



THE CENTER FOR FOOD SAFETY

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1601
Rockville, MD 20852

COMMENTS ON THE FOOD AND DRUG ADMINISTRATION'S DRAFT GUIDANCE ON THE JUDICIOUS USE OF MEDICALLY IMPORTANT ANTIMICROBIAL DRUGS IN FOOD-PRODUCING ANIMALS

August 30, 2010

Docket Number FDA-2010-D-0094

The Center for Food Safety (CFS),¹ a non-profit, membership organization, submits the following comments on the Food and Drug Administration's (FDA) Draft Guidance (Draft Guidance) entitled "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals."

FDA's Draft Guidance suggests voluntary adherence to two principles aimed at preserving the effectiveness of antibiotics and preventing the proliferation of antibiotic resistant bacteria: (1) discontinuing the administration of medically important antibiotics as growth promoters, limiting antibiotic use to only treating sick animals, and (2) requiring veterinary supervision to administer antibiotics. CFS applauds FDA for initiating discussion on this critical issue. However, CFS believes these measures will not be voluntarily implemented and that regulation mandating immediate action is required instead. Further, these principles do not provide a set timeline but a phased-in approach without set timelines or goals. This approach lacks the urgency this issue demands. Therefore, CFS submits the following comments urging FDA to regulate this important public health issue.

¹ CFS works to protect human health and the environment by curbing the proliferation of harmful food production technologies and by promoting organic and other forms of sustainable agriculture. CFS represents 100,000 members throughout the country.

INTRODUCTION

In human medicine, antibiotic use is generally confined to treatment of illness. Yet, on many industrial food-animal farms in the US, antibiotics and other antimicrobials (drugs that kill microorganisms like bacteria) are often routinely administered to healthy animals in order to speed growth and to compensate for unsanitary conditions.² In fact, an estimated 70 percent of antibiotics produced in this country are used in animal agriculture for these non-therapeutic purposes, without any requirement for veterinary consultation or prescription. This amount is more than four times the amount of drugs used to treat human illness.³

The significant non-therapeutic use of antibiotics in food animal production creates an environment in which bacteria, exposed to antibiotics at low doses for prolonged periods, can develop antibiotic resistance, a dangerous trait enabling bacteria to survive and grow instead of being inhibited or destroyed by therapeutic doses of a drug.⁴ This resistance reduces the effectiveness of important antimicrobials in human medicine.

Scientific understanding of antibiotic resistance is growing. “Researchers believe these organisms acquire resistance to antibiotics while in an animal; the resistant strain is then passed to humans through food or through direct contact with animals or animal waste. In addition to this direct transfer of antibiotic resistant organisms, some research indicates that the use of antibiotics in food animals may reduce the effectiveness of related antibiotics when used to treat humans.”⁵

Unsanitary conditions and other components of industrialized animal agriculture feed the need for non-therapeutic antimicrobials. Ralph Loglisci of the Center for a Livable Future argues that industry is “lumping the use of antibiotics to make up for poor living conditions and animal husbandry in the same therapeutic category.”⁶ According to Joshua M. Sharfstein, the FDA’s principal deputy commissioner, antibiotics should be used only to protect the health of an animal, not to help it grow or improve the way it digests its feed. He went as far as to call the problem “an urgent public health issue,” noting that in order “[t]o

² *Avoiding Antibiotic Resistance: Denmark’s Ban on Growth Promoting Antibiotics in Food Animals*, PEW CHARITABLE TRUSTS (Pew Report on Antibiotics), available at www.saveantibiotics.org/resources/DenmarkExperience.pdf.

³ *Antibiotic Resistance and Food Safety*, UNION OF CONCERNED SCIENTISTS (Nov. 12, 2009), available at http://www.ucsusa.org/food_and_agriculture/solutions/wise_antibiotics/food-safety-antibiotics.html.

⁴ *Report on Infectious Diseases*, WORLD HEALTH ORGANIZATION, at Chapter 3 (2000)(2000 WHO Report on Infectious Diseases), available at <http://www.who.int/infectious-disease-report/2000/index.html>.

⁵ *The Agricultural Use of Antibiotics and Its Implications for Human Health*, GOVERNMENT ACCOUNTING OFFICE (April 1999)(1999 GAO Report on Antibiotics).

⁶ Ralph Loglisci, *Antibiotic Resistance in Food Animals: FDA Takes Strong Stance, But Public Health May Remain at Risk Until Congress Acts*, CENTER FOR A LIVABLE FUTURE (July 6, 2010), available at <http://www.livablefutureblog.com/2010/07/antibiotic-resistance-in-food-animals-fda-takes-strong-stance-but-public-health-may-remain-at-risk-until-congress-acts/>.

preserve the effectiveness [of antibiotics], we simply must use them as judiciously as possible.”⁷

In 2009 CFS, along with the Institute for Agriculture and Trade Policy, petitioned FDA to ban the use of arsenic-based antimicrobials in food animals.⁸ Arsenic-based antimicrobials are just one form of antimicrobials potentially dangerous to human health and the environment. Now, FDA is faced with another public health threat from a different class of antimicrobials, those important for human health. FDA must reconsider the use of all antimicrobials in animal agriculture where the use of such drugs impacts human health or the environment.

