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 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]

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[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].

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.

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,

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[62] Noble, 1992.

[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.

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]

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

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[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.

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

[69] *Can We Use Less Antibiotics*, 1997.

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.
>
> 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

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[70] Wegener, personal communication, 1998.

[71] WHO meeting, 1997.

[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.

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:

> 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*:

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[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.

> 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:

> 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

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[77] Witte, 1998.

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

> 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 approved . . . . [79] [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: (l) "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, 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]

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[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].

[82] 21 U.S.C. § 360b(d)(2).

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

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.

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:

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

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