DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

September 30, 2013

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Re: Docket No. FDA-2009-P-0594

Dear Ms. Tomaselli and Dr. Wallinga:

This letter responds to the Citizen Petition (FDA-2009-P-0594) you submitted to the Food and Drug Administration ("FDA" or "the Agency") on December 11, 2009, on behalf of the Center for Food Safety and the Institute for Agriculture and Trade Policy ("petition").

The petition requests that FDA: "immediately suspend the approval of all new animal drug applications (NADAs) for arsenic-containing compounds used as feed additives for food animals," specifically those for roxarsone, arsanilic acid, nitarsone, and carbarsone and combination drugs that include those four new animal drugs; publish a "Notice of Opportunity for an Evidentiary Hearing concerning 'new evidence'" related to such applications; issue, upon completion of the hearing, an "order withdrawing the approval of all NADAs for arsenic-containing compounds used as feed additives for animals"; and "[r]evoke all regulations associated with the approval of all NADAs for arsenic-containing compounds used as feed additives for animals . . . ." Petition at 2-3.

On June 3, 2010, FDA's Center for Veterinary Medicine (CVM or "the Center") issued an interim response to the petition explaining that more time was needed to issue a final response because of the complexity and the number of issues raised in the petition. On August 9, 2011, you sent a letter to Dr. Margaret Hamburg referencing a study FDA conducted on roxarsone and the voluntary suspension of the sale of that drug by its sponsor, and reiterating the requests in your petition.

FDA has carefully considered the issues raised in your petition, the comments submitted to the docket in association therewith, your August 9, 2011, letter to Dr. Hamburg, and other information before the Agency. As discussed further below, since you submitted your petition, the sponsors of roxarsone, carbarsone, and arsanilic acid have requested that FDA withdraw approval of the NADAs for those drugs. The Agency is in the process of formally withdrawing approval of those applications and amending the new animal drug regulations referencing those approvals. Your requests regarding roxarsone, carbarsone, and arsanilic acid are therefore moot. With respect to your requests regarding nitarsone, in accordance with 21 C.F.R. 10.30(e)(1)(ii), we are denying your petition. The reasons for this decision are discussed below.

BACKGROUND

A. Legal and Regulatory Framework

Under section 512(a)(1) of the Federal Food, Drug, and Cosmetic Act ("the FD&C Act"), any new animal drug shall be deemed unsafe, and as a result adulterated, unless it is approved, conditionally approved, or index-listed[1] by FDA. Under section 512(d)(1)(B) of the FD&C Act, FDA cannot approve an NADA if the evidence "do[es] not show that such drug is safe for use" under specified conditions. The determination of safety with respect to the target animal involves balancing risks against benefits for each specific use of a drug. *Cf. United States v. Rutherford*, 442 U.S. 544, 555 (1979). Moreover, FDA will not find a new animal drug intended for use in food-producing animals to be safe unless the sponsor demonstrates that there is a reasonable certainty of no harm to human health with respect to the food produced from treated animals under the intended conditions of use.

Once a drug is approved, the drug's sponsor may at any time voluntarily withdraw the drug from the market for any reason, including safety concerns. Section 512(e)(1) of the FD&C Act establishes grounds and procedures for FDA to withdraw approval of an NADA. One of these grounds provides that FDA "shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an [NADA] with respect to any new animal drug if [FDA] finds," among other things, that "new evidence . . . evaluated together with the evidence available to [FDA] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved." Section 512(e)(1)(B) of the FD&C Act.[2]

[1] The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (the Index) is a list of new animal drugs generally intended for use in non-food producing minor species that have had their safety and effectiveness affirmed through an alternative FDA review process. They are often intended for use in species too rare or varied to be used in traditional safety and effectiveness studies. New animal drugs intended for use in early, non-food life stages of some food-producing minor species may be eligible for indexing under very limited circumstances. See Section 572 of the FD&C Act and 21 CFR 516 subpart C.