I. STATUTORY AND REGULATORY AUTHORITY

Pursuant to the Federal Food, Drug and Cosmetics Act (FFDCA), and as explained below, FDA has a statutory duty to withdraw New Animal Drug Applications (NADA) for non-therapeutic uses of antimicrobial drugs used in food animals.

The FFDCA defines a “new animal drug” as “*any* drug intended for use for animals other than man, including any drug intended for use in animal feed...”⁹ Antimicrobials used in animal agriculture are “new animal drugs.” The FDA must withdraw approval of an NADA when a drug is found to be unsafe.¹⁰ Under the FFDCA §360(b), the Secretary shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of a new animal drug if the Secretary finds:

- A. “[E]xperience 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 or the condition of use authorized under subsection (a)(4)(A);”¹¹
- B. New evidence, tests, or methods developed since approval of the application show that the drug is not safe for use “under the conditions of use upon the basis of which the application was approved,”¹² or
- C. New information, combined with the evidence available at the time the application was approved show a “lack of substantial evidence that such drug will have the effect

⁷ Lyndsey Layton, *FDA seeks less use of antibiotics in animals to keep them effective for humans*, WASH. POST, Jun. 9, 2010, available at <http://www.washingtonpost.com/wp-dyn/content/article/2010/06/28/AR2010062804973.html>.

⁸ *Citizen Petition Seeking Withdrawal of Approval of Roxarsone and Certain Other Arsenical Additives in Animal Feed*, CENTER FOR FOOD SAFETY & INSTITUTE FOR AGRICULTURE AND TRADE POLICY (December 2009), available at <http://www.healthobservatory.org/library.cfm?RefID=107024>.

⁹ 21 C.F.R. § 510.3(g) (2009) (emphasis added).

¹⁰ See 21 U.S.C. § 360b(e)(1) (2009).

¹¹ 21 U.S.C. § 360b(e)(1)(A) (2009).

¹² *Id.* at (e)(1)(B).

it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.”¹³

The FFDCA creates a mandatory duty to withdraw a NADA when new evidence shows an animal drug to be unsafe.¹⁴ When determining whether a new animal drug (or category of new animal drugs) must be withdrawn for safety purposes, two issues are considered: whether there is a reasonable basis from which serious questions about the safety of the new animal drug may be inferred and whether the use of the new animal drug under the approved conditions is shown to be safe.¹⁵

Once withdrawal procedures are initiated, the Center for Veterinary Medicine has the “initial burden of producing new evidence that raises serious questions about the ultimate safety” of the new animal drug.¹⁶ When this threshold burden is met, the manufacturer is required to demonstrate the safety and efficacy of the drug.¹⁷

New scientific evidence, in addition to four decades of international research regulation and caution (see Part II), prove that the use of medically-important antimicrobial drugs in animal agriculture is unsafe. At a minimum such use should be limited to include only veterinary-prescribed therapeutic uses.

II. THE NON-THERAPEUTIC USE OF MEDICALLY IMPORTANT ANTIMICROBIALS IN FOOD PRODUCING ANIMALS IS UNSAFE

In considering whether an animal drug is safe within the meaning of FFDCA 512(e)(1)(b) the “typical issue for the FDA is not the absolute safety of a drug...the issue for the FDA is whether to allow sale of the drug, usually under specific restrictions. Resolution of this issue inevitably means calculating whether the benefits that the drug produces outweigh the costs of its restricted use.”¹⁸ In other words, a product’s “therapeutic benefits must outweigh its risk of harm.”¹⁹

When applied to the non-therapeutic use of important human antimicrobials used in food animals, the therapeutic gain does not outweigh the risk of harm, indicating a need for withdrawal.

¹³ *Id.* at (e)(1)(C).

¹⁴ *Rhone-Poulenc, Inc. v. FDA*, 636 F.2d 750, 752-53 (D.C. Cir. 1980) (upholding FDA’s order withdrawing the new animal drug approval for the use of diethylstilbestrol (DES)).

¹⁵ *Proposal to Withdraw Approval of the New Animal Drug Application for Enrofloxacin for Poultry*, CTR. FOR VETERINARY MED., Docket No. 00N-1571 at 2 (Mar. 16, 2004) (Initial Decision).

¹⁶ *Id.* at 5; *see also Rhone-Poulenc, Inc.*, 636 F.2d at 752 (D.C. Cir. 1980).

¹⁷ *Id.*

¹⁸ *Hess & Clark, Div. of Rhodia, Inc. v. FDA*, 495 F.2d 975, 993-94 (D.C. Cir. 1974).

¹⁹ *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 140 (2000); *citing United States v. Rutherford*, 442 U.S. 544, 555 (1979) (noting that “[t]he Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use.”).

