

RECEIVED  
3/9/99



THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Petition to Rescind Approvals of the )  
Subtherapeutic Uses in Livestock of )  
Antibiotics Used in (or Related to Those )  
Used in) Human Medicine )  
\_\_\_\_\_ )

Docket No. \_\_\_\_\_

Submitted by the

Center for Science in the Public Interest  
Environmental Defense Fund  
Food Animal Concerns Trust  
Public Citizen's Health Research Group  
Union of Concerned Scientists

March 9, 1999

99P-0485

## Table of Contents

I. Action Requested .....	1
II. Executive Summary .....	2
III. Introduction .....	4
IV. Statement of Factual Grounds .....	5
A. Policy Background .....	5
B. Scientific Background .....	9
1. Subtherapeutic antibiotics are used widely in livestock. ....	10
2. Subtherapeutic antibiotic use in livestock leads to the selection of antibiotic resistance .....	11
3. Antibiotic-resistant bacteria can be transferred between animals and between animals and people .....	13
4. Antibiotic-resistant bacteria may transfer resistance genes to other bacteria .....	16
5. Subtherapeutic antibiotic use may select for multi-drug-resistant bacteria that can cause infections that are difficult to treat. ....	18
6. Subtherapeutic antibiotic use jeopardizes therapeutic options in veterinary and human medicine .....	20
7. Subtherapeutic use of antibiotics reduces the effectiveness of new human-use antibiotics, jeopardizing human health .....	22
8. Decreasing subtherapeutic uses of antibiotics on farms can reduce the prevalence of antibiotic-resistant bacteria and does not adversely affect animal health .....	23
C. Expert committees and leading scientists support a phase out of subtherapeutic antibiotic use in livestock .....	25

V. Statement of Legal Grounds .....	27
A. The FDA has legal authority to withdraw the approval of new animal drug applications that are unsafe .....	27
B. The FDA has asserted its authority to consider the public-health impact of antibiotic resistance when regulating the use of antimicrobial drugs in livestock .....	29
C. In light of recent evidence, Congress' directive to the FDA to suspend proceedings for the withdrawals of NADAs for penicillin and tetracyclines in animal feed pending additional studies is moot .....	32
D. The FDA should adopt policies consistent with the current international trend of phasing out the subtherapeutic use of medically important antibiotics .....	34
VI. Economic Impact .....	35
VII. Environmental Impact .....	38
VIII. Conclusion .....	38
IX. Certification .....	39

March 3, 1999

Dockets Management Branch  
Food and Drug Administration  
5630 Fishers Lane  
Room 10-61  
Rockville, MD 20852

## Citizen Petition

### I. Action Requested

The Center for Science in the Public Interest (CSPI)<sup>1</sup>, Environmental Defense Fund (EDF)<sup>2</sup>, Food Animal Concerns Trust (FACT)<sup>3</sup>, Public Citizen's Health Research Group<sup>4</sup> and Union of Concerned Scientists (UCS)<sup>5</sup> submit this petition under § 512(e) of the Federal Food, Drug, and Cosmetic Act (FDCA) to request the Commissioner to rescind approvals for

---

<sup>1</sup> The Center for Science in the Public Interest is a nonprofit organization based in Washington, D.C., that has been working to improve the public's health since 1971. CSPI is supported largely by its one million subscribers to *Nutrition Action Healthletter*.

<sup>2</sup> The Environmental Defense Fund, a leading national, New York-based nonprofit organization, represents 300,000 members. EDF links science, economics, and law to create innovative, equitable, and economically viable solutions to today's environmental problems.

<sup>3</sup> Food Animal Concerns Trust is a nonprofit organization that advocates for animal husbandry methods that will improve the safety of meat, milk, and eggs.

<sup>4</sup> Public Citizen's Health Research Group is a research-based health-advocacy group that devotes a majority of its time to examining the safety of drugs, medical devices, and health-care practices.

<sup>5</sup> The Union of Concerned Scientists, established in 1969, is an independent, nonprofit organization dedicated to advancing responsible public policies in areas where technology plays a critical role.

subtherapeutic uses in livestock of any antibiotic<sup>6</sup> used in (or related to those used in) human medicine. 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.

## II. Executive Summary

Shortly after the discovery and widespread introduction of antibiotics into medical practice 50 years ago, scientists observed that bacteria could develop resistance to them. The more antibiotics are used, the more rapidly resistance develops. When such resistance develops, bacterial growth is no longer stopped by the antibiotic, and, thus, the antibiotic is no longer capable of treating or curing the disease. Antibiotic resistance can transform infections from easy to treat to illnesses that require prolonged treatments, necessitate lengthy hospitalizations, or cause death.

