

EXHIBIT I

**TO DECLARATION OF
JENNIFER A. SORENSON**

1999 Citizen Petition

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) Docket No. _____
Used in) Human Medicine)
_____...)

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

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Citizen Petition

I. Action Requested

The Center for Science in the Public Interest (CSPI)¹, Environmental Defense Fund (EDF)², Food Animal Concerns Trust (FACT)³, Public Citizen's Health Research Group⁴ and Union of Concerned Scientists (UCS)⁵ submit this petition under § 512(e) of the Federal Food, Drug, and Cosmetic Act (FDCA) to request the Commissioner to rescind approvals for subtherapeutic uses in

¹ 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*.

² 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.

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

⁴ 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.

⁵ 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.

livestock of any antibiotic⁶ 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 transfer their resistance genes to disease-causing bacteria, resulting in antibiotic-resistant infections in people.

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

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.⁷ 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 levels of antibiotic-resistant bacteria in farm animals, healthier animals, and reduced need for new, medically essential antibiotics to treat livestock infections.

⁷ 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.)

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.⁸

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 confinement farming, infections which, if untreated, inhibit animal growth. Antibiotics have little or no benefit when good management practices are followed.

⁸ 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].

The subtherapeutic agricultural use of antibiotics used in (or related to other antibiotics used in) human medicine poses a significant public-health hazard. Those antibiotics include penicillin, tetracyclines, and erythromycin, as well as tylosin and lincomycin (both are related to erythromycin) and virginiamycin (related to Synercid).

Soon after it became routine to add antibiotics to animal feed in the 1950s, health officials in the U.S. and abroad became concerned that long-term treatment of livestock with low doses of antibiotics could endanger human health.⁹ In the 1970s, the FDA itself proposed rules to revoke the then-permitted subtherapeutic uses of penicillin and tetracyclines.^{10,11,12,13} At that time, the FDA also proposed that all antibiotics that are used in human medicine only be used in animals for short-term therapeutic uses prescribed by a veterinarian (unless the drug's sponsor submitted data that demonstrated that subtherapeutic use would not jeopardize human health). In 1978, Congress directed the FDA to hold such actions in abeyance until additional studies were completed by the National Academy of Sciences.

⁹ Levy, *The Antibiotic Paradox*, 1992 pp. 137-156.

¹⁰ U.S. Food and Drug Administration. Proposed statement of policy. Antibiotics and sulfonamide drugs in animal feeds. *Federal Register* 1972; 37: 2444-2445.

¹¹ U.S. Food and Drug Administration. Statement of policy and interpretation regarding animal drugs and medicated feeds. Antibiotic and sulfonamide drugs in the feed of animals. *Federal Register* 1973; 38: 9811-9814.

¹² U.S. Food and Drug Administration. Notice of opportunity for hearing. Penicillin-containing premixes; Opportunity for hearing. *Federal Register* 1977; 42: 43772-43793.

¹³ U.S. Food and Drug Administration. Notice of opportunity for hearing. Tetracycline (chlortetracycline and oxytetracycline)-containing premixes; Opportunity for hearing. *Federal Register* 1977; 42: 56264-56289.

In 1984, the nonprofit Natural Resources Defense Council (NRDC) petitioned the Department of Health and Human Services (DHHS) to ban the subtherapeutic use of penicillin and tetracyclines in animal feed.¹⁴ The petition was based largely on two new studies. One study showed that antibiotic-resistance genes in bacteria infecting humans were identical to those found in bacteria infecting animals. The other study showed that subtherapeutic use of antibiotics in cattle was linked to an outbreak of antibiotic-resistant *Salmonella* in people who ate hamburger.^{15,16}

The petitioners claimed that the subtherapeutic use of penicillin and tetracyclines in animal feed posed an “imminent hazard” to human health and should be banned. The DHHS denied the petition on the basis that the NRDC failed to establish that the continued subtherapeutic use of penicillin and tetracyclines in animal feed posed an imminent hazard to the public’s health that warranted immediate suspension of their approval.^{17,18} At that time, the FDA could have initiated

¹⁴ Natural Resources Defense Council, *Petition to Suspend New Animal Drug Applications for Subtherapeutic Uses of Penicillin and the Tetracyclines in Animal Feed*. Docket No. 84P-0399, 1984.

¹⁵ O’Brien, T.F., Hopkins, J.D., Gilleece, E.S., Medeiros, A.A., Kent, R.L., Blackburn, B.O., Holmes, M.B., Reardon, J.P., Vergeront, J.M., Schell, W.L., Christenson, E., Bissett, M.L., and Morse, E.V., Molecular epidemiology of antibiotic resistance in *Salmonella* from animals and human beings in the United States. *New England Journal of Medicine* 1982; 307: 1-6.

¹⁶ Holmberg, S.D., Osterholm, M.T., Senger, K.A., and Cohen, M.L., Drug-resistant *Salmonella* from animals fed antimicrobials. *New England Journal of Medicine* 1984; 311: 617-622 [hereinafter Holmberg, 1984].

¹⁷ The “imminent hazard” standard places a high burden of proof on the petitioner and requires that, without direct evidence of imminent and quantitative harm to human health, such a petition will be denied. We do not rely on such authority in this petition.

¹⁸ United States Department of Health and Human Services, Decision of the secretary denying petition to suspend new animal drug applications for subtherapeutic uses of penicillin and the tetracyclines in animal feed, Docket number 84P-0399, November 19, 1985 [hereinafter DHHS petition denial, 1985].

steps to withdraw the approvals by claiming that new scientific evidence demonstrated that such uses were no longer safe, but it did not do so.

Since the 1985 ruling on the NRDC petition, sufficient scientific evidence has been published to demonstrate clearly that subtherapeutic use of antibiotics used in (or related to those used in) human medicine jeopardizes human health. Below we discuss that new evidence, as well as some of the older evidence. Moreover, in the past several years, numerous scientists and professional organizations, including the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the World Veterinary Association (WVA), have urged that antibiotics that are used in humans, or that select for resistance to antibiotics use in humans, should not be used subtherapeutically in livestock.^{19,20,21} A recent United Kingdom House of Lords report called for a voluntary phasing out, or if necessary, a ban of the subtherapeutic use in livestock of antibiotics that are used in (or related to those used in) human medicine.²² Even a recent report of the National Academy of Sciences' National Research Council (NAS-NRC), acknowledged that agricultural uses of antibiotics pose a risk to the public health.^{23,24} Thus, the FDA should take action now to rescind

¹⁹ Glynn, M.K., Bopp, C., Dewitt, W., Dabney, P., Mokhtar, M., Angulo, F.J., Emergence of multidrug-resistant *Salmonella* enterica serotype typhimurium DT104 infections in the United States. *New England Journal of Medicine* 1998; 338: 1333-1338 [hereinafter Glynn, 1998].

²⁰ World Health Organization, *The Medical Impact of the Use of Antimicrobials in Food Animals, Report of a WHO Meeting*; 1997 October 13-17; Berlin, Germany [hereinafter WHO meeting, 1997].

