each have been shown to be active against protozoan parasites *in vitro*. To be sure, FDA has recognized tizoxanide and tizoxanide glucuronide as the active moieties of nitazoxanide.[16] However, the Draft Guidances do not take into account the active moiety tizoxanide glucuronide.

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

[16] Clinical Pharmacology Biopharmaceutics Review(s) (PDF), Application No.: 021497 & 021498s001; available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-497_Alinia_BioPharmr.pdf.

Instead, the Draft Guidances suggest *in vitro* dissolution of nitazoxanide and tizoxanide and BE of only *tizoxanide* in plasma following *in vivo* oral administration in fed and fasted states.

Studies have demonstrated that since tizoxanide glucuronide "has shown to be effective against both parasites and bacteria, it should be assayed directly (*i.e.*, without prior conversion to free tizoxanide) in plasma, urine and feces in order to estimate its contribution to the disposition of nitazoxanide."[17] Indeed, the pharmacokinetic ("PK") information in the Alinia® Prescribing Information ("PI") includes concentrations of tizoxanide glucuronide.[18]

The proposed studies in the Draft Guidances do not account for tizoxanide glucuronide, and therefore, cannot measure comparability of concentrations of the active moieties after administration of nitazoxanide *in vivo*.

C. FDA Should Not and Cannot Approve Any ANDA Citing Alinia® as the RLD Unless the ANDA Applicant Has Conducted Bioequivalence Studies With Clinical Endpoints Regardless Of Whether The Proposed Generic Drug Is Q1/Q2 The Same.

Even if the plasma concentrations of active moieties, tizoxanide and tizoxanide glucuronide, are taken into account for the reasons discussed *supra*, the *in vivo* BE studies with PK endpoints and *in vitro* dissolution studies described in the Draft Guidances ("Option 1 Studies") are not indicative of BE because they cannot measure comparability of concentrations of the *active moiety at the site of drug action*. In particular, the Option 1 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;

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

[18] Alinia® PI § 12.3.

(2) the *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) the quantitative and qualitative composition of the drug product fails to take into account differences in manufacturing processes, which may have significant impact on concentrations of tizoxanide and tizoxanide glucuronide at the site of action.

i. Plasma concentration of active moieties may not be indicative of concentrations of the active moiety at the site of drug action

The site of action of an effective treatment for *C. parvum* includes the epithelial cells, while the site of an effective treatment for *G. lamblia* includes the lumen of the intestinal tract and the exterior of mucosal tissues. Concentrations of tizoxanide and tizoxanide glucuronide in bile have been approximately ten-fold those observed in plasma. It is only after being eliminated in bile and deposited in the duodenum that tizoxanide glucuronide is deconjugated into the more active tizoxanide, and only tizoxanide can be recovered in feces.

Therefore, the activity of nitazoxanide and tizoxanide against *C. parvum* and *G. lamblia* in the intestinal tract likely is at least partially attributed to tizoxanide glucuronide, which is eliminated in bile, deconjugated and passes through the intestinal tract from the duodenum through the rectum.

The pharmacokinetic studies in the Draft Guidances rely only on *plasma* concentration of *tizoxanide*, and there is no data to support an assumption that a proposed generic drug with *in vitro* dissolution comparable to the reference drug and BE of tizoxanide and tizoxanide glucuronide in plasma in fed and fasted conditions translates to comparable tizoxanide and tizoxanide glucuronide excretion in bile, and therefore, comparable concentrations of tizoxanide in the gastrointestinal tract where tizoxanide is active.

It would be insufficient if FDA was merely to include plasma concentrations of tizoxanide glucuronide as a second analyte to be measured in the pharmacokinetic studies in the Draft Guidances. Studies have demonstrated that some, but not all, tizoxanide glucuronide is excreted in bile and transported to the gastrointestinal tract where it is deconjugated to the active tizoxanide form. Furthermore, the plasma concentrations of tizoxanide and tizoxanide glucuronide have a substantial standard deviation that does not lend itself to extrapolation to comparability of concentrations of the active moiety at the site of drug action.[19] It is possible that the standard deviation concentrations of tizoxanide and tizoxanide glucuronide in plasma are affected by differences in metabolism (for example, one person may be more efficient in glucurono-conjugating drugs than another) which have little if anything to do with the concentrations of tizoxanide and tizoxanide glucuronide at the site of action.

