

section 512(a)(4)(D) of the act (21 U.S.C. 360b(a)(4)(D)) gives us authority to prohibit an extralabel drug use in animals if, after affording an opportunity for public comment, we find that such use presents a risk to the public health.

In the **Federal Register** of November 7, 1996 (61 FR 57732), we published the implementing regulations (codified at part 530 (21 CFR part 530)) for AMDUCA. The sections regarding prohibition of extralabel use of drugs in food-producing animals are found at §§ 530.21 and 530.25. These sections describe the basis for issuing an order prohibiting an extralabel drug use in food-producing animals and the procedure to be followed in issuing an order of prohibition.

We may issue a prohibition order if we find that extralabel use in animals presents a risk to the public health. Under § 530.3(e), this means that we have evidence that demonstrates that the use of the drug has caused or likely will cause an adverse event.

Section 530.25 provides for a public comment period of not less than 60 days. It also provides that the order of prohibition will become effective 90 days after the date of publication, unless we revoke the order, modify it, or extend the period of public comment. The list of drugs prohibited from extralabel use is found in § 530.41.

II. Phenylbutazone

Phenylbutazone became available for use in humans for the treatment of rheumatoid arthritis and gout in 1949 (Ref. 1), but 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 (Refs. 1 and 2).

Phenylbutazone is known for its ulcerogenic, nephrotoxic, and hemotoxic effects in horses, dogs, rats, and humans (Refs. 2, 4, 5, 6, 7, and 8). It is known to induce blood dyscrasias, including aplastic anemia, leukopenia, agranulocytosis, thrombocytopenia, and deaths (Refs. 7 and 8). The reported adverse reactions were associated with the human clinical use of 200 to 800 milligrams phenylbutazone per day (Refs. 7 and 8). Hypersensitivity reactions of the serum-sickness type have also been reported in patients with phenylbutazone. The threshold for this effect has not been defined. Therefore, it is unclear what level of exposure would be required to trigger such reactions in sensitive people. Moreover,

phenylbutazone is a carcinogen, as determined by the National Toxicology Program (NTP) based on positive results in genotoxicity tests and some evidence of carcinogenicity seen in the rat and mouse in carcinogenicity bioassays NTP conducted (Ref. 3).

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 recently found phenylbutazone on farms and identified tissue residues in culled dairy cattle. In addition, the U.S. Department of Agriculture's (USDA's) Food Safety Inspection Service has reported phenylbutazone residues in culled cattle presented for slaughter for human food throughout the United States in the past 2 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. Because of the likelihood of this adverse event, we are issuing an order prohibiting the extralabel use of phenylbutazone drugs in female dairy cattle 20 months of age or older.

We will continue to monitor the extralabel use of phenylbutazone and will adjust the scope of this prohibition should we find that extralabel use in other species or classes of animals presents a risk to public health.

III. Request for Comments

We are providing 60 days from the date of this publication for you to comment. The order will become effective May 29, 2003, unless we revoke or modify the order, or extend the comment period. You may send written or electronic comments to the Dockets Management Branch (see **ADDRESSES**) by April 29, 2003. Submit a single copy of electronic comments to <http://www.fda.gov/dockets/ecomments> or two hard copies of any written comments, except that individuals may submit one hard copy. Please identify your comments with the docket number found in brackets in the heading of this document. You may read any comments that we receive at our Dockets Management Branch reading room (see **ADDRESSES**). The reading room is open from 9 a.m. to 4 p.m., Monday through Friday, except for Federal holidays.

IV. Order of Prohibition

Therefore, I hereby issue the following order under section 512(a)(4)(D) of the act and 21 CFR 530.21 and 530.25. We find that extralabel use of phenylbutazone animal drugs and human drugs in female dairy cattle 20 months of age or older likely will cause an adverse event which constitutes a finding under section 512(a)(4)(D) of the act that extralabel use of this drug presents a risk to the public health. Therefore, we are prohibiting the extralabel use of this drug in female dairy cattle 20 months of age or older.

V. References

The following references have been placed on display in the Dockets Management Branch (see **ADDRESSES**). You may view them between 9 a.m. and 4 p.m., Monday through Friday.

1. Insel, P. A., "Analgesic-Antipyretics and Anti-inflammatory Agents, and Drugs Employed in the Treatment of Gout," Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, 9th ed., edited by J. G. Hardman, L. E. Limbird, P. B. Molinoff, R. W. Ruddon, and A. G. Gilman, McGraw-Hill, pp. 642-643, 1996.

2. McEvoy, G. K., "American Hospital Formulary Service B Drug Information 93," American Society of Hospital Pharmacists, Inc., Bethesda, MD, p. 1194, 1993.

3. National Toxicology Program, "Toxicology and Carcinogenesis Studies of Phenylbutazone in F344/N rats and B6C3F1 Mice (gavage studies)" National Toxicology Program Technical Report number 367, NIH publication number 90-2822, 1990.

4. Edited by R. J. Anderson, J. G. Gambertoglio, and R. W. Schrier, "Clinical Use of Drugs in Renal Failure," Charles C. Thomas, Springfield, IL, p. 6, 1976.

5. Carpenter, S. L., and W. M. McDonnell, "Misuses of Veterinary Phenylbutazone," *Archives of Internal Medicine*, vol. 155, pp. 1229-1231, 1995.

6. Council on Drugs, "Registry on Blood Dyscrasias," Report to the Council, *Journal of the American Medical Association*, vol. 179(11), pp. 888-890, 1962.

7. Hazardous Substances Data Bank, 2000. <http://www.csi.micromedex.com/DATA/HS/HS3159F.htm>

8. Humphreys, D. J., *Veterinary Toxicology*, Baillière Tindall, p. 92, 1988.

List of Subjects in 21 CFR Part 530

Administrative practice and procedure, Advertising, Animal drugs,