ABBREVIATED NEW ANIMAL DRUG APPLICATION FOR ANIMAL DRUGS CONTAINING CARBARSONE

COPY #1
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The Institute for Agriculture and Trade Policy (IATP) and the Center for Food Safety (CFS) submit this Abbreviated New Animal Drug Application (ANADA) pursuant to 21 C.F.R. § 514. Specifically, it seeks U.S. Food and Drug Administration's (FDA) approval pursuant to 21 C.F.R. § 514.106(b)(2) as a Category II supplemental application seeking to change the tolerance for drug residues and to change the analytical methods for drug residues for all NADAs and ANADAs for products containing Carbarsone.

Identification

- Applicant #1
  - Name: Institute for Agriculture and Trade Policy
  - Address: 2105 First Avenue South, Minneapolis, MN 55404
- Applicant #2
  - Name: Center for Food Safety
  - Address: 660 Pennsylvania Ave., SE, Suite 302, Washington, DC 20003
- Date: October 4, 2011
- Trade name: See list in Attachment A.
- Chemical name: Carbarsone

This ANADA is being submitted by two applicants, the IATP and CFS, described below for all seven New Animal Drug Applications (NADAs) and ANADAs containing the ingredient Carbarsone, including those described in Attachment A. It also includes NADAs and ANADAs for the ingredient not posted or incorrectly posted by FDA on its website at http://www.accessdata.fda.gov/scripts/animaldrugsatfda/ on September 15, 2011 made before the date FDA receives this application.

Please note that IATF and CFS are not the same applicants for the NADAs and ANADAs of the products that this ANADA seeks to modify. The following firm sponsored those applications:

- Alpharma Inc. (NADA/ANADA #010-285 (Carb-O-Sep® Type A Medicated Article), 038-879 (Carb-O-Sep® / Zoamix®), 039-646 (Carb-O-Gain), 136-484 (Baciferm® / Carb-O-Sep®), and 200-203 (Albac® / Carb-O-Sep®))
- Huvepharma AD (NADA/ANADA #130-661 Carb-O-Sep / Flavomycin®)
- Merial Ltd. (NADA/ANADA # 118-507 Amprol® / Carb-O-Sep®)

According to 21 U.S.C. Section 360b(b)(2), "Any person may fill with the Secretary an abbreviated application for the approval of a new animal drug." Congress expressly allowed any person to file an ANADA and did not limit it to the sponsors that submitted the NADA or ANADA that the applicants seek to modify.

Also note that this ANADA addresses at least the seven NADAs and ANADAs containing Carbarsone. The applicants considered separate applications for each product. Based on applicant's analysis of the regulations, FDA does not appear to require one application for each product. It does allows applicants to submit periodic drug experience reports pursuant to 21 C.F.R. § 514.80(c). Since the contents of each application would be essentially the same, except for the product name and number, the applicants determined that it was most appropriate to follow the example FDA set with drug experience reports and submit one application for multiple approved NADAs and ANADAs. If FDA prefers a separate application for each approved NADA and ANADA, please contact the applicants.

Summary

In a June 8, 2011 press release, FDA announced that it reached an agreement with Pfizer to voluntarily suspend the sale of the animal drug 3-Nitro. See http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm258342.htm. 3-Nitro is also known as Roxarsone. FDA based its action on a recent study it conducted that detected inorganic arsenic in the livers of chickens treated with 3-Nitro compared with untreated chickens. Inorganic arsenic is a known carcinogen.

The press release indicates that FDA's study used a new analytical method capable of detecting very low levels of inorganic arsenic in edible tissue. The website cited above provides links to the FDA study. After reviewing the study, it is clear that the study was well done and robust. It is also clear that the method, based on a procedure developed at the University of Cincinnati, is:

- Able to be conducted by other labs including commercial and academic labs;
- May be used with equal effectiveness on other meats including pork; and
- Would provide similar results for other organic arsenic-based new animal drugs including those where the only difference with Roxarsone is the attachments to the benzene ring such as Nitarsone, Carbarsone, and Arsanilic Acid.