[2] Although your petition cites section 512(e)(1)(A)-(C), *see* p.24, your petition only contains arguments related to subsection (B).

FDA regulations in 21 CFR parts 12 and 514 describe the notice and hearing process required by section 512(e)(1) of the FD&C Act. First, FDA notifies in writing the person holding the approved application and affords an opportunity for a hearing on a proposal to withdraw that application's approval. 21 CFR 514.115(b). FDA publishes a notice of opportunity for a hearing in the Federal Register. 21 CFR 514.200(a). The sponsor then has 30 days to request a hearing, which the Commissioner will grant if, among other criteria, "genuine and substantial issues of fact" exist regarding whether withdrawal of approval is appropriate. 21 CFR 514.200(c). At the hearing, FDA has the initial burden of producing evidence that the drug at issue is not shown to be safe. *See Rhone-Poulenc, Inc. v. FDA*, 636 F.2d 750, 752 (D.C. Cir. 1980). If FDA meets that initial burden, the sponsor has the burden of showing that the drug is safe. *Id.* The matter is decided by an administrative law judge, 21 CFR 12.120(a)-(b) and 514.200(c), whose decision may be appealed to the Commissioner, 21 CFR 12.125(a).[3]

Section 512(e)(1) of the FD&C Act also provides for a special summary procedure that permits the Secretary to suspend approval of an NADA temporarily in advance of a hearing, and thereby remove the drug from the market, if the Secretary finds that the drug represents an "imminent hazard" to the health of man or the animals for which the drug is intended. FDA has interpreted the phrase "imminent hazard" in 21 CFR 2.5 to mean that such a hazard exits "when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held." After suspending approval, the Secretary must provide the sponsor with an expedited evidentiary hearing on whether the drug should be permanently removed from the market. Section 512(e)(1) of the FD&C Act. This special authority is vested solely in the Secretary (or in her absence the officer acting as Secretary), and may not be delegated. *Id.*

B. Arsenic-based Animal Drugs

Arsenic is an element that is present in the environment as a naturally-occurring substance or as a result of contamination from human activity. It is found in water, air, and soil in organic and inorganic form.

There are four FDA-approved arsenic-based animal drugs – roxarsone, arsanilic acid, nitarsone, and carbarsone – and a number of approved combination drug medicated feeds containing an approved arsenic-based new animal drug plus at least one approved non-arsenic-based new animal drug. The four arsenic-based animal drugs, which have been approved for several decades for use in animal feed for poultry and swine, all have as their active ingredient forms of organic arsenic, which is less toxic than inorganic arsenic and not known to be carcinogenic.

The scientific evidence at the time of the approval of all four arsenic-based animal drugs indicated that animals exposed to organic arsenic rapidly excrete the compound in its original form – as organic arsenic. FDA approved the products at doses and withdrawal times that, based on the available

[3] Alternatively, an NADA holder may request FDA withdraw approval of its NADA. Approval of an NADA "will be withdrawn on the basis of a request for its withdrawal submitted in writing by a person holding an approved [NADA] on the grounds that the drug subject to such application is no longer being marketed," so long as certain other criteria are met. 21 CFR 514.115(d).

information, allowed for the safe and effective use of the products when used according to label directions.

Below is summary information for each of the four approved arsenic-based animal drugs approved for use in medicated feed:

Roxarsone (3-nitro-4-hydroxyphenylarsonic acid)

- Drug form: Type A medicated article
- Trade names: 3-NITRO, Roxarsone
- Sponsor: Zoetis, Inc.
- Indications for Use: Chickens and turkeys (growing) - For increased rate of weight gain, improved feed efficiency and improved pigmentation. Swine (growing and finishing) - For increased rate of weight gain and improved feed efficiency.
- Marketing Status: Inactive, has not been marketed in U.S. since 2011

Carbarsone (p-ureidophenylarsonic acid)