A. NEW SCIENTIFIC EVIDENCE RAISES SERIOUS QUESTIONS ABOUT THE SAFETY OF USING MEDICALLY IMPORTANT ANTIMICROBIALS IN FOOD PRODUCING ANIMALS

“‘Serious questions’ [about the safety of a new animal drug] can be raised where the evidence is not conclusive, but merely suggestive of an adverse effect.”²⁰ The scope of ‘new evidence’ is not limited to data developed after an NADA is approved but includes the re-evaluation or novel application of pre-existing data.²¹

The substantial evidence outlined in FDA’s Draft Guidance, further reproduced herein, and contained in the materials submitted to the docket, suggests that the non-therapeutic dosing of antimicrobials on food animals has an adverse effect by contributing to the development of antibiotic resistant bacteria and harming human health. The CDC states that antibiotic resistance “can cause significant danger and suffering for children and adults who have common infections, once easily treatable with antibiotics.”²²

Antibiotic resistant bacteria are transferred from animals to humans, adversely affecting human health and threatening the efficacy of important human antibiotics. In 1998, an outbreak of DT 104, an especially virulent strain of foodborne disease that causes diarrhea, fever, abdominal cramps, and in some cases death, infected 21 people, killing one.²³ This infection was caused by contaminated pork. In the US, five thousand people were infected with multi drug-resistant campylobacteriosis caused by contaminated chicken. Evidence suggests that antibiotic resistant campylobacter, salmonella, and vancomycin have all been transferred from animals to humans from consumption and handling of contaminated meat.

B. FOUR DECADES OF INTERNATIONAL RESEARCH, REGULATION, AND CAUTION DEMONSTRATE THE NEED FOR REGULATION

Since the late 1960s, scientists and politicians have expressed concern that the use of antimicrobial feed additives in food animals leads to increased antimicrobial resistance and potential human health effects. FDA begins to outline this evidence in the Draft Guidance. Yet, FDA fails to include vital evidence illustrating the danger of non-therapeutic dosing of food animals. It also omits critical evidence that industrial agriculture can in fact thrive without non-therapeutic dosing.

²⁰ *Id.*

²¹ *Id.*

²² *Antibiotic Resistance Questions & Answers*, CENTERS FOR DISEASE CONTROL AND PREVENTION (June 30, 2009) available at <http://www.cdc.gov/getsmart/antibiotic-use/antibiotic-resistance-faqs.html#b>.

²³ *Outbreak of a Resistant Foodborne Illness*, UNION OF CONCERNED SCIENTISTS (July 18, 2003), available at http://www.ucsusa.org/food_and_agriculture/science_and_impacts/impacts_industrial_agriculture/outbreak-of-a-resistant.html.

1. THE 1969 UK REPORT & SUBSEQUENT BANNING OF CERTAIN ANTIBIOTICS FOR GROWTH PROMOTION

Following a prolonged outbreak of salmonella-caused illnesses in the 1960s, the United Kingdom convened a Joint Committee to determine whether to regulate the use of antibiotics in food animals.²⁴ The Committee reported that the “administration of antimicrobials in food-producing animals, particularly at sub-therapeutic levels, poses a hazard to human and animal health,²⁵ concluding antimicrobials used for therapeutic purposes in food-producing animals should remain available but only under veterinary supervision.²⁶ Based on this report, in 1971, the UK banned the use of penicillin and tetracycline for growth promotion.²⁷

2. US RESEARCH INTO EFFECTS OF NON-THERAPEUTIC USES OF CERTAIN ANTIBIOTICS

In 1970, the US assembled its own task force of scientists to review the use of antibiotics in animal feed. The FDA task force came to the same conclusion as UK’s Joint Committee: prohibit the non-therapeutic administration of certain antimicrobial drugs commonly used in human clinical medicine.²⁸ This prompted FDA to undertake a massive data gathering effort. FDA required sponsors of animal administered antimicrobials to submit evidence that their product did not promote resistance.²⁹

Based on the evidence received, FDA began proceedings to withdraw the new animal drug uses of penicillin and tetracyclines (two important human antibiotics) in animal feed in 1977.³⁰ Congress, however, disagreed, directing the agency to conduct further research on the matter. “Critics say that influential farm-state legislators led the opposition, at the urging of the livestock and pharmaceutical industries.”³¹ FDA delegated the suggested research.

²⁴ *Animal Legal Defense Fund Boston v. Provimi Veal Corp.*, 626 F.Supp. 278, 286 (D.Mass. 1986); citing O. Shell, MODERN MEAT at 18 (1984).

²⁵ Draft Guidance, *The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals*, CTR. FOR VETERINARY MED., US FOOD AND DRUG ADMINISTRATION at 5 (June 28, 2010) (Draft Guidance), available at <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf> (citing *Report of the Joint Committee of the Use of Antibiotics in Animal Husbandry and Veterinary Medicine* (1969)).

²⁶ Draft Guidance at 5 (citing *Report of the Joint Committee of the Use of Antibiotics in Animal Husbandry and Veterinary Medicine* (1969)).