²¹ World Veterinary Association, *Antibiotics Should Not Be Used As Growth Promotants*. Press release, Sept. 9, 1998 at <<http://www.worldvet.org/press27.htm>>.

²² House of Lords, *Resistance to Antibiotics and Other Antimicrobial Agents: Seventh Report of the Select Committee on Science and Technology*, United Kingdom; 1998.

²³ That report was prepared by a panel that did not include a single public-health official (but did include several people associated with drug companies and agricultural interests).

approvals for subtherapeutic uses in livestock of any antibiotic used in (or related to those used in) human medicine.

B. Scientific Background

Bacteria have the capacity to develop defense mechanisms against antibiotics and become resistant to the drugs' effects. When such resistance develops, bacteria are no longer killed by the antibiotic, and, thus, the antibiotic is no longer capable of treating or curing the disease. The more an antibiotic is used, the greater the selective pressure, and the more likely it is that natural selection will foster the growth of bacteria that evade the effects of the antibiotic.

Natural selection plays a key role in the development of antibiotic resistance. Most bacteria die or their growth is inhibited when exposed to antibiotics to which they are sensitive (not resistant). The death of sensitive bacteria leaves more space and nutrients available for the surviving resistant bacteria, allowing the resistant bacteria to multiply freely.

Not only can resistant bacteria proliferate after sensitive bacteria are killed off by an antibiotic, but resistant bacteria also can transfer that resistance to other bacteria (even bacteria that are of different genera) that have never been exposed to the antibiotic. That transfer may occur when bacteria exchange with other bacteria either loops of DNA (plasmids) or portions of their chromosomes that may contain antibiotic-resistant genes.²⁵

1. Subtherapeutic antibiotics are used widely in livestock.

²⁴ National Research Council, *The Use of Drugs in Food Animals: Benefits and Risks*. Washington, D.C.: National Academy Press; 1998 [hereinafter *The Use of Drugs in Food Animals*, 1998].

²⁵ Levy, *The Antibiotic Paradox*, 1992 pp. 71-82.

Subtherapeutic antibiotics are used widely and frequently in livestock in the United States. It is estimated that more than 16 million pounds of antibiotics (about one third of all antibiotics) are used subtherapeutically for growth promotion.²⁶ Seventeen different agents (including antibiotics and coccidiostats) are approved for subtherapeutic use for growth promotion and improved feed efficiency. Of those agents, four are used in human medicine (penicillin, tetracycline, erythromycin, and bacitracin) and three are related to those used in human medicine (lincomycin, tylosin, and virginiamycin). Those seven antibiotics are used widely in livestock. We are not aware of any publicly available data on how much of each antibiotic is used. The remaining 10 agents are not used in human medicine and are not addressed in this petition.²⁷

2. Subtherapeutic antibiotic use in livestock leads to the selection of antibiotic resistance.

Agricultural uses of antibiotics (including subtherapeutic uses) promote the spread of antibiotic-resistant bacteria in treated livestock.²⁸ Those resistant bacteria can be transferred to humans via contaminated food products or through direct or indirect contact with animals.

A number of studies show that the subtherapeutic use of antibiotics leads to the development of antibiotic-resistant bacteria in livestock. A 1976 study showed that subtherapeutic antibiotic use in poultry selects for antibiotic resistance in *E. coli*.²⁹ The researchers inoculated a few chickens

²⁶ Levy, S., Multidrug resistance -- A sign of the times. *New England Journal of Medicine* 1998; 338: 1376-1378.

²⁷ It is impossible to determine what antimicrobials currently used in livestock will be needed to treat antibiotic-resistant infections in people in the future. For example, Synercid, which soon will be approved for treating deadly antibiotic-resistant infections in people, is related to the feed additive, virginiamycin, which scientists previously thought would be too toxic to give to people. To protect the effectiveness of future antibiotics, and to protect humans and animals from any adverse side effects, the petitioners urge the FDA to phase out the remaining 10 antimicrobials, as recommended by the World Health Organization.

²⁸ Although it is impossible to evaluate the relative contribution of therapeutic and subtherapeutic use of antibiotics to the development of antibiotic resistance, subtherapeutic uses of antibiotics play a key role by exerting selective pressure that enables antibiotic-resistant bacteria to flourish. In countries that have banned or decreased the subtherapeutic uses of antibiotics, resistance levels have declined dramatically (see discussion on pp. 23-25).

²⁹ Levy, S.B., Fitzgerald, G.B., Macone, A.B., Spread of antibiotic-resistant plasmids from
10

with tetracycline-resistant *E. coli* and housed them with uninoculated birds. Then, half of the chickens were fed a tetracycline-supplemented diet. During the course of the experiment, researchers isolated tetracycline-resistant *E. coli* from tetracycline-fed chickens that had not been inoculated with those bacteria, but that had been housed with the inoculated chickens. In comparison, researchers found no tetracycline-resistant *E. coli* in chickens that were housed with inoculated birds but not fed tetracycline-supplemented feed. That suggests that the tetracycline given in the feed provides the selective pressure that allows antibiotic-resistant strains to proliferate.

In 1983, farmers in certain parts of Germany began using a new antibiotic, nourseothricin, for growth promotion in swine.³⁰ Before then, nourseothricin resistance had never been observed. By 1985, nourseothricin-resistant *E. coli* bacteria were found in swine and in pork products.

Enterococci are a common hospital-acquired pathogen. When they are multi-drug resistant, they are difficult to treat and sometimes fatal. In Denmark, where the subtherapeutic use of tylosin in livestock is common, 90 percent of enterococci in pigs are resistant to tylosin.³¹ In contrast, in Finland, where tylosin rarely is used subtherapeutically, only 15 percent of enterococci are tylosin resistant.

Similarly, in the Netherlands, where avoparcin was used subtherapeutically in pigs, 39 percent of enterococci isolated from pigs were resistant to avoparcin (and the related human-use antibiotic,

chicken to chicken and from chicken to man. *Nature* 1976; 260: 40-42 [hereinafter Levy, 1976].

³⁰ Hummel, R., Tschäpe, H., Witte, W., Spread of plasmid-mediated nourseothricin resistance due to antibiotic use in animal husbandry. *Journal of Basic Microbiology* 1986; 26: 461-466 [hereinafter Hummel, 1986].

³¹ Ministry of Agriculture, Food and Fisheries, *Can We Use Less Antibiotics?*, Stockholm, Sweden; 1997 [hereinafter *Can We Use Less Antibiotics?* 1997].

vancomycin).³² In contrast, in Sweden, which banned the use of all antibiotics (including avoparcin) as growth promoters in 1986, avoparcin- and vancomycin-resistant enterococci are not found in fecal samples from pigs.

