EXHIBIT 21

U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Anim[redacted]& Veterinary

FDA Order Prohibits Extralabel Use of Phenylbutazone in Certain Dairy Cattle

February 28, 2003

The Food and Drug Administration (FDA) is issuing an order prohibiting the extralabel use of phenylbutazone animal and human drugs in female dairy cattle 20 months of age or older. FDA is issuing this order based on evidence that extralabel use of phenylbutazone in these dairy cattle will likely cause an adverse event in humans. The Agency finds that such extralabel use presents a risk to the public health for the purposes of the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA).

AMDUCA amended the Federal Food, Drug, and Cosmetic Act to allow licensed veterinarians to prescribe extralabel uses of approved animal drugs and human drugs in animals. Section 2(a)(4)(D) of the AMDUCA provides that the Agency may prohibit an extralabel drug use in animals if, after affording an opportunity for public comment, the Agency finds that such use presents a risk to the public health.

Phenylbutazone became available for use in humans for the treatment of rheumatoid arthritis and gout in 1949. However, it is no longer approved, and thus not marketed, for any human use in the United States. This is because some patients treated with phenylbutazone have experienced severe toxic reactions, and other effective, less toxic drugs are available to treat the same conditions

Phenylbutazone is known to induce blood dyscrasias, including aplastic anemia, leukopenia, agranulocytosis, thrombocytopenia and deaths. Hypersensitivity reactions of the serum-sickness type have also been reported. In addition, phenylbutazone is a carcinogen, as determined by the National Toxicology Program.

For animals, phenylbutazone is currently approved only for oral and injectable use in dogs and horses. Use in horses is limited to use in horses not intended for food. There are currently no approved uses of phenylbutazone in food-producing animals.

Investigation by FDA and State regulatory counterparts has found phenylbutazone on farms and identified tissue residues in culled dairy cattle. In addition, USDA's Food Safety Inspection Service has reported phenylbutazone residues in culled dairy cattle presented for slaughter for human food throughout the U.S. in the past two calendar years. This evidence indicates that the extralabel use of phenylbutazone in female dairy cattle 20 months of age or older will likely result in the presence, at slaughter, of residues that are toxic to humans, including being carcinogenic, at levels that have not been shown to be safe.

FDA will consider all comments on this order that the Agency receives by April 29, 2003. Written comments should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. All comments should include Docket number 03N-0024. The order will become effective May 29, 2003, unless FDA revokes or modifies the order or extends the comment period.

Additional information on this prohibition is contained in the February 28, 2003, Federal Register. Questions about this prohibition may be directed to: Gloria J. Dunnavan, Center for Veterinary Medicine (HFV-230), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-1168, e-mail: gdunnava@cvm.fda.gov.

Additional Information

- Final Rule: New Animal Drugs; Phenylbutazone; Extralabel Animal Drug Use; Order of Prohibition [1]

Contact FDA

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Links on this page:

1. http://edocket.access.gpo.gov/2003/03-4741.htm