²⁷ *Animal Legal Defense Fund Boston v. Provimi Veal Corp.*, 626 F.Supp. 278, 286 (D. Mass. 1986)

²⁸ Draft Guidance at 5 (citing *Report of the Joint Committee of the Use of Antibiotics in Animal Husbandry and Veterinary Medicine* (1969)).

²⁹ *Id.*

³⁰ *Id.* at 6; see also *United States v. An Art. Of Drug Con. Of 4,680 Pails*, 725 F.2d 976, 988-89 (5th Cir. 1984).

³¹ *Animal Legal Defense Fund Boston v. Provimi Veal Corp.*, 626 F.Supp. 278, 286 (D. Mass. 1986); citing NY Times, Sept 16, 1984, at A1, col. 5.

FDA contracted with the National Academy of Science (NAS), the Seattle-King County Health Department, and the Institute of Medicine (IOM) to further study the issue. While the NAS report findings were not dispositive, NAS cautioned that the “lack of data linking human illness with non-therapeutic levels of antimicrobials *must not be equated with proof that the proposed hazards do not exist.*”³² The Seattle King study further concluded that bacteria do flow from poultry to humans during consumption.³³ Finally, in 1987, the IOM found a considerable body of indirect evidence implicating both the non-therapeutic use and therapeutic use of antimicrobials as a potential human health hazard.³⁴ FDA was armed with at least three new reports indicating that at a minimum, there is a risk of serious threat to human health from non-therapeutic antimicrobial use. Despite this demonstrated risk, and despite its clear implications under section 360b(e)(1)(B) (2009) of the FFDCA, FDA chose not to act.

More than ten years later, responding to a request from Congress, the Government Accountability Office (GAO) initiated another study on the use of antibiotics in agriculture.³⁵ The GAO reported that “CDC researchers believe that some antibiotics should not be used in animal feed to promote growth,” and “in treating diseases, veterinarians need to ensure that they are prescribing the appropriate doses of antibiotics.”³⁶

The GAO also reported that FDA officials shared CDC’s concerns about *floroquinolone* resistance.³⁷ FDA, however, did not initiate an action to withdraw its earlier approval for *fluoroquinolones* on poultry and instead FDA approved *flouroquinolones* for use in beef cattle.³⁸ Eleven years later, as evidence of the dangers of the non-therapeutic use of antimicrobials continue to build, FDA is reluctant to regulate.³⁹

In the meantime, members of the international community have adopted measures combating antimicrobial resistance. Sweden and Denmark provide two important examples. (See Appendix A)

³² Report, *The Effects on Human Health of Subtherapeutic Use of Antimicrobial Drugs in Animal Feeds*, NATIONAL ACADEMY OF SCIENCES (1980).

³³ *Surveillance of the Flow of Salmonella and Campylobacter in a Community*, COMMUNICABLE DISEASE CONTROL SECTION, SEATTLE–KING COUNTY DEPARTMENT OF PUBLIC HEALTH (1984).

³⁴ Draft Guidance at 7.

³⁵ *Id.* at 8.

³⁶ 1999 GAO Report on Antibiotics.

³⁷ *Id.*

³⁸ *Id.*

³⁹ *Id.*

3. SWEDEN'S BAN ON ANTIMICROBIAL GROWTH PROMOTERS AND ITS RESULTS ON PRODUCTION

Sweden banned the use antimicrobial growth promoters [AMGP] in 1986.⁴⁰ The results of the Swedish ban demonstrate that it is possible to achieve competitive production results without a continuous use of antibiotics as growth promoters.⁴¹ In the production of slaughter pigs, specialized beef, and turkeys, no negative clinical effects were reported as a consequence of the ban.⁴² In broiler production and piglet production, there were minimal complications.⁴³ The AMGP ban illustrated that “under good production conditions it is possible to reach good and competitive production results for the rearing of poultry, calves and pigs without the continuous use of AMGP.”⁴⁴ As a result of the ban, the total use of antimicrobial drugs to animals in Sweden decreased by approximately 55% from 1986 to 2001.⁴⁵ (Norway and Finland reported similar results.)

4. THE “DANISH EXPERIMENT”: FURTHER EVIDENCE THAT BANS ON AMGP DO NOT NEGATIVELY IMPACT PRODUCTION

The Danish decision to terminate the non-therapeutic use of antimicrobials is possibly the most important illustration of the need to mandate the recommendations in the Draft Guidance. Denmark is a major food producer in Europe and the world's largest exporter of pork.⁴⁶ Like the US, “the Danish food animal production is industrialized, highly intensive and applies modern management principles.”⁴⁷

“Recognizing the potential for a health crisis,”⁴⁸ and “reacting to consumer concerns over food safety,”⁴⁹ Denmark stopped the administration of antibiotics used for growth promotion in broiler chickens and adult swine in 1998 and young swine in 1999.⁵⁰ Today, in order to administer antibiotics to an animal in Denmark, a valid prescription from a

⁴⁰ Martin Wierup, *The Swedish Experience of the 1986 Year Ban of Antimicrobial Growth Promoters, with Special Reference to Animal Health, Disease Prevention, Productivity, and Usage of Antimicrobials*, 7 MICROBIAL DRUG RESISTANCE 183 (2001).