In northern European countries, where avoparcin is used as a growth promotant, enterococci resistant to the related antibiotic vancomycin are common in healthy people.^{33,34} However, in the U.S., where agricultural uses of avoparcin and vancomycin are not approved, vancomycin-resistant enterococci are not found in animals or in people outside the hospital setting.³⁵

3. Antibiotic-resistant bacteria can be transferred between animals and between animals and people.

It has long been known that once bacteria in animals develop resistance to antibiotics, those bacteria can be transferred to other animals and to people. As described previously (p. 11), a 1976 study showed that antibiotic-resistant bacteria can be transferred from chicken to chicken and from chicken to people.³⁶ Tetracycline-resistant *E. coli* were isolated from uninoculated chickens that were fed tetracycline-supplemented feed and were housed with chickens inoculated with tetracycline-

³² Stobberingh, E.E., Usage of antimicrobial growth promoters in food animals poses a public health threat. Abstract from 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, 1998 September 24-27; San Diego, CA.

³³ Van der Auwera, P., Pensart, N., Korten, V., Murray, B., Influence of oral glycopeptides on the faecal flora of human volunteers: selection of highly glycopeptide resistant enterococci. *Journal of Infectious Disease* 1996; 173:1129-1136.

³⁴ Schouten, M.A., Voss, A., Hoogkamp-Korstanje, J.A.A., VRE and meat [letter]. *The Lancet* 1997; 349: 1258.

³⁵ Silverman, J., Thal, L.A., Perri, M.B., Bostic, G., Zervos, M.J., Epidemiological evaluation of antimicrobial resistance in community-acquired enterococci. *Journal of Clinical Microbiology* 1998; 36: 830-832.

³⁶ Levy, 1976.

resistant *E. coli*. Additionally, those researchers isolated bacteria with the resistance plasmid from animal handlers. A 1977 study showed that antibiotic-resistant bacteria from animals can be transferred to people who handle raw meat.³⁷

Salmonella, a food-borne pathogen that sickens an estimated 1.4 million and kills 500 Americans each year,³⁸ is readily transmissible from animals to humans. In the developed world, the majority of *Salmonella* infections in humans come from food, with additional cases arising from direct contact with animals. If *Salmonella* bacteria carried by animals developed resistance to antibiotics, those resistant bacteria could be transferred to humans.

A study in 1980 showed that an outbreak of antibiotic-resistant *Salmonella* in infants in a hospital nursery originated from farm animals.³⁹ A farmer's daughter who was pregnant worked with calves up until four days before she delivered her baby. The pregnant woman fed sick calves from her hand in an effort to teach them to drink from a bucket. After the woman gave birth, she had diarrhea. In addition, her baby developed diarrhea three days after he was born, as did two other babies in the nursery. Culturing the patients and calves revealed that all were infected with *Salmonella heidelberg* that was resistant to chloramphenicol, sulfamethoxazole, and tetracycline. All three of those antibiotics are, or were previously, used in agriculture. Those cases suggest that

³⁷ Linton, A.H., Animal to man transmission of Enterobacteriaceae. *Royal Society of Health Journal* 1977; 97: 115-118.

³⁸ Center for Disease Control and Prevention, National Center for Infectious Disease Branch, *FoodNet*, 1998.

³⁹ Lyons, R.W., Samples, C.L., DeSilva, H.N., Ross, K.A., Julian, E.M., Checko, P.J., An epidemic of resistant *Salmonella* in a nursery: animal-to-human spread. *Journal of the American Medical Association* 1980; 243: 546-547.

antibiotic-resistant *Salmonella* spread to a woman through direct contact with sick farm animals. The bacteria also spread from baby to baby in the hospital setting.

An outbreak of multiple-antibiotic-resistant *Salmonella typhimurium* (resistant to ampicillin, chloramphenicol, kanamycin, streptomycin, sulfadiazine, and tetracycline) occurred among newborns in a Canadian hospital in 1983.⁴⁰ That outbreak was traced back to local dairy cattle which were infected with the same strain of antibiotic-resistant bacterium. The mother of the first infant to become sick lived on the farm with the infected cattle and drank unpasteurized milk. (The other babies became ill three to four days later, probably from cross-contamination by nurses who cared for them.)

A study by Holmberg, published in 1984, demonstrated animal-to-human transmission of antibiotic-resistant *Salmonella newport* (resistant to ampicillin, carbenicillin, and tetracycline).⁴¹ The genes for resistance were located on a plasmid. Eighteen patients had consumed hamburger meat from a herd of cattle that had been fed subtherapeutic amounts of tetracycline to promote growth. Although the suspect meat was not available for testing, all of the patients came from Minnesota, South Dakota, and Iowa, states where the suspect meat was distributed. In addition, the only isolation of that particular antibiotic-resistant strain in the previous year occurred in dairy cows on a farm adjacent to the beef herd.

⁴⁰ Bezanson, G.S., Khakhria, R., Bollegraaf, E., Nosocomial outbreak caused by antibiotic-resistant strain of *Salmonella typhimurium* acquired from dairy cattle. *Canadian Medical Association Journal* 1983; 128: 426-427.

⁴¹ Holmberg, 1984.

4. Antibiotic-resistant bacteria may transfer resistance genes to other bacteria.

Using antibiotics subtherapeutically increases the prevalence of antibiotic-resistant bacteria. Those bacteria could colonize people and pass their resistant genes to human pathogens by a process called horizontal gene transfer.⁴² For example, a person might consume meat that is contaminated with nonpathogenic bacteria. If those benign bacteria contained genes that confer antibiotic resistance, the resistance genes could be transferred in a person's gut from the harmless bacteria to pathogenic bacteria.

One example of horizontal gene transfer was observed in Germany.⁴³ In 1983, farmers in certain parts of Germany began using a new antibiotic, nourseothricin, for growth promotion in swine. That use quickly led to the development of nourseothricin resistance among *E. coli* isolated from swine and from pork products. By 1990, nourseothricin-resistant *E. coli* had been passed to farm workers, farmers' families, citizens in the community in which nourseothricin was used, and patients suffering from urinary tract infections. A few years later, the nourseothricin-resistance gene was found in *Shigella*, a bacterium found in primates (including humans) but not in swine.⁴⁴ No nourseothricin-resistant bacteria were isolated from people or animals in other parts of Germany where the antibiotic was not being used. The appearance of nourseothricin-resistant *Shigella* indicated that the resistance moved from bacteria exposed to antibiotics on the farm to a human pathogen.

⁴² Levy, *The Antibiotic Paradox*, 1992 pp. 78-89.

⁴³ Hummel, 1986.

⁴⁴ Tschäpe, H., The spread of plasmids as a function of bacterial adaptability. *FEMS Microbiology Ecology* 1994; 15: 23-31.

Another example of horizontal transfer was demonstrated in the laboratory. Scientists facilitated the transfer of an unusual tetracycline-resistance gene, tet (Q), from *Prevotella rumincola* isolated from sheep to *Bacteroides fragilis*, a human pathogen.⁴⁵ *P. rumincola* is found in high numbers in the normal gut bacteria of sheep and cattle. Although that experiment does not prove that horizontal transfer of resistance occurs in nature, it shows that transfer is biologically possible. Further research suggested that such transfer likely does occur in nature. The identical tet (Q) gene was found in *B. fragilis* in humans and in *P. rumincola* isolated from animals.⁴⁶ A 1992 study showed that *Staphylococcus aureus* and enterococci can transfer antibiotic-resistance genes in the laboratory setting.⁴⁷ Presumably, that transfer also could happen in nature.