ii. The *in vitro* dissolution studies are incapable of meaningfully comparing the BE of the test and reference products at the site of drug action

The deficiencies in the Option 1 Studies are not limited to the *in vivo* PK studies. The proposed *in vitro* dissolution studies also present issues that may limit their probative value. For instance, during the approval process, FDA addressed the difficulties finding suitable parameters for dissolution testing, and FDA recommended that the applicant develop a dissolution method using pH 7.5 phosphate buffer+ 6% hexadecyltrimethyl ammonium bromide conducted at 25°C

[19] Alinia® PI § 12.3.

rather than at 37°C.[20] None of the *in vitro* dissolution studies described in the Draft Guidances have been shown to be predictive of BE of tizoxanide or tizoxanide glucuronide in plasma or at the site of drug action.

Given the recognized difficulties in performing *in vitro* dissolution studies of nitazoxanide and the lack of data establishing a relationship between *in vitro* dissolution and BE at the site of drug action, it is unlikely that the dissolution studies in the Draft Guidances would provide meaningful information indicative of BE.

iii. Quantitative and qualitative composition of the drug product fails to take into account differences in manufacturing processes, which may have significant impact on bioequivalence

Furthermore, the mere fact that a proposed generic drug product is Q1/Q2 the same as Alinia® cannot ensure comparability of concentrations of the active moiety at the site of action because the quantitative and qualitative composition of the drug product fails to take into account differences in manufacturing processes, which may have significant impact on concentrations of tizoxanide and tizoxanide glucuronide at the site of action.

Failure to provide comparable concentrations of tizoxanide and tizoxanide glucuronide in the gastrointestinal tract would likely adversely affect the safety and/or efficacy of the drug and present a danger to public health.

Given the variable extent and timing of active moieties at the point of activity in the gastrointestinal tract, the pharmacokinetic studies described in the Draft Guidances cannot

[20] Clinical Pharmacology Biopharmaceutics Review(s) (PDF), Application No.: 021497 & 021498s001; available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-497_Alinia_BioPharmr.pdf.

accurately measure comparability of concentrations of the active moiety at the site of drug action.

When PK studies are insufficient, then bioequivalence studies with clinical endpoints should be used to demonstrate bioequivalence. As noted *supra*, the PK studies are insufficient, and FDA should require any ANDA citing Alinia® to conduct bioequivalence studies with clinical endpoints.

D. FDA Should Not and Cannot Approve Any ANDA Citing Alinia® as the RLD Unless the ANDA Applicant Has Conducted Two Bioequivalence Studies With Clinical Endpoints – One In Subjects With *G. lamblia* And Another In Subjects With *C. parvum*.

The BE studies described in the Draft Guidances are insufficient to ensure public safety because each Draft Guidance suggests only a single BE study with clinical endpoints in patients with *G. lamblia* infection. As explained herein, a BE study with clinical endpoints in patients with *G. lamblia* infection cannot ensure activity against *C. parvum*. *C. parvum* infection can be fatal. Indeed, in a clinical trial conducted in young children immunosuppressed due to malnutrition and presenting to the hospital with cryptosporidiosis, 18% of the patients treated with placebo died within eight days of enrollment compared to none of the patients treated with Alinia® Oral Suspension.[21] A lack of the active moiety at the site of action would likely place some patients with *C. parvum* at unreasonable risk creating a danger to public health.

C. parvum and *G. lamblia* are both waterborne protozoan parasites, nevertheless there are important differences in the nature of disease caused by these organisms, their life cycles and sites of infection. In the case of *C. parvum*, oocysts are ingested, then undergo excystation, then

[21] Amadi, Beatrice, et al. "Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial." *The Lancet* 360.9343 (2002): 1375-1380.

release four sporozoites, which invade epithelial cells. Epithelial cell infection consists of two sequential steps: (1) attachment of sporozoites to the plasma membrane of epithelial cells, and (2) invasion of sporozoites into host cells via invagination of the host cell plasma membrane, resulting in the formation of a parasitophorous vacuole where the parasite remains intracellular, but extracytoplasmic.[22]

In the case of *G. lamblia*, ingested cysts release trophozoites that colonize and replicate in the small intestine of the host. *G. lamblia* trophozoites do not invade the epithelial or deeper layers of the mucosa, but rather attach to the mucosal tissues of the duodenum and upper jejunum. Propagation occurs on the epithelial surface. Both *C. parvum* and *G. lamblia* can enter the bile ducts causing biliary infection. Notably, the administration of nitazoxanide has been reported to be effective in reducing biliary infection by *C. parvum* in immunosuppressed gerbils.