⁴¹ Martin Wierup, *The Swedish Experience of the 1986 Year Ban of Antimicrobial Growth Promoters, with Special Reference to Animal Health, Disease Prevention, Productivity, and Usage of Antimicrobials*, 7 MICROBIAL DRUG RESISTANCE 183, 189 (2001).

⁴² *Id.*

⁴³ *Id.*

⁴⁴ *Id.*

⁴⁵ *Id.*

⁴⁶ *Information note regarding the Danish and EU restrictions of non-therapeutical use of antibiotics for growth promotion*, MINISTRY OF FOOD, AGRICULTURE AND FISHERIES, DANISH VETERINARY AND FOOD ADMINISTRATION (Aug. 12, 2009)(Aug. 2009 Danish Veterinary and Food Admin. Information Note), available at http://www.uk.foedevarestyrelsen.dk/nr/rdonlyres/63497aa7-8e8a-4c6a-9c74-e56c3383f26a/0/info_om_vaekstfremmerforbud_samt_oevrige_riskmanagement_str_uk.pdf.

⁴⁷ Aug. 2009 Danish Veterinary and Food Admin. Information Note.

⁴⁸ Pew Report on Antibiotics.

⁴⁹ Mary C. Evens and Henrik C. Wegener, *Antimicrobial Growth Promoters and Salmonella spp., Campylobacter spp. In Poultry and Swine, Denmark*, 9 EMERGING INFECTIOUS DISEASES 489 (2007).

⁵⁰ Pew Report on Antibiotics.

veterinarian is required.⁵¹ Further legitimizing the safe and effective therapeutic use of antibiotics, Denmark has a policy prohibiting veterinarians from profiting from the sale of antibiotics.

Despite critics' attempts to claim that these measures were "costly and ineffective," reports from both Denmark and outside observers plainly indicate otherwise.⁵² Antibiotic use in Denmark has drastically declined since the ban. "From 1992, the peak of AGP [Antibiotic Growth Promoter] usage in pigs, to 2008, overall antibiotic use in swine production declined substantially—by over 50 percent—as a result of the ban on growth promoters in Denmark."⁵³

This significant decrease in antibiotic use comes without any serious long-term effects on swine health.⁵⁴ "The World Health Organization found that the Danish ban reduced human health risks without significantly harming animal health or farmers' incomes."⁵⁵ Contrary to concerns that withdrawal of antimicrobial growth promoters would cause an increase in pathogen load, the Danish ban resulted in a decrease in *Salmonella* prevalence in broilers, chicken, swine and pork and no change in the prevalence of *Campylobacter* in broilers.⁵⁶

Antibiotic resistance has also declined. Livestock and poultry production has increased since the ban, and after several years of implementation, data shows that antibiotic resistance has declined on farms and in meat.⁵⁷ Halting "use of different non-therapeutic antibiotic growth promoters has resulted in [a] major reduction in antimicrobial resistance as measured among several different bacterial species in food animals and food."⁵⁸

5. THE WORLD HEALTH ORGANIZATION CALL TO ACTION

In 2003, the World Health Organization concluded that the "Danish Experiment" had "no serious negative effects," and that under conditions similar to those found in Denmark, the use of antimicrobials for the sole purpose of growth promotion can be discontinued."⁵⁹

⁵¹ Pew Report on Antibiotics.

⁵² Pew Report on Antibiotics; Aug. 2009 Danish Veterinary and Food Admin. Information Note; Mary C. Evens and Henrik C. Wegener, *Antimicrobial Growth Promoters and Salmonella spp., Campylobacter spp. In Poultry and Swine, Denmark*, 9 EMERGING INFECTIOUS DISEASES 489 (2007); and *Impacts of antimicrobial growth promoter termination in Denmark: The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark*, WORLD HEALTH ORGANIZATION (2003)(2003 WHO Report on Impacts of Antimicrobial Growth Promoter Termination in Denmark), available at http://whqlibdoc.who.int/hq/2003/WHO_CDS_CPE_ZFK_2003.1.pdf.

⁵³ Pew Report on Antibiotics.

⁵⁴ Pew Report on Antibiotics.

⁵⁵ Pew Report on Antibiotics; citing 2003 WHO Report on Impacts of Antimicrobial Growth Promoter Termination in Denmark.

⁵⁶ Mary C. Evens and Henrik C. Wegener, *Antimicrobial Growth Promoters and Salmonella spp., Campylobacter spp. In Poultry and Swine, Denmark*, 9 EMERGING INFECTIOUS DISEASES 489, 490 (2007).

⁵⁷ Pew Report on Antibiotics.

⁵⁸ 2009 Danish Veterinary and Food Admin. Information Note.