A fourth example that suggests that transfer of antibiotic-resistant genes can occur between different species of bacteria comes from the U.K.⁴⁸ The use of apramycin, an aminoglycoside, caused the emergence of resistance in *E. coli* found in feces of treated animals. The resistant bacteria had a unique plasmid profile and were resistant to apramycin, gentamicin (another aminoglycoside), and hygromycin B (an antiparasitic agent used in agriculture). Resistant *E. coli* with the identical

⁴⁵ Shoemaker, N.B., Salyers, A.A., unpublished data, cited in Speer, B.S., Shoemaker, N.B., Salyers, A.A., Bacterial resistance to tetracycline: mechanisms, transfer, and clinical significance. *Clinical Microbiology Reviews* October 1992: 387-399.

⁴⁶ Shoemaker, N.B., Wang, G., Salyers, A.A., Evidence for natural transfer of a tetracycline resistance gene between bacteria from the human colon and bacteria from the bovine rumen. *Applied Environmental Microbiology* 1992; 58: 1313-1320.

⁴⁷ Noble, W.C., Virani, Z., Cree, R.G., Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus*. *FEMS Microbiology Letters* 1992; 72: 195-198 [hereinafter Noble, 1992].

⁴⁸ Johnson, A.P., Burns, L., Woodford, N., Threlfall, E.J., Naidoo, J., Cooke, E.M., George, R.C., Gentamicin resistance in clinical isolates of *Escherichia coli* encoded by genes of veterinary origin. *Journal of Medical Microbiology* 1994; 40: 221-226.

pattern of resistance were subsequently found in hospital patients. One of those patients also was infected with *Klebsiella pneumonia* (a human pathogen) that had the same resistance pattern. The resistance gene apparently was horizontally transferred between *E. coli* and *Klebsiella pneumoniae*.

5. Subtherapeutic antibiotic use may select for multi-drug-resistant bacteria that can cause infections that are difficult to treat.

Subtherapeutic use of one antibiotic can select for bacteria that are resistant to several antibiotics. That is because several resistance genes may be grouped together on bacterial DNA. Use of any of the antibiotics to which the bacteria are resistant could select for resistance to all of the antibiotics. Because they are resistant to multiple antibiotics, multi-drug-resistant infections may be particularly difficult to treat.

Multi-drug-resistant *Salmonella typhimurium*, which accounts for about 10 percent of all *Salmonella* infections, poses a major health concern.⁴⁹ Most of those infections are caused by *Salmonella typhimurium* DT104, which usually is resistant to ampicillin (a penicillin), chloramphenicol, streptomycin, sulfonamides, and tetracycline. Since 1979, the prevalence of human *Salmonella typhimurium* isolates that are resistant to those antibiotics increased from 0.6 percent to 34 percent.

Multi-drug-resistant DT104 caused an outbreak at a dairy farm in Vermont that sickened and killed cattle and sickened nine people (one almost died) who cared for the cattle or who drank unpasteurized milk.⁵⁰ Because the infections were multi-drug resistant, physicians had difficulty

⁴⁹ Glynn, 1998.

⁵⁰ Friedman, C.R., Epidemic Intelligence Service Officer, Center for Disease Control and Prevention, memo to Epidemiology Program Office, Centers for Disease Control and Prevention, June 27, 1997.

finding an antibiotic that was effective against those infections. After several failed attempts, physicians finally were able to treat the one hospitalized victim with the one class of drug to which the DT104 strain was not resistant (and to which the patient was not allergic): fluoroquinolones.

Salmonella typhimurium DT104 also may be a particularly virulent strain of *Salmonella*. Infections may be associated with greater morbidity and mortality than other *Salmonella* infections.^{51,52} In the U.K., where DT104 is the predominant strain of *Salmonella* isolated from people, a 1994 study reported that 41 percent of people who became ill with that strain required hospitalization, and three percent died.⁵³ In addition, in some DT104 outbreaks in the U.K., the mortality rate among DT104-infected cattle ranges from 40 to 60 percent.⁵⁴

In 1998, an outbreak in Denmark of multi-drug-resistant DT104 that also was resistant to fluoroquinolones was traced to a herd of pigs. Among the 22 victims were several people who did not respond to fluoroquinolone therapy. One death was indirectly attributable to treatment failure.⁵⁵

6. Subtherapeutic antibiotic use jeopardizes therapeutic options in veterinary and human medicine.

⁵¹ Wall, P.G., Morgan, D., Lamden, K., A case control study of infection with an epidemic strain of multiresistant *Salmonella typhimurium* DT104 in England and Wales. *Communicable Disease Report CDR Review* 1994; 4: R130-R135 [hereinafter Wall, 1994].

⁵² A recent study suggests that DT104 may not be more virulent than other subtypes of *Salmonella typhimurium*. (Threlfall, E.J., Ward, L.R., Rowe, B., Multiresistant *Salmonella typhimurium* DT104 and salmonella bacteraemia. *The Lancet* 1998; 352: 287-288.) This issue has yet to be resolved.

⁵³ Wall, 1994.

⁵⁴ U.S. Department of Agriculture, Food Safety and Inspection Service, *Situation Assessment: Salmonella typhimurium* DT104. December 1997 [hereinafter *Situation Assessment: Salmonella typhimurium* DT104, December 1997].

⁵⁵ Anonymous, Outbreak of quinolone-resistant, multiresistant *Salmonella typhimurium* DT104, Denmark. *Weekly Epidemiological Record* 1998; 42 :327-328.

Subtherapeutic use of older antibiotics such as penicillin and tetracycline has rendered them less effective in treating animal disease. Consequently, veterinarians and farmers have had to use newer antibiotics to treat animal disease, which in turn accelerates the development of antibiotic resistance to those newer antibiotics.

In the U.K., the use of antibiotics has fostered the emergence of multi-drug-resistant *Salmonella typhimurium* DT104 that often is lethal to cattle. Because of the agricultural use of antibiotics, multi-drug-resistant-DT104 infections are resistant to the antibiotics typically used to treat *Salmonella* in cattle. As a result, to treat those infections, farmers must resort to the same antibiotics that are used for treating human cases of invasive *Salmonella*: Bactrim (trimethoprim-sulfamethoxazole) and fluoroquinolones. Not surprisingly, the use of Bactrim and fluoroquinolones to treat DT104 infections in cattle is leading to the development of resistance to those drugs. In 1995, only two years after fluoroquinolones commonly were used in cattle, 16 percent of multi-drug-resistant DT104 isolated from cattle were resistant to fluoroquinolones.⁵⁶ From 1993 to 1996, the proportion of DT104 isolates from cattle resistant to trimethoprim, one of the active ingredients in Bactrim, rose from less than two percent to 24 percent in the U.K.⁵⁷ If DT104 bacteria resistant to fluoroquinolones and Bactrim were to cause bloodstream infections in humans, those infections would be difficult to treat.

