DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

HFA-305

Food and Drug Administration
Rockville MD 20857

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Mr. Richard Wood
Food Animal Concerns Trust (FACT)
P. O. Box 14599
411 W. Fullerton #1402 W.
Chicago, Illinois 60614-9966

Docket 99P-0485/CP

Dear Mr. Wood:

This is the second tentative response to the citizen petition that was submitted to the Food and Drug Administration (FDA or Agency) on March 9, 1999 on behalf of the Center for Science in the Public Interest (CSPI), the Environmental Defense Fund, the Food Animal Concerns Trust, the Public Citizen's Health Research Group, and the Union of Concerned Scientists.

The petition requests that FDA withdraw the approvals for subtherapeutic uses of medically important antibiotics in livestock feeds. The petition alleges that the drugs are unsafe when used subtherapeutically because they endanger human health due to selection and transfer of antibiotic resistance that may compromise human therapy.

CSPI provided further information related to the petition to me in its letter of February 10, 2000.[1] That letter addressed my request for prioritization for withdrawal of seven antibiotic drugs from use in livestock feed,[2] which I made during a January 6, 2000 meeting involving the then FDA Commissioner Dr. Jane Henney and representatives of nonprofit groups including CSPI, the Environmental Defense Fund, the Food Animal Concerns Trust and the Union of Concerned Scientists. The February 10, 2000 letter identified virginiamycin as CSPI's top priority for withdrawal.

In my first tentative response, a letter to CSPI dated August 19, 1999, I explained that because of the complex nature of the action requested, FDA would require additional time to issue a final response to your citizen petition. This second tentative response explains further why we cannot yet issue a final response to your petition.

In order for the Agency to withdraw a new animal drug approval, two processes need to be completed. First, FDA's Center of Veterinary Medicine (Center or CVM) needs to determine whether to initiate formal withdrawal proceedings. Second, if the Center

[1] The letter is included in Docket 99P-0485/CP.

[2] The seven antibiotics are penicillin, tetracycline, erythromycin, bacitracin, lincomycin, tylosin and virginiamycin.

99P-0485

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determine whether to initiate formal withdrawal proceedings. Second, if the Center decides to initiate formal withdrawal proceedings, it must then undertake the formal withdrawal process required by statute. For legal, scientific and resource reasons, withdrawal actions for the petitioned drugs need to be considered on a drug by drug basis. Data and information will need to be reviewed and analyzed for each drug. Thus the petitions can only be granted or denied on a drug by drug basis as reviews are completed and resources permit.

The Center's determination on whether to initiate action to withdraw an approval is primarily an internal process, although participation by drug sponsors and the public may be requested. This process may include, among other things, an in-depth review and evaluation of available data and information related to the particular drug, collection of additional data if needed, and a risk assessment. These reviews will be used to determine whether statutory grounds exist to support a withdrawal action.

An approved new animal drug application can be withdrawn if, among other things, experience or scientific data show that the drug is unsafe, as provided in section 512(e)(1)(A), or if the drug is not shown to be safe (section 512(e)(1)(B)). If the Center concludes that a drug's approval should be withdrawn, it is required by section 512(e)(1) to provide the drug's sponsor with notice and an opportunity for a formal administrative hearing (NOOH). A separate NOOH is ordinarily issued for each individual drug, because most of the relevant scientific evidence is likely to be unique to the individual drug, although actions involving chemically related drugs may be consolidated.[3]

Issuance of NOOHs and requests for a hearing are governed by the federal regulations dealing with formal evidentiary public hearings. A sponsor who requests a formal hearing is required to submit detailed data to justify the request. The request will be reviewed and, if the Commissioner determines that a hearing is justified, the Commissioner will issue a notice of hearing. A presiding officer will conduct a formal evidentiary hearing and render an initial decision, which can be appealed to the Commissioner. A sponsor may appeal the Commissioner's decision to withdraw an approval of a new animal drug to the U.S. Court of Appeals under provision of section 512(h).

The Agency's experience with contested, formal withdrawal proceedings is that the process can consume extensive periods of time and Agency resources. For example, the first NOOHs for withdrawal of nitrofuran approvals were issued in 1971, but the final rule withdrawing the approvals was not issued until 1991.[4] Withdrawal of diethylstilbestrol (DES) approvals became final in 1979, six years after issuance of an NOOH.[5]

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[3] For example, separate NOOHs were issued for the proposed withdrawals of approval for nitrofurazone (36 Fed. Reg. 5927, March 31, 1971) and furazolidone (36 Fed. Reg. 14343, August 4, 1971), but the actions involving both nitrofurans were consolidated for hearing. See 56 Fed. Reg. 41902 (August 23, 1991).