⁵⁹ 2003 WHO Report on Impacts of Antimicrobial Growth Promoter Termination in Denmark.

The WHO also recommended a reduction in the use of antimicrobials in livestock to help tackle the development of resistant bacteria. “Growing evidence reveals the impact of drug resistance on human health. In 1997 WHO recommended antimicrobials normally proscribed for humans be prohibited as growth promoters in animals.”⁶⁰ Additionally, WHO “recommended that antimicrobials not be used as an alternative to high-quality animal hygiene.”⁶¹

In 1998, the EU followed the WHO recommendation, banning all antimicrobials generally prescribed for the treatment of human infections as growth promoters in animals. Despite increasing incidents of illness caused by antibiotic resistant bacteria, the United States did not.⁶²

In 2000, the WHO issued a global call to action, urging countries to rid cultivated foodstuffs of various destructive organisms.⁶³ In doing so, it stated that the “ongoing and often low-level dosing for growth and prophylaxis inevitably results in the development of resistance in bacteria in or near livestock.”⁶⁴ The WHO recommended critical investments of time, effort, money, cooperation, flexibility, philanthropy, and personal commitment on the part of individuals, government, NGOs, large pharmaceutical companies, and private and public organizations to halt the spread of the growing problem of antibiotic resistance.⁶⁵

Taken together, scientific research and experience indicate that the use of non-therapeutic antibiotics in food animals is unsafe and unnecessary.

III. VOLUNTARY MEASURES ARE INADEQUATE TO PREVENT ANTIBIOTICS RESISTANCE —FDA MUST REGULATE

NADA withdrawal, FDA regulations or mandatory legislation are necessary to end the non-therapeutic use of antibiotics.⁶⁶ Absent a government mandate, producers are not likely to voluntarily cut their dependence on non-therapeutic use of antimicrobials in food animals.

Unfortunately, FDA’s Draft Guidance is not legally binding. A guidance is “merely a suggestion.”⁶⁷ It is not legally binding or enforceable. “FDA’s guidance documents, including

⁶⁰ 2000 WHO Report on Infectious Diseases, Chapter 5.

⁶¹ *Id.*

⁶² For instance, “[i]n 1998, 5 000 people in the United States learned the hard way about antimicrobial resistance when they fell ill with multi drug-resistant campylobacteriosis caused by contaminated chicken. The same drugs that eventually failed them had also been used in the poultry that turned up on their plates. 2000 WHO Report on Infectious Diseases, Chapter 3.

⁶³ 2000 WHO Report on Infectious Diseases, Chapter 3.

⁶⁴ *Id.*

⁶⁵ *Id.* at Chapter 5.

⁶⁶ Ralph Loglisci, *Antibiotic Resistance in Food Animals: FDA Takes Strong Stance, But Public Health May Remain at Risk Until Congress Acts*, CENTER FOR A LIVABLE FUTURE, available at <http://www.livablefutureblog.com/2010/07/antibiotic-resistance-in-food-animals-fda-takes-strong-stance-but-public-health-may-remain-at-risk-until-congress-acts/>.

this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word 'should' in Agency guidances means that something is suggested or recommended, but not required."⁶⁸

Voluntary programs are not only unenforceable, they lack incentive for producers to comply.⁶⁹ Here, industrial producers are more concerned about profit than protecting public health. "Many livestock producers, such as those represented by the National Pork Producers Council, oppose any ban on certain drugs considered essential for livestock health. Many producers believe the FDA has not produced enough scientific evidence on which to base such regulation."⁷⁰ Industry's main fear is that "[t]his guidance could eliminate certain antibiotics that are extremely important to the health of animals."⁷¹ Despite decades of science and success eliminating non-therapeutic use of antibiotics in food animal production in other countries, industry advocates claim that "FDA didn't present any science on which to base this [guidance]," pointing instead to the potential "tremendous negative impact on animal health and ... safety of food."⁷² Industry demands "every available tool to protect animal health."⁷³

Recently, Deputy Commissioner Sharfstein informed the public that the guidance was a first step, and that the agency would issue new regulations if industry does not comply

⁶⁷ Draft Guidance at 2.

