DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 22 2015

Tracey L. Ward, B.S., M.S.
Director, Regulatory Surveillance and Compliance
Elanco Animal Health, Inc.
2500 Innovation Way
Drop Code EL 05
Greenfield, IN 46140

RE: NADA 141-361
Pulmotil® AC (tilmicosin phosphate)

Dear Ms. Ward:

The U.S. Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM), Division of Surveillance, has reviewed promotional materials for Pulmotil AC (tilmicosin phospate) aqueous concentrate formulation for pigs, including a detailer entitled "The Newest Member of your Team to Help Control Swine Respiratory Disease" (USSBUPAC00004) submitted under FDA Form 2301 on February 24, 2014, a detailer entitled "Dosing Guide" (USSBUPAC00011) submitted under FDA Form 2301 on April 29, 2014, and a detailer entitled "The Newest Member of your Team to Help Control Swine Respiratory Disease" (USSBUPAC00012).

These promotional materials are misleading because they minimize or omit the risks associated with Pulmotil AC. These materials cause Pulmotil AC to be misbranded under section 502(f)(1) of the Food, Drug, & Cosmetic Act (FD&C Act) [21 U.S.C. § 352(f)(1)]. The introduction of a misbranded drug into interstate commerce is a violation of section 301(a) of the FD&C Act [21 U.S.C. § 331(a)].

Background

According to the FDA-approved product labeling, Pulmotil AC is a water-soluble concentrate solution containing 250 mg of tilmicosin per milliliter, which is approved for the control of swine respiratory disease associated with *Pasteurella multocida* and *Haemophilus parasuis* in groups of swine in buildings where a respiratory disease outbreak is diagnosed. The approved package insert for Pulmotil AC contains important risk information, including a boxed warning statement that reads as follows:

WARNING

Exposure to tilmicosin in humans has been associated with chest pain, increased heart rate, dizziness, headache, and nausea. Death has been reported following ingestion or injection of tilmicosin.

Avoid ingestion. Avoid direct skin and eye contact. In case of human exposure, call 1-800-722-0987 and consult a physician immediately.

NOTE TO THE PHYSICIAN:

The cardiovascular system is the target of toxicity and should be monitored closely. The primary cardiac effects are tachycardia and decreased contractility. Cardiovascular toxicity may be due to calcium channel blockade.

See User Safety Warnings for additional information.

The approved package insert also includes the following important risk information:

- Wear overalls, impervious gloves and eye protection when mixing and handling the product. Wash hands after handling the product. Wash affected parts if skin contact occurs. If accidental eye contact occurs, immediately rinse thoroughly with water.

- Always treat the fewest number of animals necessary to control a respiratory disease outbreak. Prescriptions shall not be refilled.

The approved indication for Pulmotil AC contains important antimicrobial resistance and human food safety risk mitigation language, specifically "in groups of swine in buildings where a respiratory disease outbreak is diagnosed." The intent of this language is to limit use of Pulmotil AC to treatment only of groups of swine in specific buildings that are exposed to *Pasteurella multocida* and *Haemophilus parasuis*.

Under CVM's Guidance for Industry #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern,"[1] macrolide antibiotics are considered critically important to human medicine, which is the highest level of risk as described in the guidance. On the basis of the qualitative risk assessment submitted in support of the new animal drug application, FDA concluded that Pulmotil AC poses a high risk for antimicrobial resistance and, thus, a threat to human food safety. Because the product poses a high risk for antimicrobial resistance, it was approved with the "extent of use" limitation described above. This "extent of use" limitation is explained in the Microbial Food Safety (Antimicrobial Resistance) section of the Freedom of Information (FOI) Summary for Pulmotil AC (NADA 141-361):

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1 http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf

> "After review of the sponsor's complete, qualitative microbial food safety risk assessment, the Agency determined that the risk of development of transferable macrolide resistance elements from this use of tilmicosin phosphate in swine is high, and the risk of human exposure to macrolide resistant microbes resulting from this use of tilmicosin phosphate is medium. Macrolides are ranked as critically important drugs in human medicine; therefore, by default, the consequence assessment yields a high ranking. The overall risk estimation is derived to be high. The conditions of use are compatible with the Agency's risk management strategies associated with a product having an overall risk estimation of high – the product will be marketed by prescription only (Rx), can only be administered to individual or limited groups of swine in buildings experiencing an outbreak of SRD, and monitoring for macrolide resistance within FDA's National Antimicrobial Resistance Monitoring System continues."

Minimization of Risk – Omission of Safety Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials [FD&C Act §321(n)].

The promotional pieces cited above are misleading because they omit the important human user safety information included in the boxed warning on the approved label. These pieces also omit the additional human safety risk information listed above. Omission of the human user warnings, and other safety information relevant to public health, is misleading because these materials do not communicate material facts relating to warnings necessary to mitigate the serious exposure risks that the product poses for human users, and the risk of development of resistant bacterial pathogens caused by injudicious use. This omission causes the product to be misbranded. *See* FD&C Act sections 21 U.S.C. §§ 352(a) and 321(n).

Conclusion and Requested Action

The Division of Surveillance requests that Elanco Animal Health, Inc. immediately cease misbranding Pulmotil AC and/or cease introducing the misbranded drug into interstate commerce.

The violations cited in this letter do not necessarily constitute an exhaustive list. It is your responsibility to assure that your promotional materials for Pulmotil AC comply with all the requirements of the FD&C Act and its implementing regulations. You should take prompt action to correct the violations cited in this letter.

Please submit a written response within thirty (30) calendar days of receipt of this letter

stating whether you intend to comply with this request, listing all promotional materials (with the Form FDA 2301 submission date) for Pulmotil AC that contain presentations such as those described above that minimize or omit important risk information as those described above, and explaining your plan for discontinuing use of such materials or, in the alternative, your plan to cease distribution of Pulmotil AC.

Please direct your response to Dr. Dorothy McAdams at the Food and Drug Administration, Center for Veterinary Medicine, Division of Surveillance, HFV-216, 7519 Standish Place, Rockville, Maryland 20855.

Sincerely yours,

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Neal Bataller, ME, DVM
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Cc:

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