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

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,

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[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.

Congress directed the FDA to hold such actions in abeyance until additional studies were completed by the National Academy of Sciences.

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

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[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].

public's health that warranted immediate suspension of their approval.[17,18] At that time, the FDA could have initiated 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

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[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].

[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>.

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 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.

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[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 included several people associated with drug companies and agricultural interests).

[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].

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.

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

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

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

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 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

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

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

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[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].

antibiotic, 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

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[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.