⁶⁸ *Id.*

⁶⁹ Two particularly salient examples are the failures of voluntary measures intended to reduce greenhouse gas emissions and voluntary nanotechnology reporting. *See, e.g.,* D. Kerret and A. Tal, *Greenwash or Green Gain? Predicting the Success and Evaluating the Effectiveness of Environmental Voluntary Agreements*, 14 Penn State Environmental Law Rev. 37 (2005) (concluding that there is "irrefutable evidence suggesting that voluntary programs may produce less actual reductions of emissions and improvement in general environmental practices, and less awareness than a command and control alternative"); *Voluntary Efforts Won't Work: Why We Need Mandatory Limits on Carbon Dioxide*, NATURAL RESOURCES DEFENSE COUNCIL (NRDC), available at <http://www.nrdc.org/globalWarming/fmandatory.asp>; George A. Kimbrell, *Governance of Nanotechnology and Nanomaterials: Principles, Regulation, and Renegotiating the Social Contract*, 37 J.L. Med. & Ethics 706, 708-710 (2009); Interim Report, NANOSCALE MATERIALS STEWARDSHIP PROGRAM (NMSP), EPA (January 2009) at 3, 27 ("The low rate of engagement in the In-Depth Program suggests that most companies are not inclined to voluntarily test their nanoscale materials."), available at <http://www.epa.gov/oppt/nano/nmsp-interim-report-final.pdf>; S. F. Hansen and J. A. Ticker, *The Challenges of Adopting Voluntary Health, Safety and Environment Measures for Manufactured Nanomaterials: Lessons from the Past for More Effective Adoption in the Future*, 4 NANOTECHNOLOGY LAW & BUSINESS 341, 341-359 (2007).

⁷⁰ *Antibiotics In Agriculture - The Real Story*, PORK Magazine, August 19, 2010, available at http://www.porkmag.com/news_editorial.asp?pgID=675&ed_id=9783.

⁷¹ *FDA's Guidance Document Recommends Less Antibiotics*, NATIONAL HOG FARMER, Jun 29, 2010, available at <http://nationalhogfarmer.com/health-diseases/fda-guidance-document-recommends-antibiotics-0629/>.

⁷² *Id.*

⁷³ *Id.*

voluntarily.⁷⁴ FDA cannot wait for voluntary industry compliance but must immediately take whatever measures necessary to ensure that antimicrobials are only used in animal agriculture out of medical necessity and not for growth-promotion or to mask unsanitary conditions.

A. FDA MUST REQUIRE MANDATORY VETERINARY CONSULTATION

The debate on the non-therapeutic use of antimicrobials has come out strongly in favor of veterinarian intervention in the administration of *all* antimicrobials.⁷⁵ In the early 1970s, the UK panel concluded that antimicrobials used for therapeutic purposes in food-producing animals *should remain available but only under veterinary supervision*.⁷⁶ In Denmark, a valid prescription from a veterinarian is required for the administration of antimicrobials.⁷⁷ The CDC also indicates that veterinarians need to ensure that they are prescribing the appropriate doses of antibiotics to treat diseases in food animals.

The Draft Guidance seeks to promote veterinary oversight or consultation for the use of medically important antimicrobial drugs in food animal production. Yet, the voluntary nature of the Guidance makes this action implausible in light of producers' belief that "animal pharmacology already is regulated and monitored by veterinarians much the same way human pharmaceuticals are monitored by physicians."⁷⁸ This is not the case. Human antibiotics are administered only via prescription while "[m]ost of the [animal] feed-use antimicrobial drugs are currently approved for over-the-counter use."⁷⁹ (Draft Guidance at 17).

FDA itself argues that ensuring that veterinarians oversee the administration of antibiotics in food animals "is an important mechanism for helping to ensure appropriate use" of antibiotics in food animal production.⁸⁰ CFS encourages FDA to use its regulatory authority to mandate veterinary intervention and require prescriptions for the use of all antimicrobials in animal agriculture to further protect against the spread of antibiotic resistant bacteria.

B. FDA MUST CREATE AN ENFORCEABLE TIMELINE FOR COMPLIANCE

Finally, FDA's Draft Guidance lacks suggested dates for the implementation of the proposed measures. CFS understands the necessity of a phased-in approach, but strongly

⁷⁴ Lyndsey Layton, *FDA seeks less use of antibiotics in animals to keep them effective for humans*, WASH. POST, Jun. 9, 2010, available at <http://www.washingtonpost.com/wp-dyn/content/article/2010/06/28/AR2010062804973.html>.

⁷⁵ *Report on Discussions of the Antimicrobial Use Task Force*, AMERICAN VETERINARY MEDICAL ASSOCIATION (2009), available at <http://www.avma.org/AUTFreport/default.asp>.

⁷⁶ Draft Guidance at 5 (citing *1969 Report of the Joint Committee of the Use of Antibiotics in Animal Husbandry and Veterinary Medicine*).

⁷⁷ Pew Report on Antibiotics.

⁷⁸ *Antibiotics In Agriculture - The Real Story*, PORK Magazine, August 19, 2010, available at http://www.porkmag.com/news_editorial.asp?pgID=675&ed_id=9783.

⁷⁹ Draft Guidance at 17.

⁸⁰ *Id.*

believes that without deadlines, some producers will not comply.

In the EU, the progression from partial restrictions in a few countries to a comprehensive EU wide ban on growth promoters, along with limitations on antibiotics for veterinary therapeutic and prophylactic use, did not happen overnight; it took some 20 years. In part, this was because evidence of harm and harm reduction, particularly with respect to AMR pathogens, necessarily took time to accumulate. As well, however, this slow pace was because of the need to overcome opposition by farmers, who were concerned about the effects of economic competition from other countries, and who also needed time to adapt their production methods.⁸¹

Unlike the EU, the US has the benefit of over 40 years of research and several examples of successful bans in countries that employ industrial animal agriculture. A 20-year phase out is not necessary. Instead, “[a]n immediate ban on classes of antibiotics used therapeutically in humans, when used for growth promotion and prophylaxis in livestock”⁸² is required. FDA has the necessary authority to require adherence to the principles in the Draft Guidance within a reasonable timeframe and ensure compliance with these principles.