Since the 1950s, farmers have been using antibiotics as a production tool in raising livestock. They add antibiotics to livestock feed to counteract the effects of crowded living conditions and poor hygiene. In the U.S., as much as one third of all antibiotics produced are added to feed each year. Such use causes the development of antibiotic resistance among foodborne pathogens that can sicken people who consume tainted meat or touch infected animals. It also can result in antibiotic resistance in nonpathogenic bacteria. Those bacteria may

---

<sup>6</sup> For the purpose of this petition, the term antibiotic is used interchangeably with antimicrobial.

transfer their resistance genes to disease-causing bacteria, resulting in antibiotic-resistant infections in people.

This petition summarizes the scientific evidence that agricultural uses of antibiotics cause the development of antibiotic resistance in human pathogens. Recent data show that more bacteria are becoming resistant to one, or sometimes several, antibiotics. For example, the prevalence of resistance to five antibiotics among a particular strain of *Salmonella* has increased from 0.6 percent in 1979 to 34 percent in 1996.

This petition calls upon the Food and Drug Administration (FDA) to rescind approvals of certain agricultural uses of antibiotics when such uses endanger human health. Specifically, the FDA should not allow an antibiotic to be used as a livestock feed additive if that antibiotic is used in (or related to one used in) human medicine. That position is supported by the World Health Organization, the Centers for Disease Control and Prevention, the American Public Health Association, the Association of State and Territorial Health Officials, the Natural Resources Defense Council, the American Medical Women's Association, and other organizations.

The FDA has the legal authority and responsibility to ensure that the use of antibiotics in livestock does not endanger human health. In the 1970s it proposed rescinding the approvals of penicillin and tetracycline as feed additives because of the human-health risk associated with such use, but that proposal was never finalized.

In 1998, the FDA proposed a new framework for approving antibiotics for livestock designed to ensure that the agency consider whether such use would cause antibiotic resistance and, therefore, pose a threat to public health. The FDA's action on this issue reaffirms its

statutory authority to ensure that agricultural uses do not jeopardize human health by increasing antibiotic resistance. However, the framework falls short by not adequately addressing existing uses of antibiotics. In order to be truly protective, the FDA must rescind already-approved uses of medically important antibiotics in livestock feed, in order to protect those invaluable drugs.

### III. Introduction

Subtherapeutic levels of antibiotics are used by the cattle, swine, and poultry industries to promote growth and reduce the costs of raising livestock. Unfortunately, that use fosters antibiotic resistance in bacteria which can be transmitted to humans -- via the food supply or through direct contact with livestock or manure.<sup>7</sup> If a person is infected by pathogenic antibiotic-resistant bacteria, antibiotic treatment could be ineffective, thereby jeopardizing human health.

The subtherapeutic use of antibiotics also leads to increased levels of antibiotic resistance in animal pathogens on the farm. That resistance endangers livestock because it makes the antibiotics less useful for treating common animal infections. Consequently, veterinarians and animal-drug manufacturers are pushing for new approvals of antibiotics for use in animals that are essential for treating human diseases. The use of those antibiotics on farms may compromise their effectiveness in human medicine. Reducing nonessential uses of antibiotics in livestock and improving hygiene conditions and husbandry methods on farms would likely result in lower

---

<sup>7</sup> While subtherapeutic antibiotic uses contribute to antibiotic resistance, so do medical and other agricultural uses. The FDA and other agencies need to identify and reduce other problematic agricultural and medical uses of antibiotics. See CSPI report (Center for Science in the Public Interest. *Protecting the Crown Jewels of Medicine: A Strategic Plan to Preserve the Effectiveness of Antibiotics*. Washington, D.C.: CSPI; 1998.)

levels of antibiotic-resistant bacteria in farm animals, healthier animals, and reduced need for new, medically essential antibiotics to treat livestock infections.

Although the exact contribution of agricultural subtherapeutic uses of antibiotics to human health problems is not known, there is wide agreement among experts around the world that they do result in adverse human-health consequences. The Food and Drug Administration (FDA) should take action before the problem reaches crisis proportions. It is intolerable that people (and livestock) should be sick for longer periods of time or die, simply because agribusiness thinks it might reduce its operating costs.

#### **IV. Statement of Factual Grounds**

##### **A. Policy Background**

Subtherapeutic use of antibiotics is the administration of those drugs at a dosage less than is necessary and/or for a period of time longer than is necessary to treat an infection. The FDA defines subtherapeutic use as the use of antibiotics in livestock for more than 14 days.

Antibiotics are used subtherapeutically in raising poultry, cattle, and swine and are estimated to account for as much as 80 percent of the antibiotics used in agriculture.<sup>8</sup>

The mechanisms by which antibiotics promote growth are not well understood. Researchers have hypothesized that antibiotics improve feed-conversion efficiency. That improvement may be because antibiotics suppress low-level infections that result from

---

<sup>8</sup> Levy, S., *The Antibiotic Paradox: How Miracle Drugs are Destroying the Miracle*. New York (NY): Plenum Publishing Corporation; 1992: pp. 137-156 [hereinafter Levy, *The Antibiotic Paradox*, 1992].