

EXHIBIT A

TO THE DECLARATION OF MITCHELL S. BERNARD



DEPARTMENT OF HEALTH & HUMAN SERVICES

NOV 7 2011

Food and Drug Administration
Rockville MD 20857

Ms. Sarah Klein, Esq.
Food Safety Program
Center for Science in the Public Interest
• 1875 Connecticut Avenue, NW
Suite 300
Washington, DC 20009

Re: Original Docket No. 99P-0485/CP
New Docket No. FDA-1999-P-1286

Dear Ms. Klein:

This is the final response from the Food and Drug Administration ("FDA" or the "Agency") to Citizen Petition (Original Docket No. 99P-0485/CP; New Docket No. FDA-1999-P-1286) submitted on March 9, 1999, on behalf of the Center for Science in the Public Interest, Environmental Defense Fund, Food Animal Concerns Trust, Public Citizen's Health Research Group, and Union of Concerned Scientists. Your petition requests that FDA rescind already-approved subtherapeutic uses¹ of medically important antibiotics in livestock feed. The petition alleges the drugs are unsafe under the Federal Food, Drug, and Cosmetic Act ("FD&C Act") when used for subtherapeutic purposes in animal agriculture because such use can drive the selection and transfer of antibiotic resistance in human pathogens, thereby compromising the effectiveness of antibiotics for treating infections in humans.

FDA's Center for Veterinary Medicine ("Center" or "CVM") has already issued two tentative responses to this Citizen Petition. CVM's first tentative response, dated August 19, 1999, explained that due to the complex nature of the action requested, FDA needed additional time to issue a final response. On February 28, 2001, CVM issued a second tentative response explaining that comments had been received from more than 38,000 people concerning the petition and that the comments and other relevant data and information needed to be evaluated by the Agency before action would be taken. The letter further stated that a final response granting or denying the petition would not be issued until FDA makes a decision about whether to withdraw the drug approvals listed in the petition.

We have reviewed the issues raised in your petition. Although we share your concern about the use of medically important antimicrobial drugs in food-producing animals for growth promotion and feed efficiency indications (i.e., production uses), in accordance with 21 CFR 10.30(e)(1)(ii), FDA is denying your petition. The reasons for this decision

¹ We understand that petitioners use the term "subtherapeutic uses" to include growth promotion, improved feed efficiency, and disease prevention indications. However, FDA does not generally consider disease prevention to be a subtherapeutic use. See FDA's draft guidance entitled, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals," draft Guidance for Industry #209, at 16.

are discussed below.

In your citizen petition, you call upon this Agency to withdraw “subtherapeutic uses” of certain antibiotics in livestock feed. Specifically, the petition requests the FDA Commissioner to “rescind approvals for subtherapeutic uses in livestock of any antibiotic used in (or related to those used in) human medicine” (footnote omitted).² The petition further states that the Agency “should take action now to rescind approvals for subtherapeutic uses in livestock of any antibiotic used in (or related to those used in) human medicine.” It is not entirely clear to us whether the action you are requesting is for the FDA Commissioner to issue an order now withdrawing approval or whether you instead are asking that formal withdrawal proceedings be initiated. Because it is unclear which of these two alternative interpretations is intended, we will address them both.

ISSUANCE OF WITHDRAWAL ORDER

To the extent the petition is seeking the immediate issuance by the FDA Commissioner of an order withdrawing the approvals of subtherapeutic uses of medically important antimicrobials in livestock feed, we must deny your petition because there is a formal evidentiary process that must be followed before new animal drug approvals may be withdrawn. In order to withdraw a new animal drug’s approval, FDA must follow a number of statutory requirements, such as providing the sponsor of the new animal drug with notice that the Agency proposes to withdraw approval of the drug and an opportunity for a formal evidentiary hearing on the matter. FDA cannot withdraw approval of a new animal drug until the legally-mandated process is complete.

Prior to initiating formal proceedings to withdraw approval of a new animal drug, CVM makes a determination about whether such action is warranted after analyzing the relevant data and information. The Center’s determination about whether to initiate action to withdraw approval of a new animal drug 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 in some instances a risk assessment. This process will be used to determine whether statutory grounds may exist to support a withdrawal action. If the Center concludes that grounds exist to withdraw a new animal drug approval, before moving forward to withdraw under section 512(e) of the FD&C Act, FDA must provide the drug’s sponsor with notice and an opportunity for a formal administrative hearing (“NOOH”).

