> 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:

> 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.

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[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

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 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

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[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.

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 tetracycline[91] 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]

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[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 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].

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

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[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 Bill, 1986).

development of 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 Prevention[98] and the World Health Organization[99] 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 number of countries have banned the subtherapeutic use of medically important

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[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).

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

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[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

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[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.

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[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.