FDA's action is preceded by an 18-month old citizen's petition submitted by the applicants seeking withdrawal of approval of Roxarsone, Nitarsone, Carbarsone, and Arsanilic Acid and certain other arsenical additives in animal feed. FDA has made no decision on that citizen's petition.

Despite the fact that Carbarsone is chemically similar to Roxarsone, we are informed by the FDA that the Pfizer / Alpharma voluntary suspension does not apply to Carbarsone.

For these reasons, the IATP and CFS submit this Abbreviated New Animal Drug Application pursuant to 21 C.F.R. § 514. Specifically, it seeks FDA's approval pursuant to 21 C.F.R. § 514.106(b)(2) as a Category II supplemental application seeking to change the tolerance for drug residues and to change the analytical methods for drug residues for all NADAs and ANADAs for products containing Carbarsone.

Specifically, the applicants request that FDA, for all NADAs and ANADAs covered by this application:

- Require the use of its new method to detect inorganic arsenic in meat and tissue treated with Carbarsone; and
- Revise the tolerances for the inorganic arsenic for the meat and tissue from food animals treated with Carbarsone at the limit of detection for the method pursuant to 21 U.S.C. Section 360b(d)(1).

The applicants prepared this ANADA pursuant to FDA "Guidance for Industry: Development of Supplemental Applications for Approved New Animal Drugs" published on-line at http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052411.pdf.

Table of Contents

Incorporation by Reference

The applicants incorporate by reference the following:

- The citizen's petition the applicants submitted on December 8, 2010 to FDA. Pursuant to 21 C.F.R. § 514.1, the applicants made this written authorization to use the information in the petition.
- FDA's June 8, 2011 press release titled "FDA: Pfizer will voluntarily suspend sale of animal drug 3-Nitro" announcing its agreement with Pfizer. This document is publicly available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm258342.htm.
- FDA's webpage at www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm257540.htm titled 3-Ntiro (Roxarsone) and Chicken including the four items in the study lists on the page.
- FDA's "Arsenic Speciation in Broiler Chickens – Summary Final Report" publicly available on-line at http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/UCM257545.pdf. This document is the Final Report on Study 275.30.
- FDA's "Arsenic Speciation in Broiler Chicken – Amendments to Final Report" publicly available at http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/UCM258193.pdf. This document is the Amendment to Final Report on Study 275.30.
- FDA's "Arsenic Speciation in Broiler Tissues – Analyst's Report" publicly available at http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/UCM257547.pdf. This document is the Analysts Report Amendment to Final Report on Study 275.30.
- FDA's "Arsenic Speciation in Broiler Tissues – Statistician's Report" publicly available at http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/UCM257548.pdf. This document consists of two reports from the Final Report on Study 275.30 statisticians.
- NADAs and ANADAs as follows 007-616 and 141-088.

Chemistry

In this application, the applicants request FDA's approval pursuant to 21 C.F.R. § 514.106(b)(2) as a Category II supplemental application seeking to change the tolerance for drug residues and to change the analytical methods for drug residues for all NADAs and ANADAs for products containing Carbarsone

Pursuant to FDA "Guidance for Industry: Development of Supplemental Applications for Approved New Animal Drugs," the application relies on the existing information regarding the chemistry of the products. Therefore, it references the relevant technical sections contained within the approved NADAs and ANADAs that are incorporated by reference.

The chemical formula for Roxarsone is 3-nitro-4-hydroxyphenylarsonic acid. http://www.accessdata.fda.gov/scripts/animaldrugsatfda/details.cfm?dn=005-414. The chemical formula for Carbarsone is [4-(Carbamoylamino)phenyl]arsonic acid. In essence, the difference is that the nitro group is removed and the hydroxyl group is replaced with a carbamoylamino group.