⁵⁶ Hughes, J.M., Assistant Surgeon General and Director, National Center for Infectious Diseases, letter to Stephen Sundlof, Center for Veterinary Medicine, Food and Drug Administration, May 14, 1997.

⁵⁷ *Situation Assessment: Salmonella typhimurium* DT104, December 1997.

In the U.S., where tetracycline is used subtherapeutically in livestock, tetracycline-resistance among animal isolates of *Salmonella* ranges from 24 percent in cattle to 50 percent in swine.⁵⁸

Because tetracycline is ineffective against many cases of *Salmonella* infections in livestock, other antibiotics, such as ceftiofur (a third-generation cephalosporin), must be used. However, in children, third-generation cephalosporins are the drugs of choice for treating invasive *Salmonella* infections.⁵⁹

As ceftiofur is used more in animals, resistance is likely to develop, potentially leaving no therapeutic options for those infected children.

7. Subtherapeutic use of antibiotics reduces the effectiveness of new human-use antibiotics, jeopardizing human health.

The subtherapeutic use of antibiotics can threaten the value not only of currently available antibiotics, but also of antibiotics that will be developed and marketed in the future.

A new class of antibiotics called streptogramins may become one of the only effective measures against deadly bloodstream infections caused by antibiotic-resistant enterococci. Although it has not yet been approved for use in humans, the potential value of one streptogramin -- Synercid -- already has been compromised because of agricultural use of another antibiotic in the same class. That is because resistance to one antibiotic can cause resistance to an entire class of antibiotics. Turkeys that had been fed subtherapeutically another streptogramin, virginiamycin, harbor

⁵⁸ Tollefson, L., Angulo, F.J., Fedorka-Cray, P.J. National surveillance for antibiotic resistance in zoonotic enteric pathogens. *Veterinary Clinics of North America: Food Animal Practice* 1998; 14: 141-150.

⁵⁹ Fluoroquinolones can be used to treat invasive *Salmonella* infections in adults, but are not approved for use in children under 18 years of age.

enterococci bacteria that also are resistant to Synercid.⁶⁰ If people touch or consume turkey meat that is contaminated with those streptogramin-resistant enterococci and become ill, Synercid, if and when it is approved for human use, would be ineffective against that illness. In the U.S., Synercid-resistant bacteria have not yet been found in humans. However, in Germany, where Synercid also is not yet used in humans but where virginiamycin is used subtherapeutically in livestock, enterococci resistant to Synercid have been detected in humans.⁶¹

The development of widespread streptogramin resistance from subtherapeutic uses of one streptogramin, virginiamycin, also is a concern because it is possible that the gene responsible for streptogramin resistance could be transferred from enterococci to other human pathogens, such as *Staphylococcus aureus*. Gene transfer between those types of bacteria has been demonstrated in *in vitro* experiments.⁶²

Staphylococcus aureus is a leading cause of deadly hospital-acquired (nosocomial) bloodstream infections. Staph infections are becoming increasingly resistant to all approved antibiotics. Synercid, once approved, is expected to be an important tool for treating resistant staph infections. If resistance to Synercid were passed from enterococci to *Staphylococcus aureus* due to the subtherapeutic use of virginiamycin, Synercid might not be effective.

⁶⁰ Thal, L.A., Welton, L.A., Perri, M.B., Donabedian, S., McMahon, J., Chow, J.W., Zervos, M.J., Antimicrobial resistance in enterococci isolated from turkeys fed virginiamycin. *Antimicrobial Agents and Chemotherapy* 1998; 42: 705-708.

⁶¹ Witte, W., Medical consequences of antibiotic use in agriculture. *Science* 1998; 279: 996-997 [hereinafter Witte, 1998].

⁶² Noble, 1992.

8. Decreasing subtherapeutic uses of antibiotics on farms can reduce the prevalence of antibiotic-resistant bacteria and does not adversely affect animal health.

Some critics of limiting antibiotics for growth promotion have claimed that once resistance develops, it is impossible to get rid of and that, therefore, no purpose would be served by banning subtherapeutic uses of antibiotics.^{63,64} However, in countries that have banned certain subtherapeutic uses of antibiotics, decreases in resistance to those antibiotics have occurred, thereby restoring the effectiveness of those antibiotics to treat disease. For example, in Denmark, following a 1995 ban on the use of avoparcin as a growth promoter, glycopeptide-resistant enterococci in Danish broiler flocks declined from 82 percent to 12 percent.⁶⁵ Although no reduction has been seen in swine, that is likely due to the facts that: a) swine production is continuous (as compared to broilers which is all-in, all-out production allowing for cleaning between flocks), and b) swine producers changed from avoparcin to tylosin (which also selects for glycopeptide-resistant enterococci), whereas Danish broiler producers stopped using any kind of antimicrobial growth promoters.⁶⁶ In contrast, other countries that have not banned subtherapeutic use of antibiotics, such as the U.S., have seen continuing increases in resistance to antibiotics used subtherapeutically.⁶⁷

⁶³ Hays, V.W., Black, C.A., *Antibiotics for animals: the antibiotic resistance issue*. Ames, IA: Comments from Council for Agricultural Science and Technology (CAST); 1989.

⁶⁴ Gustafson, R.H., Symposium: Antibiotic residues in meat and milk: use of antibiotics in livestock and human health concerns. *Journal of Dairy Science* 1991; 74: 1428-1432.

⁶⁵ Danish Zoonosis Centre, *DANMAP 1997. Consumption of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark*. Copenhagen; 1998.

⁶⁶ Wegener, H., director of Danish veterinary diagnostic laboratory, personal communication, November 1998 [hereinafter Wegener, personal communication, 1998].

⁶⁷ Glynn, 1998.

Critics also have claimed that animal health suffers when subtherapeutic antibiotics are not used.⁶⁸ However, improvements in animal husbandry methods can mitigate the need for subtherapeutic use of antibiotics with no increase in animal disease. Shortly after the Swedish ban on subtherapeutic uses of antibiotics, there was increased mortality among farm animals.⁶⁹ However, after Swedish farmers improved their animal husbandry practices, those increases disappeared. Similarly, after the voluntary ban of growth promoters in Denmark in January 1998, disease incidence in broilers did not increase.⁷⁰

C. Expert committees and leading scientists support a phase out of subtherapeutic antibiotic use in livestock.

Since the FDA first proposed limiting the agricultural use of subtherapeutic antibiotics in 1972 and the NRDC petition of 1984, a number of authoritative organizations have recommended, and a number of countries have implemented, limits. One of the strongest calls for halting such uses came from the World Health Organization in 1997. WHO concluded that excessive use of antimicrobials, especially as growth promotants in livestock, presents a growing risk to human health.⁷¹ The WHO recommended that:

The use of any antimicrobial agent for growth promotion in animals should be terminated if it is: used in human therapeutics; or known to select for cross-resistance to antimicrobials used in human medicine.

⁶⁸ Animal Health Institute, *Fast Facts about Antibiotics and Animals*. Alexandria, VA: Animal Health Institute; 1998.