- Drug form: Type A medicated article
- Trade name: CARB-O-SEP
- Sponsor: Zoetis, Inc.
- Indications for Use: As an aid in the prevention of blackhead in turkeys.
- Marketing Status: Inactive, has not been marketed in U.S. since at least 1996

Nitarsone (4-nitrophenylarsonic acid)

- Drug form: Type A medicated article
- Trade name: HISTOSTAT 50
- Sponsor: Zoetis, Inc.
- Indications for Use: As an aid in the prevention of blackhead[4] in chickens and turkeys
- Marketing Status: Active

Arsanilic acid (p-arsanilic acid)

- Drug form: Type A medicated article
- Trade name: PRO-GEN
- Sponsor: Fleming Labs, Inc.
- Indications for Use: Chickens and turkeys (growing) - For increased rate of weight gain, improved feed efficiency, and improved pigmentation. Swine (growing and finishing) - For increased rate of weight gain and improved feed efficiency.
- Marketing Status: Inactive, has not been marketed in U.S. since 2005

Currently, there are 101 approved NADAs for products containing one of the four arsenic-based animal drugs. Five NADAs are for single-ingredient Type A medicated articles used to manufacture single-ingredient medicated feeds (including two NADAs for roxarsone and one NADA each for carbarsone, nitarsone, and arsanilic acid). Five NADAs are for roxarsone tablets or concentrate solution used to make medicated drinking water. The remaining 91 NADAs are applications that permit the manufacture

[4] Blackhead is a form of histomoniasis caused by a protozoan which may be transmitted by a parasite.

of combination drug medicated feeds containing an approved arsenic-based new animal drug plus at least one approved non-arsenic-based new animal drug. There are 80 NADAs for combination drug medicated feeds containing roxarsone; 3 NADAs for combination drug medicated feeds containing arsanilic acid; 2 NADAs for combination drug medicated feeds containing nitarsone; and 6 NADAs for combination drug medicated feeds containing carbarsone. As discussed below, roxarsone, arsanilic acid, and carbarsone are not currently being marketed in the United States. Thus, none of the products, including drug combinations, containing roxarsone, arsanilic acid, and carbarsone, is currently marketed.

C. Recent FDA Activities Related to Safety of Arsenic-based Animal Drugs

Scientific reports over the last several years began to question whether organic arsenic could transform into inorganic arsenic in the environment or in the edible tissues of animals that consume it. Since publication of these reports, FDA has been gathering and analyzing relevant data and information, including data the Agency generated in a self-initiated research study, in order to evaluate whether there may be safety risks associated with arsenic-based animal drugs that were previously unknown.

As noted above, carbarsone has not been marketed since at least 1996 and arsanilic acid has not been marketed since 2005. Of the two remaining arsenic-based new animal drugs, roxarsone was the much more commonly used arsenic-based animal drug. As FDA began to reevaluate arsenic-based new animal drugs, the Agency decided to concentrate its research efforts on roxarsone in light of its more common use. In September 2009, FDA initiated a research study intended to determine whether treating chickens with roxarsone results in increased levels of inorganic arsenic in the edible tissues of those chickens. To FDA's knowledge, no previous study had detected inorganic arsenic in edible tissues of birds known to be treated with an arsenic-based animal drug.[5]

Scientists from CVM and FDA's Center for Food Safety and Applied Nutrition ("CFSAN") developed a new analytical method capable of detecting very low levels of inorganic arsenic in chicken liver.[6] This test method used state-of-the-art instrumentation (ion chromatography inductively coupled plasma mass spectrometry) to identify and measure very low levels (less than 10 parts per billion (ppb)) of inorganic arsenic in the presence of much higher concentrations (nearly 2 ppm or 2000 ppb) of roxarsone. The method was evaluated and validated by a second laboratory, FDA's Office of Regulatory Affairs ("ORA") Forensic Chemistry Center.