Scientific Rationale and Purpose

In this application, the applicants request FDA's approval pursuant to 21 C.F.R. § 514.106(b)(2) as a Category II supplemental application seeking to change the tolerance for drug residues and to change the analytical methods for drug residues for all NADAs and ANADAs for products containing Carbarsone.

Pursuant to FDA "Guidance for Industry: Development of Supplemental Applications for Approved New Animal Drugs," the application relies on the existing information regarding the scientific rationale and purpose of the product. Therefore, it references the relevant technical sections contained within the approved NADAs and ANADAs that are incorporated by reference.

Labeling

In this application, the applicants request FDA's approval pursuant to 21 C.F.R. § 514.106(b)(2) as a Category II supplemental application seeking to change the tolerance for drug residues and to change the analytical methods for drug residues for all NADAs and ANADAs for products containing Carbarsone.

Pursuant to FDA "Guidance for Industry: Development of Supplemental Applications for Approved New Animal Drugs," the application relies on the existing information regarding the labeling of the products. Therefore, it references the relevant technical sections contained within the approved NADAs and ANADAs that are incorporated by reference.

The labels will need to be altered to identify the new tolerances.

Analytical Methods for Residues

In this application, the applicants request FDA's approval pursuant to 21 C.F.R. § 514.106(b)(2) as a Category II supplemental application seeking to change the tolerance for drug residues and to change the analytical methods for drug residues for all NADAs and ANADAs for products containing Carbarsone.

Pursuant to FDA "Guidance for Industry: Development of Supplemental Applications for Approved New Animal Drugs," the application relies on the existing information regarding the analytical methods for residues of the products. Therefore, it references the relevant technical sections contained within the approved NADAs and ANADAs that are incorporated by reference.

This application relies on the study #275.30, conducted by FDA and published in 2011, that is incorporated by reference and was conducted at FDA's facilities in Maryland. The study title was "Provide Data on Various Arsenic Species Present in Broilers Treated with Roxarsone: Comparison with Untreated Birds." JC Kawalek was the study director.

Note that it is not clear from the documentation whether the FDA performed it in compliance with the good laboratory practice (GLP) regulations set forth in 21 C.F.R. § 58. If it did not use GLPs, then such noncompliance should not be a barrier to FDA's acceptance of the study since it performed it and used in as the basis of its agreement with Pfizer to voluntarily suspend production of Roxarsone that was announced on June 8, 2011.

The study report describes the method FDA developed to identify the inorganic arsenic and organic arsenic components of arsenic in the meat or tissue from poultry. The FDA experts extracted 0.5g tissue with 3mL of an aqueous solution of tetramethylammonium hydroxide (TMAH), diluted with 6.5mL water, filtered thru 30K Centri-prep tubes to remove proteins and other macromolecules, and analyzed by ion chromatography-inductively coupled plasma-mass spectrometry (IC-ICP-MS). The MS was set to detect As ions (*m/z* 75). Peak identification was by retention time matching with external standards, with standard addition used when necessary. Quantification was by comparison to an external calibration curve.

From the perspective of an IC-ICP-MS method, the structural differences between Carbarsone and Roxarsone are minor. The loss of a nitro group and replacement of the hydroxyl group with a carbamoylamino group should not affect the analysis using properly calibrated equipment.

The applicants request that FDA establish that this method be used to measure inorganic arsenic in meat or tissue of chicken and turkey treated with Carbarsone. While the study was conducted on chicken, the methodology would be equally relevant for turkey and swine.

Tolerances

In this application, the applicants request FDA's approval pursuant to 21 C.F.R. § 514.106(b)(2) as a Category II supplemental application seeking to change the tolerance for drug residues and to change the analytical methods for drug residues for all NADAs and ANADAs for products containing Carbarsone.

Pursuant to FDA "Guidance for Industry: Development of Supplemental Applications for Approved New Animal Drugs," the application relies on the existing information regarding the tolerances of the products. Therefore, it references the relevant technical sections contained within the approved NADAs and ANADAs that are incorporated by reference.