⁶⁹ *Can We Use Less Antibiotics*, 1997.

⁷⁰ Wegener, personal communication, 1998.

⁷¹ WHO meeting, 1997.

Increased concerns regarding risks to public health resulting from the use of antimicrobial growth promoters indicate that it is essential to have a systematic approach towards replacing growth-promoting antimicrobials with safer non-antimicrobial alternatives.

Currently, most developed nations, with the notable exception of the United States and Canada, have banned the subtherapeutic use of penicillin and tetracycline.⁷² In addition, in December 1998, the agricultural ministers of the European Union banned the subtherapeutic agricultural uses of bacitracin, spiramycin, virginiamycin, and tylosin. Along with the antibiotics that already were banned by the EU, this completed the ban of all medically important antibiotics. Prior to that ban, Sweden banned the use of *any* antibiotic for growth promotion; Denmark banned the subtherapeutic use of virginiamycin; Finland banned the subtherapeutic use of tylosin and spiramycin.^{73,74} To prevent resistance to antibiotics useful in treating animal disease from developing, Finland proposed that any antibiotic used in veterinary medicine for therapeutic purposes should not also be approved for use as a subtherapeutic additive in feed.⁷⁵

A 1998 report of the Economic and Social Committee of the European Communities also supported limits on agricultural uses of antibiotics.⁷⁶ It stated:

⁷² Although countries like the U.K. have banned the practice of using penicillin and tetracycline in subtherapeutic doses by farmers, veterinarians may still prescribe antibiotics for those purposes. It is unclear how much subtherapeutic dosing of livestock still takes place.

⁷³ Ministry of Agriculture, Food and Fisheries, Sweden, *Today We Defeat Bacteria. What About Tomorrow?* 1997 November 13; Brussels, Belgium.

⁷⁴ *Can We Use Less Antibiotics?*, 1997.

⁷⁵ *Can We Use Less Antibiotics?*, 1997.

⁷⁶ European Communities, Opinion of the Section for Protection of the Environment, Public Health and Consumer Affairs of the Economic and Social Committee on the Resistance to Antibiotics as a Threat to Public Health, July 7, 1998.

The use of antibiotics should be limited to (well established) veterinary medical purposes. In this connection, the Committee shares the view expressed by the Expert Committee at the October 1997 WHO meeting in Berlin that “increased concerns regarding risks to public health resulting from use of antimicrobial growth promoters indicate that it is essential to have a systematic approach towards replacing growth promoting antimicrobials with safer, non-antimicrobial alternatives.” In this context, the emphasis should be first and foremost on limiting the use of antibiotics that can provoke cross-resistance to drugs that are or will become relevant in human health care.

In February 1998, Wolfgang Witte of the Robert Koch Institute in Germany stated in a commentary in *Science*:

In the future, it seems desirable to refrain from using any antimicrobials for the promotion of animal growth. As exemplified by the use of virginiamycin in animal feed and the subsequent emergence of enterococci resistant to antibiotics, the use of any antimicrobial can lead to unexpected consequences that limit medical choices.⁷⁷

In May 1998, Stuart Levy, a Professor of Molecular Biology at Tufts University Medical School, president of the American Society for Microbiology, and director of the Alliance for the Prudent Use of Antibiotics, wrote in a *New England Journal of Medicine* editorial, that recent findings have:

made it even clearer that the use of growth promoters affects the drug resistance of environmental reservoirs, with direct consequences for the treatment of disease in humans [and that] such findings led to a ban on avoparcin in the European Union countries and, recently, on virginiamycin in Denmark.⁷⁸

V. Statement of Legal Grounds

A. The FDA has legal authority to withdraw the approval of new animal drug applications that are unsafe.

The FDCA provides in pertinent part that:

⁷⁷ Witte, 1998.

⁷⁸ Levy, S., Multidrug resistance -- a sign of the times. *New England Journal of Medicine* 1998; 338: 1376-1378.

The Secretary shall, after due notice and opportunity for a hearing to the applicant, issue an order withdrawing approval of an application filed pursuant to subsection (b) with respect to any new animal drug if the Secretary finds:

(A) that experience or scientific data show that such drug is *unsafe* for use under the conditions of use upon the basis of which the application was approved; [emphasis added]

(B) that new evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is *not shown to be safe* for use under the conditions of use upon the basis of which the application was approved⁷⁹ [emphasis added]

As used in that provision, the word “safe” in section 512, “has reference to the health of man or animal.”⁸⁰

Recently, the FDA issued a notice of availability of a guidance for industry that is directly on point.⁸¹ The guidance relies on two statutory provisions in 21 U.S.C. § 360b(d)(2)(A) and (B) as legal authority. Those provisions require the FDA, in determining whether an animal drug is “safe,” to consider: (1) “the probable consumption of such drug and of any substance formed in or on food because of the use of such drug”; and (2) “the cumulative effect in man or animal of such drug,

⁷⁹ FDCA § 512(e), 21 U.S.C. § 360b(e). Implementing regulations parallel the language of the statute. 21 C.F.R. § 514.115(b).

⁸⁰ FDCA § 201(u), 21 U.S.C. § 321(u).

⁸¹ 63 Fed. Reg. 64094 -95. Food and Drug Administration, *Guidance for Industry: Evaluation of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals*; Availability (Nov. 18, 1998) [hereinafter FDA Notice of Availability of Guidance to Industry, 1998].

taking into account any chemically or pharmacologically related substance.” In evaluating safety, the FDA may also consider “other relevant factors.”⁸²

The FDCA thus provides the FDA with ample authority to withdraw approval of the new animal drug applications (NADAs) of the antibiotic uses at issue in this petition. In the past, the FDA has used such authority to withdraw the approvals of NADAs for diethylstilbestrol (DES),⁸³ chloramphenicol,⁸⁴ and furazolidone and nitrofurazone.⁸⁵ Although the withdrawals in those cases were based on the fact that residues from the drugs would have adverse effects on humans, the overriding principle that led to withdrawal in all of those cases is that their use in food-producing animals was unsafe for humans.

As discussed above (pp. 9-27), the subtherapeutic use of antibiotics selects for antibiotic resistance in bacteria in animals. Those antibiotic-resistant bacteria can infect people and make them sick. Additionally, people can become colonized with non-pathogenic antibiotic-resistant bacteria from animals that can pass their resistance genes to pathogenic bacteria. Leading experts in infectious disease agree that the subtherapeutic use of antibiotics dangerously compromises the effectiveness of approved and future antibiotics for treating infections in humans. Therefore, the subtherapeutic agricultural use of antibiotics that are used in (or related to those used in) human medicine is “unsafe” within the meaning of the FDCA, and the FDA should withdraw the approvals of those uses.

⁸² 21 U.S.C. § 360b(d)(2).

⁸³ 44 Fed. Reg. 54852 (Sept. 21, 1979).

⁸⁴ 51 Fed. Reg. 1367 (Jan. 13, 1986), 50 Fed. Reg. 27059 (July 1, 1985).