One hundred chickens were fed either medicated feed containing roxarsone at the approved dose or a control feed for a six-week period. FDA analyzed liver tissue from the chickens in the study to determine whether inorganic arsenic could be detected. FDA's analysis indicated that very low levels of inorganic arsenic were present in the livers of chickens treated with the roxarsone, while no measurable residues of inorganic arsenic were present in the livers from the untreated control chickens. Although

[5] IATP's study referenced in your petition tested for *total* arsenic in retail packages of raw chicken and fast food chicken but did not speciate inorganic arsenic from organic arsenic. See David Wallinga, Inst. for Agric. and Trade Policy, Playing Chicken: Avoiding Arsenic in Your Meat 11 (2006), available at http://www.iatp.org/iatp/publications.cfm?accountID=421&refID=80529.

[6] Given that humans mostly consume chicken muscle, FDA attempted to develop an analytical method for detecting levels of inorganic arsenic in muscle. Due to technical difficulties in developing an analytical method for muscle tissue, FDA developed the method for the analysis of liver samples instead.

the analytical method FDA had developed could not be used to measure inorganic arsenic levels in chicken muscle, other appropriate methods were available to measure levels of total arsenic (both organic and inorganic) in muscle. Using those methods, FDA found substantially lower levels of total arsenic in muscle than in liver, reflective of the typical distribution of veterinary drug residues at higher levels in liver and kidney than in muscle. Data collection, analysis, and peer evaluation for the analytical method were completed in December 2010, and the study's final report was completed in February 2011.[7]

After FDA advised roxarsone's sponsor, Pfizer, Inc. ("Pfizer") (now Zoetis, Inc. ("Zoetis")[8]), of the results of FDA's study, Pfizer voluntarily suspended the sale of roxarsone in the United States in July 2011, and roxarsone has remained off the market since then.[9] Since 2010, the last full year that roxarsone was marketed, total U.S. sales of arsenic-based products have dropped by 84 percent. The only remaining arsenic-based animal drug marketed is nitarsone, the only marketed product approved for preventing blackhead (histomoniasis) in turkeys and chickens.

Although roxarsone's sponsor voluntarily suspended the sale of the drug, the sponsor also raised certain questions regarding FDA's study. For example, the sponsor expressed concerns that the study did not provide complete analyses to affirm the frozen storage stability and freeze-thaw stability of tissue samples for arsenical speciation. As a follow-up to its original study, FDA commenced additional analytical work to address this and other questions raised by the sponsor. This additional analytical work is ongoing. FDA's ongoing analyses include, but are not limited to, affirming the frozen storage stability and freeze-thaw stability of tissue samples for arsenical speciation, affirming the stability of arsenical species in the feed matrix, within laboratory validation of our analytical methods in a new analytical facility, and affirming the homogeneity and delivered dose of roxarsone in the medicated feed. This additional analytical work is an important aspect of FDA's ongoing evaluation of arsenic-based animal drugs as it is intended to address questions raised about the original study and to affirm and build upon the original study's findings. In addition, it will add to the body of scientific knowledge and assist the Agency in the determination of appropriate next steps.

In addition to this ongoing analytical work, FDA recently sent letters to the sponsors of the four arsenic-based animal drugs pursuant to section 512(l) of the FD&C Act.[10] Specifically, FDA ordered the sponsors to provide any data and information in their possession related to whether inorganic arsenic can be detected in edible tissues of animals administered their particular arsenic-based new animal drug(s);

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[7] See *Final Report on Study 275.30*, available at http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/UCM257545.pdf.

[8] In January of 2012, Pfizer announced that its animal health businesses would become a new company called Zoetis. In January 2013, Zoetis offered a minority ownership stake through an Initial Public Offering and became a standalone company. See http://www.zoetis.com/about/history.

[9] See Pfizer Media Statement, Pfizer To Suspend Sale Of 3-Nitro (Roxarsone) In The United States, June 11, 2011, available at http://www.pfizer.com/files/news/suspending_sale_3nitro_060711.pdf.