The study report describes the method FDA developed to identify the inorganic arsenic and organic arsenic components of arsenic in the meat or tissue from poultry. FDA's analyst report discussed the limit of detection (LOD) and the lower limit of quantification (LLOQ). Based on Table 3a of page 19 of 52, the LOD is 0.15 parts per billion in the meat or tissue.

In its June 8, 2011 press release, FDA acknowledged that inorganic arsenic is a known carcinogen. Therefore, 21 U.S.C 360b(d)(1)(I) and 21 CFR 500.4 apply. Therefore, the tolerance for Carbarsone must ensure no inorganic arsenic residues are in the edible portions of the poultry or swine treated with the chemical. Pursuant to 21 CFR 500.4(c)(3), "FDA will conclude that the provisions of this subpart are satisfied when no residue of the compound is detectable (that is, the marker residue is below the LOD) using the approved regulatory method under the conditions of use of the sponsored compound, including any required preslaughter withdrawal period or milk discard time."

The applicants request that the tolerance for inorganic arsenic be 0.15 ppb in the edible meat or tissue for poultry or swine.

Veterinary Feed Directive

In this application, the applicants request FDA's approval pursuant to 21 C.F.R. § 514.106(b)(2) as a Category II supplemental application seeking to change the tolerance for drug residues and to change the analytical methods for drug residues for all NADAs and ANADAs for products containing Carbarsone.

Pursuant to FDA "Guidance for Industry: Development of Supplemental Applications for Approved New Animal Drugs," the application relies on the existing information regarding the veterinary feed directive of the products. Therefore, it references the relevant technical sections contained within the approved NADAs and ANADAs that are incorporated by reference.

Environmental Assessment

In this application, the applicants request FDA's approval pursuant to 21 C.F.R. § 514.106(b)(2) as a Category II supplemental application seeking to change the tolerance for drug residues and to change the analytical methods for drug residues for all NADAs and ANADAs for products containing Carbarsone.

Pursuant to FDA "Guidance for Industry: Development of Supplemental Applications for Approved New Animal Drugs," the application relies on the existing information regarding the environmental assessment of the products. Therefore, it references the relevant technical sections contained within the approved NADAs and ANADAs that are incorporated by reference.

Applicants' Commitments

Applicants understand that the labeling and advertising for the new animal drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application and, if the article is a prescription new animal drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the new animal drug will also contain, in the same language and emphasis, information for its use including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant hazards, contraindications, side effects, and precautions contained in the labeling which is part of this application. It is understood that all representations in this application apply to the drug produced until changes are made in conformity with 21 C.F.R. § 514.8.

With respect to the nonclinical laboratory study contained in the application, applicants do not know whether the study conducted by FDA was performed in compliance with the GLP regulations set forth in 21 CFR 58. If it did not use GLPs, then such noncompliance should not be a barrier to FDA's acceptance of the study since it performed it and used it as the basis of its agreement with Pfizer to voluntarily suspend production of Roxarsone that was announced on June 8, 2011.

Attachment A

NADAs and ANADAs Containing Carbarsone Covered by ANADA Submitted by the Institute for Agriculture and Trade Policy and the Center for Food Safety		
NADA/ ANADA	Sponsor	Proprietary Name
010-285	Alpharma, Inc.	Carb-O-Sep® Type A Medicated Article
038-879	Alpharma, Inc.	Carb-O-Sep® / Zoamix®
039-646	Alpharma, Inc.	Carb-O-Gain
136-484	Alpharma, Inc.	Baciferm® / Carb-O-Sep®
200-203	Alpharma, Inc.	Albac® / Carb-O-Sep®
130-661	Huvepharma AD	Carb-O-Sep / Flavomycin®
118-507	Merial Ltd.	Amprol® / Carb-O-Sep®