⁸⁵ 56 Fed. Reg. 41902 (Aug. 23, 1991).

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.

In a May 4, 1998, discussion paper on antimicrobial use in food animals, Dr. Stephen Sundlof, director of the Center for Veterinary Medicine (CVM) stated:

CVM believes it is critical that prudent use of antimicrobials be emphasized in order to minimize the development of antimicrobial resistance and to ensure the continued efficacy and availability of antimicrobial products for use in food producing animals.⁸⁶

He defined “prudent use” as “[u]se that maximizes therapeutic effect while minimizing the development of resistance.”⁸⁷

Under Dr. Sundlof’s definition of prudent use, the subtherapeutic use of antibiotics used medically should not be allowed. Subtherapeutic use is *not prudent* because it promotes the development of antimicrobial resistance and jeopardizes the continued efficacy and availability of antimicrobial products for medical and veterinary uses. Nontherapeutic uses of antibiotics should not be allowed to erode the value of essential uses.

More recently, the FDA underscored the importance of antibiotic resistance by issuing in the Federal Register a notice of availability of a guidance document.⁸⁸ The notice announced the FDA’s determination that:

⁸⁶ Dr. Stephen Sundlof, director, Center for Veterinary Medicine, Food and Drug Administration, *The Issue of Antimicrobial Use in Food Animals*. May 4, 1998 [hereinafter Sundlof, May 1998].

⁸⁷ Sundlof, May 1998

⁸⁸ FDA Notice of Availability of Guidance to Industry, 1998

It is necessary to evaluate the human health impact of the microbial effects associated with all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals when approving such drugs.

The FDA also proposed a “Framework Document” for addressing the adverse microbial effects of antimicrobial animal drugs.⁸⁹ At the time that this petition was submitted, the “Framework Document” was not finalized.⁹⁰ Thus, the criteria for approving new antimicrobial animal drugs are still undefined and the FDA’s approach to reviewing the safety of currently approved veterinary uses of antibiotics is still unclear. The “Framework Document” acknowledges that the FDA will review already-approved antibiotics only “as resources permit.” We believe that any new public-health safeguards adopted for future antibiotic approvals must also be applied to already-approved antibiotics.

This petition calls upon the FDA to address immediately the longstanding problem of subtherapeutic use of antibiotics, which for decades has jeopardized the effectiveness of those drugs

⁸⁹ Food and Drug Administration, Center for Veterinary Medicine, *Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs For Use in Food-Producing Animals*, December 9, 1998 [hereinafter FDA Framework Document, 1998].

⁹⁰ Petitioners CSPI, EDF, and UCS provided testimony at an FDA meeting on July 25, 1999, which raised a number of concerns about the proposed Framework Document. In order to provide adequate public-health safeguards, the framework must be applied retroactively, to antibiotics already on the market. The process to withdraw an already-approved antimicrobial from the market must be expeditious, in order to prevent human harm from resistance. We also are concerned about the categorization of antibiotics in the Framework Document. Category I drugs should not be permitted in livestock because they are vital to treating human diseases. Category II drugs (which should include any antibiotic that is used in human medicine not in Category I, including little-used drugs) should not be allowed for use in livestock if such use causes any increase in antibiotic resistance. Category III drugs should include drugs that are not used in human medicine, such as ionophores.

and the health of Americans. Under FDA's proposed Framework, all of the antibiotics at issue in this petition should be considered Category I or II drugs, because of their importance in human medicine. Therefore, if the "Framework Document" is implemented and applied to existing subtherapeutic uses of antibiotics, it should trigger steps to rescind approvals of those uses. If the "Framework Document" is not implemented or not applied to existing subtherapeutic uses of antibiotics, the FDA could initiate withdrawal proceedings immediately under current law because the subtherapeutic uses of antibiotics at issue in this petition are not safe (See discussion pp. 9-27).

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.

In 1977, the FDA issued proposed notices of withdrawal for the NADAs for premixes containing penicillin or tetracycline⁹¹ because of its concerns over the transfer of drug resistance from animals to humans, as well as efficacy concerns. Congress, however, required that the FDA suspend further action on those withdrawals pending further study by the National Academy of Sciences (NAS). In particular, Congress authorized the FDA to contract with NAS "to review data on the subject, identify data gaps, and make recommendations for further action."⁹²

The subsequent NAS report concluded that:

The postulated hazards to human health from the subtherapeutic use of antimicrobials in animal feeds were neither proven nor disproven. The lack of data linking human illness with this subtherapeutic use must not be equated with proof that the proposed hazards do not exist.⁹³

⁹¹ 42 Fed. Reg. 56,264 (Oct. 21, 1977).

⁹² H.R. No. 96-1095 at 105-06 (Agriculture, Rural Development and Related Agencies Appropriation Bill, 1981) [hereinafter H.R. No. 96-1095 Appropriations Bill, 1981].

⁹³ National Research Council, *Effects on Human Health of Subtherapeutic Use of*

The NAS further concluded that a single comprehensive study to settle the issue was considered technologically impractical. Nevertheless, the NAS recommended that:

future epidemiological studies . . . be carefully planned to fill gaps in our present knowledge and especially to avoid the errors of ambiguous design and small sample size that have caused such difficulties in interpreting the data.⁹⁴

In response to NAS' recommendations, Congress stated that the FDA would be expected to continue to hold in abeyance any implementation of its proposal pending the final results of [research generating new epidemiological information] and evidentiary hearings.⁹⁵

In 1986, in considering another appropriations bill for the FDA, Congress concluded that:

The evidence presented to support the position that discontinuing the use of subtherapeutic antibiotics in animal feeds would improve human health is inconclusive The Committee is aware that the FDA is continuing to study this issue and, therefore, will expect the FDA to consider the final reports of the several epidemiological studies commissioned by the Animal Health Institute before the Agency takes further action restricting the use of antibiotics in animal feeds.⁹⁶

As discussed in above (pp. 9-27), in the years since Congress halted the FDA's proposed withdrawals of NADAs for penicillin and tetracycline, numerous studies have shown that antibiotic use in livestock selects for antibiotic-resistant bacteria that pose a risk to human health. In addition, a more recent NAS report, entitled *The Use of Drugs in Food Animals: Benefits and Risks*, acknowledges that "there is a link between the use of antibiotics in food animals, the development of

Antimicrobials in Animal Feeds, Washington, D.C.: National Academy Press; 1980 [hereinafter *Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds*, 1980].

⁹⁴ *Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds*, 1980.

⁹⁵ H.R. No. 96-1095 Appropriations Bill, 1981.

⁹⁶ S. 99-137 at 116 (Agriculture, Rural Development, and Related Agencies Appropriation

bacterial resistance to these drugs, and human disease, although the incidence of such disease is very low.”⁹⁷

In addition, authoritative scientific bodies such as the U.S. Centers for Disease Control and Prevention⁹⁸ and the World Health Organization⁹⁹ consider it a human-health risk to permit subtherapeutic use in livestock of antibiotics that are used in (or related to those used in) human medicine.