Thus, the site of action for *C. parvum* and *G. lamblia* are different, and the inference from a single BE study with clinical endpoints in patients with *G. lamblia* infection are not sufficient to support a conclusion that the same composition would be successful in treating *C. parvum* infection.

In addition to the different sites of action for *C. parvum* and *G. lamblia*, the nature of illness caused by *C. parvum* and *G. lamblia* are also different. *C. parvum* often causes fulminant diarrhea and can be fatal, particularly in children and immunosuppressed persons.[23]

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[22] Amadi, Beatrice, et al. "Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial." *The Lancet* 360.9343 (2002): 1375-1380.

[23] Amadi, Beatrice, et al. "Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial." *The Lancet* 360.9343 (2002): 1375-1380.

Comparatively, *G. lamblia* is rarely fatal.[24] *G. lamblia* infection is typically associated with persistent diarrhea, weight loss and malabsorption.

In view of the different sites of action in treating *C. parvum* and *G. lamblia*, clinical trials supporting efficacy should be conducted in subjects with *G. lamblia* infection and in subjects with *C. parvum* infection. Failure to demonstrate equivalent efficacy to the reference drug in treating *C. parvum* infection could create a significant public health risk due to the potentially life-threatening nature of the disease.

Indeed, FDA required Romark to conduct two pivotal trials of Alinia® Tablets in patients with *G. lamblia* and two in patients with *C. parvum*. Likewise, FDA required Romark to conduct two pivotal trials of Alinia® Oral Suspension in patients with *G. lamblia* and three pivotal trials of Alinia® Oral Suspension in patients with *C. parvum*. It is notable that FDA did not extrapolate efficacy in treating *G. lamblia* infection to conclude efficacy in treating *C. parvum* infection.[25] Likewise, FDA did not extrapolate efficacy of one formulation to the other (Alinia® Tablets to Alinia® Oral Suspension or vice versa). The requirement of at least two adequate and well-controlled trials to support efficacy of each of these products in each of these indications is attributed to the differences in the site of action of the drug for treating each of the two infections.

Furthermore, if FDA only requires one BE study with clinical endpoints it should be in patients suffering from *C. parvum* infection in view of the potentially fatal consequence of *C.*

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[24] Giardiasis - The Center for Food Security and Public Health (available at http://www.cfsph.iastate.edu/Factsheets/pdfs/giardiasis.pdf) (accessed on Nov. 19, 2019).

[25] Alinia® PI § 14.

parvum infection. Appropriate measures to ensure the safety of participants can be taken when developing the BE study, and any risks or costs associated with the study are far outweighed by the potential risk to the public that is associated with a purported ANDA product that has been inadequately evaluated as a result of incomplete PK and/or BE studies.

IV. Conclusion

The FDCA requires an ANDA applicant to demonstrate, among other things, that the new drug has the "same" active ingredient as the approved RLD. For the reasons stated herein, demonstrating sameness to Alinia® presents complex scientific issues that are not currently adequately addressed in the Draft Guidances. For these reasons, Romark requests that FDA not approve any ANDA application for a purported generic nitazoxanide until and unless these requirements are met.

V. Required Material

A. Environmental Impact

Petitioner believes that this petition does not require an environmental impact analysis report under 21 C.F.R. § 25.1(g)(1995).

B. Economic Impact

An economic impact report is required only when requested by the Administration and such report has not been requested. 21 C.F.R. § 10.30(b).

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to me and/or Romark on or about the following dates: November 22, 2002 with respect to information about Alinia Suspension; July 21, 2004 with respect to information about Alinia tablets; and September 1, 2019 with respect to information about the Draft Guidances on Nitazoxanide.

If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Romark. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Nathan A. Beaver
Regulatory Counsel to
Romark Laboratories, L.C.

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