[10] Section 512(l) of the FD&C Act provides a procedure whereby the Agency may order a sponsor to submit records and reports to the agency if the Agency finds that such records and reports are necessary in order to enable the Agency to determine, or facilitate a determination, whether there is or may be ground for invoking section 512(e) to withdraw approval of the drug.

whether organic arsenic converts to inorganic arsenic *in vivo* in any animals administered any form of organic arsenic in any amount; and whether and to what extent information related to the behavior of one arsenic-based new animal drug is applicable to other arsenic-based new animal drugs. These orders were issued to help FDA obtain and review any relevant data and information in the possession of the sponsors that FDA may not have and thereby facilitate a determination about whether there are or may be grounds for invoking section 512(e) of the FD&C Act to withdraw approval of any of these drugs.

After receiving FDA's order pursuant to section 512(l) of the FD&C Act, by letter dated September 19, 2013, Zoetis requested that FDA withdraw approval of the NADAs for roxarsone and carbarsone. In addition, by letter dated September 26, 2013, Fleming Laboratories, Inc. (Fleming), requested that FDA withdraw approval of the NADA for its drug, arsanilic acid. FDA is preparing to issue notices of withdrawal of those applications in the Federal Register and to revoke the new animal drug regulations covering the conditions of use of the drugs as provided for in their applications. *See* 21 CFR 514.115(e) and 514.116.

FDA also continues to review and evaluate newly-published, relevant scientific literature, such as the study released on May 10, 2013, by researchers at the Johns Hopkins Center for a Livable Future at the Bloomberg School of Health ("Johns Hopkins"), which collected chicken breast samples from December 2010 to June 2011 (before the sale of roxarsone was suspended) and analyzed them for the presence of roxarsone and inorganic arsenic.[11] We have reached out to the Johns Hopkins investigators with questions about their reported results, primarily regarding the analytical method used, to inform our ongoing evaluation.

DISCUSSION

In your petition, you contend that the arsenic-based animal drugs roxarsone, arsanilic acid, nitarsone, and carbarsone are not safe for consumption and that their approvals must be suspended immediately and the products withdrawn from the market. You argue that consuming edible tissues of animals treated with arsenic-based new animal drugs is unsafe; that arsenic-based new animal drugs convert into inorganic arsenic, which can lead to an increased risk of cancer and other health risks for humans; that exposure to organic arsenic can also cause adverse health effects; that the use of arsenic-based animal drugs has a detrimental environmental impact and contributes to a cumulative exposure to arsenic that could create health risks for humans; and that the use of arsenic-based animal drugs likely contributes to antimicrobial resistance.

We considered your petition, the evidence cited in it, and your letter to Dr. Margaret Hamburg of August 9, 2011, discussing FDA's roxarsone study and Pfizer's suspension of the sale of roxarsone, as well as the comments submitted to the docket for your petition and other information before the Agency. We reviewed every publication you referenced and referenced by the comments and carefully considered your arguments.

[11] Keeve E. Nachman, Patrick A. Baron, Georg Raber, Kevin A. Francesconi, Ana Navas-Acien, David C. Love. Roxarsone, Inorganic Arsenic, and Other Arsenic Species in Chicken: A U.S.-Based Market Basket Sample. *Environmental Health Perspectives*, 2013; DOI: 10.1289/ehp.1206245.

As noted above, Zoetis has requested that FDA withdraw approval of the NADAs for roxarsone and carbarsone, and Fleming has requested that FDA withdraw approval of the NADA for arsanilic acid. The Agency is in the process of formally withdrawing approval of those applications and amending the new animal drug regulations referencing those approvals. Your requests regarding roxarsone, carbarsone, and arsanilic acid are therefore moot.