Issuance of NOOHs and requests for a hearing are governed by the federal regulations dealing with formal evidentiary hearings. A sponsor who requests a formal hearing is required to submit detailed data to justify the request. The sponsor’s request and supporting documentation will be reviewed and, if the Commissioner determines that a hearing is justified, the Commissioner will issue a notice of hearing. If the Commissioner

² The petition also states that the “ban should include subtherapeutic applications of such medically important antibiotics as penicillin, tetracyclines, erythromycin, lincomycin, tylosin, and virginiamycin, as well as other antibiotics used in (or related to those used in) human medicine for growth promotion, improved feed efficiency, and disease prevention.”

grants a hearing, a formal evidentiary hearing is held. Generally, the Commissioner will appoint a presiding officer to conduct the hearing and render an initial decision, which can be appealed to the Commissioner. An order withdrawing the approval of a new animal drug will issue only after this process is completed and the Commissioner has found that the cited grounds for withdrawing the drug have been demonstrated. Because no hearings have been held with respect to the animal drugs at issue in the Citizen Petition, and because the Commissioner has not made any final determination about whether grounds for withdrawal under section 512(e) of the FD&C Act have been satisfied, the relief requested in the Citizen Petition cannot be granted at this time.³

INITIATION OF WITHDRAWAL PROCEEDINGS

If petitioners are asking FDA to immediately institute formal withdrawal proceedings, we deny your request. As discussed below, for various reasons the Agency has decided not to institute formal withdrawal proceedings at this time and instead is currently pursuing other alternatives to address the issue of antimicrobial resistance related to the production use of antimicrobials in animal agriculture.

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 nitrofurans approvals were issued in 1971, but the final rule withdrawing the approvals was not issued until 1991. Withdrawal of diethylstilbestrol (DES) approvals became final in 1979, seven years after issuance of an NOOH. More recently, the withdrawal of approved uses of enrofloxacin in poultry took almost five years and cost FDA approximately \$3.3 million.

Recognizing that the process of reviewing safety information for antimicrobial drugs approved before 2003, and pursuing withdrawal proceedings in some cases, would take many years and would impose significant resource demands on the Agency, in June 2010, FDA proposed a different strategy to promote the judicious use of medically important antimicrobials in food-producing animals in a draft guidance entitled, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" draft Guidance for Industry #209 ("draft GFI #209"). Generally speaking, judicious uses would be those uses that are appropriate and necessary to maintaining the health of humans and animals.

Draft GFI #209 proposes two principles aimed at ensuring the judicious use of medically important antimicrobials in food-producing animals. The first principle set out in the draft guidance is that the use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health. As set out in the draft guidance, FDA does not consider production uses of such drugs to be necessary for assuring animal health because, unlike other uses, production uses are not directed at any specifically identified disease but

³ Although the Agency did publish two Notices for Opportunity for a Hearing in 1977 on proposals to withdraw approvals of the new animal drug applications for all uses of penicillin and some uses of tetracyclines in animal feed, no hearings were held on these proposals and no final findings were made by the Commissioner.

rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products (e.g., promoting faster weight gain or improving feed efficiency). The second principle set out in the draft guidance is that the use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation. This principle speaks to the need for the scientific and clinical training of licensed veterinarians in assuring that medically important antimicrobials are used in a judicious manner.

Based on feedback this Agency has received following the issuance of draft GFI #209, FDA believes that the animal pharmaceutical industry is generally responsive to the prospect of working cooperatively with the Agency to implement the principles recommended in draft GFI #209. FDA intends to work with sponsors who approach FDA and are interested in working cooperatively with the Agency to phase out production uses of medically important antimicrobials and to transition medically important antimicrobials currently approved for over-the-counter use in food-producing animals to a marketing status that involves veterinary oversight (i.e., veterinary feed directive ("VFD") status for feed use drugs and prescription status for drugs approved for use through other routes of administration).

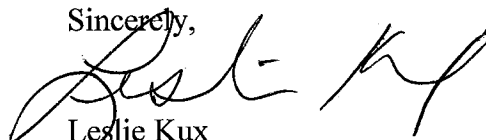
As part of the proposed strategy, FDA issued an advance notice of proposed rulemaking ("ANPRM") in March 2010 to seek public comment on whether and to what extent efficiency improvements should be made to the current VFD process as set forth in FDA's regulation at 21 CFR 558.6. FDA received numerous public comments in response to the ANPRM and is taking those comments into consideration in drafting a revised rule.

FDA believes that the strategy set out in draft guidance #209 is a pathway to achieving the same goals as those advocated by your organization, i.e., judicious use of medically-important antimicrobials. Additionally, given the considerable amount of Agency resources that are required to pursue withdrawal proceedings, we believe the current proposed approach will accomplish these goals in a more timely and resource-efficient manner than would otherwise be the case. Moreover, this strategy does not foreclose initiating withdrawal proceedings in the future.

CONCLUSION

For the foregoing reasons, FDA denies your petition. FDA is committed to working with animal drug sponsors, the veterinary and public health communities, the animal agriculture community, and all other interested stakeholders in developing a strategy to address antimicrobial resistance concerns in a manner that is protective of both human and animal health.

Sincerely,



Leslie Kux

Acting Assistant Commissioner for Policy