Congress’ concerns as to whether subtherapeutic use of antibiotics leads to human-health risks has been satisfied by ample research. Thus, the FD should consider that Congress’ directive has been satisfied and take the action requested in this petition.

D. The FDA should adopt policies consistent with the current international trend of phasing out the subtherapeutic use of medically important antibiotics.

The FDA should consider any decision regarding the continued subtherapeutic use of antibiotics in the context of international harmonization. In recent legislation, Congress concluded that as part of the FDA’s mission, it must participate through appropriate processes with representatives of other countries to “harmonize regulatory requirements, and achieve appropriate reciprocal arrangements.”¹⁰⁰ As mentioned previously (pp. 23-25), the European Union and a

Bill, 1986).

⁹⁷ *The Use of Drugs in Food Animals*, 1998.

⁹⁸ Glynn, 1998.

⁹⁹ WHO meeting, 1997.

¹⁰⁰ Food and Drug Administration Modernization Act of 1997 (FDAMA), P.L. No. 105-115, 111 Stat. 2295 (1997), codified at 21 U.S.C. § 393(b)(3).

number of countries have banned the subtherapeutic use of medically important antibiotics. Prohibiting the subtherapeutic use of medically important antibiotics in the U.S. would serve to harmonize U.S. regulatory policy with that of many other nations and help ensure that U.S. farmers and processors have full access to global markets.

VI. Economic Impact

In a recent report, a committee of the National Academy of Sciences (NAS) attempted to estimate the economic impact of banning subtherapeutic uses of antibiotics.¹⁰¹ Using data from the industry-financed advocacy group, the Council for Agricultural Science and Technology (CAST), the committee estimated that banning subtherapeutic uses of antibiotics could cost the average consumer as much as 18 cents per week (\$9.72 per year) in higher food costs. That estimate is based on elimination of all subtherapeutic uses of all antibiotics, not just those antibiotics that are used in (or related to those used in) human medicine. Additionally, CAST's estimate assumed a certain level of growth promotion from subtherapeutic antibiotic use that is poorly documented. In fact, in Sweden, where antimicrobial growth promotants are not used, cattle production rates have not changed.¹⁰² Therefore, it is unclear if there will be an increase in food costs as estimated by the industry.

According to the NAS report, the farmers who would experience the largest losses due to a ban of all antibiotics in subtherapeutic doses would be those who have the worst management

¹⁰¹ *The Use of Drugs in Food Animals*, 1998.

¹⁰² Wierup, M., Swedish University of Agricultural Sciences, Sweden, personal communication, January 1999.

practices.¹⁰³ Subtherapeutic antibiotics have the greatest effect in animals that are under stress due to inadequate nutrition and poor sanitation.¹⁰⁴ One study showed that pork producers who wash hoghouses every time a group of pigs is moved out and who grow piglets in off-site growing facilities can reduce their antibiotic use without suffering economic hardship.¹⁰⁵

In fact, it is possible to raise animals economically without growth-promoting antibiotics. For example, in Sweden antibiotics are not allowed for growth promotion and are used only sparingly for therapeutic purposes in farm animals. Swedish officials say reductions in antibiotic use have been done cost effectively.¹⁰⁶ In Denmark, where broiler producers stopped using growth promoters starting in January of 1998, producers have estimated that the cost of raising a broiler has increased by one quarter of a Danish Crown (less than four cents).¹⁰⁷

Also, other growth promotants and/or improved management practices are commercially viable. For instance, spokespersons for two of the leading poultry producers in the U.S., Tyson Foods, Inc., and Perdue Farms, Inc., say that their companies do not use subtherapeutic doses of human-use antibiotics for growth promotion because they do not consider that practice cost

¹⁰³ *The Use of Drugs in Food Animals*, 1998.

¹⁰⁴ Braude, R., Kon, S.K., Porter, J.W.G., Antibiotics in nutrition. *Nutrition Abstracts and Reviews* 1953; 23: 473-495.

¹⁰⁵ Dial, G.D., Wiseman, B.S., Davies, P.R., Marsh, W.E., Molitor, T.W., Morrison, R.B., Thawley, D.G., Strategies employed in the U.S.A. for improving the health of swine. *Pig News and Information* 1992; 13(3): 111N-123N.

¹⁰⁶ Fox, J.L., WHO experts recommend reducing antibiotic use in food animals, *ASM News* 1998; 64(1): 29.

¹⁰⁷ Wegener, personal communication, 1998.

effective.^{108,109} Advances in research to find alternatives to antibiotics, such as competitive exclusion and vaccines, also may make subtherapeutic antibiotic use obsolete.

When considering the economic costs to the agriculture and animal-drug industry of banning the subtherapeutic uses of certain antibiotics, an important consideration is the economic benefits that a ban would create by decreasing medical expenses for treating antibiotic-resistant infections. Antibiotic-resistant infections have been estimated to cost between \$100 million and \$30 billion annually.¹¹⁰ The proportion that is due to subtherapeutic uses of antibiotics is unknown. What is known is that antibiotic-resistant infections are more difficult and more costly to treat. Patients with antibiotic-resistant infections may need to be hospitalized to receive intravenous antibiotic treatment, may be hospitalized for longer periods of time, or may miss work due to illness.

Reducing subtherapeutic uses of antibiotics may or may not have adverse economic consequences on drug makers and farmers. However, even if they do have some adverse consequences, those costs would be balanced in whole or in part by reductions in health-care costs and more importantly, by health benefits to the public.

VII. Environmental Impact

¹⁰⁸ Fussell, L., veterinarian, Tyson Foods, Inc., personal communication, February 1998.

¹⁰⁹ Auletta, R., attorney to Perdue Farms, Inc., personal communication, February 1998.

¹¹⁰ Phelps, C.E., Bug/drug resistance: sometimes less is more. *Med Care* 1989; 27: 194-203.

The proposed ban on subtherapeutic uses of medically important antibiotics likely will have little or no adverse environmental impact. Although the industry claims that halting all subtherapeutic uses of antibiotics might increase the amount of waste produced by animals, they provide little, if any, evidence to support their claim. Indeed farmers may find that raising livestock under less crowded conditions is an effective way to reduce antibiotic use. Less intensive farming could lead to less concentrated animal waste, thereby providing an environmental benefit. In addition, since this petition does not request a ban on all growth promotants, the action requested here may merely result in a substitution of the type of growth promotants used, which likely will have no net adverse environmental impact. The FDA should monitor increases in use of other antimicrobials (or other methods) that are substituted for the banned antibiotics and ensure their safety.

With regard to the microflora environment, ending the subtherapeutic use of certain antibiotics in livestock would remove an unnatural pressure on bacteria that promotes the prevalence of antibiotic resistance.

VIII. Conclusion

The FDA should ensure that agricultural uses of antibiotics do not endanger the public health by rescinding current approvals that permit the subtherapeutic use in livestock of antibiotics that are used in (or related to those used in) human medicine. That use of antibiotics leads to the development of antibiotic-resistance that could cause bacterial infections that are difficult or impossible to treat.

IX. Certification

The undersigned certify that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

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