With respect to your requests for FDA to suspend approval of the NADA for nitarsone, initiate withdrawal proceedings by publishing a Notice of Opportunity for an Evidentiary Hearing, issue an order withdrawing the NADA approval, and revoke all associated regulations, FDA has not yet made a finding that the grounds for initiation of such proceedings are present under section 512(e)(1) of the FD&C Act. We acknowledge your concerns regarding the safety of arsenic-based animal drugs. However, three of the four arsenic-based drugs you mention are no longer being marketed, resulting in a substantial decrease of arsenic-based animal drugs on the market. Of the 101 NADAs for products containing one of the four arsenic-based new animal drugs, only three are currently marketed in the U.S.: nitarsone and two combination drugs containing nitarsone.

FDA believes, as a matter of science and regulatory policy, that the most appropriate course of action at this time is to continue to pursue the Agency's ongoing scientific research and evaluation. As discussed above, FDA is seeking additional information to enable the Agency to more fully evaluate any potential concerns related to the safety of arsenic-based animal drugs. This information includes completing our ongoing analytical work to address questions raised by roxarsone's then-sponsor and build upon the Agency's first study related to inorganic arsenic in the edible tissue of birds known to be treated with roxarsone. It also includes requiring the sponsor of nitarsone to submit any data and information in its possession related to whether inorganic arsenic can be detected in edible tissues of animals administered its arsenic-based new animal drug, whether organic arsenic converts to inorganic arsenic *in vivo* in any animals administered any form of organic arsenic in any amount, and whether and to what extent information related to the behavior of one arsenic-based new animal drug is applicable to other arsenic-based new animal drugs.

The Agency has decided to review the results of the analytical work and evaluate the response from Zoetis prior to reaching any conclusions about whether there may be grounds to undertake the actions you request regarding nitarsone. Review of this information will enable FDA to better understand the current state of the science surrounding arsenic-based new animal drugs and thus make a more informed scientific determination regarding nitarsone. Moreover, we anticipate that most of the additional information FDA is seeking will be available for review by the Agency's scientific staff by the end of the first quarter of 2014. Specifically, by that time, we plan to have completed a critical portion of our ongoing analytical work,[12] and we also expect to have received and reviewed the response from Zoetis

[12] The additional analytical work that FDA is in the process of completing is resource intensive and has required significant time to complete. Currently, there are three ongoing studies. One study examines feed stability and distribution of roxarsone in the feed. This study involves mixing and testing of multiple feed samples. A second study entails feeding a small group of chickens medicated feed and a control group of chickens non-medicated feed in order to generate liver samples from both groups to use in the third study. The third study analyzes some of the liver samples after they have been frozen for various periods and some samples that have not been frozen in order to affirm the frozen storage stability and freeze-thaw stability of tissue samples for arsenical speciation. We

to the order we sent regarding nitarsone, as well as the answers to the questions we sent to the investigators from the Johns Hopkins study noted above.

Once we have completed the efforts discussed above, we intend to promptly evaluate all of the information before the Agency to reach a conclusion about next steps, including whether there may be grounds for initiating withdrawal proceedings for nitarsone.

CONCLUSION

We appreciate your concerns regarding the safety of roxarsone, arsanilic acid, nitarsone, and carbarsone. Prior to receiving your petition and since that time, we have been actively gathering additional information to enable us to more fully evaluate any potential concerns regarding the safety of those drugs. The applications for roxarsone, carbarsone, and arsanilic acid are in the process of being withdrawn at the sponsors' requests, and therefore your requests regarding those drugs are moot. For the reasons discussed above, the Agency has decided to review the results of its analytical work and evaluate the response from the sponsor of nitarsone to the order issued by the Agency prior to reaching any conclusions about whether there may be grounds to initiate proceedings to withdrawal approval of that drug. Although we are not taking the actions you request regarding nitarsone at this time, we are committed to promptly collecting the additional data and completing our evaluation of the safety of that drug.

Sincerely,

Michael R. Taylor
Deputy Commissioner for Foods and
Veterinary Medicine

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cannot complete the third study until we have completed the feeding study and have collected and stored liver samples from the treated birds. In addition, CVM will determine whether to conduct a fourth study after it reviews the results of the other three studies.