[4] See 56 Fed. Reg. 41902 (August 23, 1991).

[5] See 44 Fed. Reg. 54851 (1979).

The Agency recognizes that there are issues related to the role that antimicrobial drug use in food-producing animals plays in the emergence of antimicrobial drug resistant bacteria. To address these issues, the FDA is undertaking an extensive process to evaluate issues related to the use of antimicrobial drugs in both humans and animals, and to develop policies that protect the public health.

The Agency has prepared two documents addressing issues concerning antimicrobial use in food-producing animals. One is Guidance for Industry 78 (GFI 78), which addresses how FDA intends to consider the potential human health impact of the microbial effects associated with all uses of antimicrobial new animal drugs in food-producing animals when approving such drugs.[6] The other is a discussion paper, referred to as the "Framework Document," which sets out a conceptual risk-based framework for evaluating the microbial safety of antimicrobial drugs intended for use in food-producing animals.[7] The Framework Document, if implemented, could apply to both drugs being considered for approval and previously approved drugs. Further, as stated in the two documents, the Agency is considering all uses of antimicrobial drugs in food-producing animals.

FDA continues to solicit comments on these issues from interested parties. The majority of the general public comments received on the Framework Document agreed that the Agency should address the issue of the use of antimicrobial drugs in food-producing animals. FDA agrees with the comments stating that the scientific evidence is robust enough to cause the Agency to further evaluate the microbial safety of antimicrobial drugs intended for use in food-producing animals.[8] Moreover, on January 22-24, 2001, the Agency held a public meeting to discuss the use of antimicrobial drugs in food-producing animals and the establishment of regulatory thresholds on antimicrobial resistance. The Agency received many comments during the meeting and expects additional comments before the close of the public comment period on April 9, 2001.

Several comments on the Framework Document support the use of risk assessments as a tool in decision-making for food safety issues. The Center has begun to apply risk assessment techniques on issues related to antimicrobial drug resistance. For example, CVM has developed a risk assessment that models the human health impact of fluoroquinolone-resistant *Campylobacter* infections associated with the consumption of chicken.[9] The results from this risk assessment is one of many factors supporting CVM's recent proposal to withdraw the fluoroquinolone enrofloxacin, for use in poultry, based on antimicrobial resistance concerns. That proposal was published as an NOOH in the

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[6] Guidance for Industry 78, "Consideration of Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals," December 13, 1999, 64 Fed. Reg. 70715 (December 17, 1999).

[7] "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals," 64 Fed. Reg. 887 (January 6, 1999).

[8] A complete analysis of the comments to the Framework Document can be found at www.fda.gov/cvm.

[9] The risk assessment is available on CVM's homepage at: http://www.fda.gov/cvm/antimicrobial/Risk_asses.htm.

October 31, 2000, Federal Register,[10] with a corrected NOOH published on January 22, 2001.[11] In addition, the Center recently announced plans to develop a prototypic risk assessment model to assess the association between the development of streptogramin (quinupristin/dalfopristin) resistant *Enterococcus faecium* in humans and the use of virginiamycin in food-producing animals.[12] As noted above, CSPI has indicated that virginiamycin is its highest priority for withdrawal among the petitioned drugs.

FDA received comments from more than 38,000 people concerning your petition. These comments, as well as other relevant data and information, will have to be evaluated by the Agency before any action will be taken. Therefore, at this time, it would be premature to grant or deny the petition, in whole or in part.

As explained above, the petition can only be granted or denied when the Agency makes a final decision on whether to withdraw any of the drug approvals listed in your petition. The Agency will issue a final response to your citizen petition upon completion of our analysis of the comments received on your citizen petition, the Framework Document, numerous consultations, and the resolution of the scientific, legal, and policy issues.

Sincerely yours,

Stephen F. Sundlof, D.V.M., Ph.D.
Director, Center for Veterinary Medicine

Identical letters were sent to:
Center for Science in the Public Interest
Environmental Defense Fund
Public Citizen's Health Research Group
Union of Concerned Scientists

[10] 65 Fed. Reg. 64954 (Oct. 31, 2000).
[11] 66 Fed. Reg. 6623 (Jan. 22, 2001).
[12] See 65 Fed. Reg. 20992 (April 19, 2000).