IV. FAILURE OF FDA TO INVESTIGATE NEW EVIDENCE INDICATING THAT THE NON-THERAPEUTIC USE OF IMPORTANT HUMAN ANTIBIOTICS IS UNSAFE, ARBITRARY AND CAPRICIOUS

In making a factual inquiry concerning whether an agency decision was “arbitrary and capricious,” a reviewing court must consider whether the decision was based on a reasoned evaluation of the relevant factors and whether there has been a clear error of judgment.⁸³ An agency must cogently explain why it has made a particular decision and enable a court to conclude that it was the product of reasoned decision making.⁸⁴

Scientific evidence demonstrates the adverse effects caused by the non-therapeutic use of antimicrobials in food animal production. The undeniable risk to human health outweighs any possible benefit in food animal production. It is FDA’s duty to regulate or withdraw non-therapeutic uses of antimicrobials. A failure to do so is unreasoned decision making by the agency, a clear error in judgment and arbitrary and capricious agency action.

⁸¹ Susan Holtz, *Reducing and Phasing Out the Use of Antibiotics and Hormone Growth Promoters in Canadian Agriculture*, CANADIAN INSTTT. FOR ENVIRONMENTAL LAW AND POLICY (2009) available at www.cielap.org/pdf/AHGP.pdf.

⁸² *Id.*

⁸³ *Marsh v. Oregon Natural Resources Council*, 490 U.S. 360, 378 (1989).

⁸⁴ See *Motor Vehicle Mfrs. Assn. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 49 (1983).

CONCLUSION

For the foregoing reasons, CFS urges FDA to use its regulatory authority to require producers to discontinue the non-therapeutic use of antimicrobial drugs in food animals.

Respectfully Submitted,

Paige Tomaselli
Staff Attorney

APPENDIX A TIMELINE OF INTERNATIONAL ACTION

- 1971: The UK banned the use of penicillin and tetracycline for growth promotion⁸⁵
- 1986: Sweden banned the use of all antibiotics for growth promotion⁸⁶
- 1995: Denmark banned the non-therapeutic use of avoparcin for growth promotion in Denmark⁸⁷
- 1996: Norway and Germany banned the non-therapeutic use of avoparcin for growth promotion⁸⁸
- 1997: The European Union banned the non-therapeutic use of avoparcin for growth promotion⁸⁹
- 1997: The World Health Organization recommended terminating the use of antibiotics for growth promotion in animals if they are also used in human medicine or are known to potentially become cross-resistant to antibiotics used in human medicine⁹⁰
- 1998: Denmark banned the non-therapeutic use of virginiamycin for growth promotion⁹¹
- 1998: Denmark instituted a voluntary ban on all antibiotic growth promoters and a national tax on antibiotic growth promoters⁹²
- 1998: Finland banned the use of spiramycin for growth promotion
- 1998: The EU implemented an overall ban of virginiamycin, bacitracin, tylosin and spiramycin for growth promotion⁹³
- 2000: The EU voted to phase out all non-therapeutic use of antibiotics for growth promotion beginning in 2006⁹⁴
- 2006: The EU discontinued all non-therapeutic use of antibiotics for growth promotion⁹⁵

APPENDIX B NANO DRUGS

⁸⁵ 1999 GAO Report on Antibiotics.

⁸⁶ *Id.*

⁸⁷ Aug. 2009 Danish Veterinary and Food Admin. Information Note.

⁸⁸ *Emerging Infection Diseases: Use of Antimicrobial Growth Promoters in Food Animals and Enterococcus faecium Resistance to Therapeutic Antimicrobial Drugs in Europe*, CENTER FOR DISEASE CONTROL (July 1999), available at <http://www.cdc.gov/ncidod/eid/vol5no3/wegener.htm>

⁸⁹ *Id.*

⁹⁰ 1999 GAO Report on Antibiotics.

⁹¹ *Id.*

⁹² Aug. 2009 Danish Veterinary and Food Admin. Information Note.

⁹³ *Id.*

⁹⁴ *Id.*

⁹⁵ *Id.*

FDA's decision on the non-therapeutic use of medically important antibiotics in livestock will have a critical affect in the coming years as companies increasingly combine and incorporate antimicrobials into household products. The combined use of and ingestion of various antimicrobials may open the door towards even greater levels of resistance among bacteria, further threatening the efficacy of medically important antibiotics.

One example is the increased use of nano-silver in consumer products. Nano-silver is an antimicrobial biocide that can kill or inhibit the growth of microbes, yet it also poses a unique threat to humans in the form of bacterial and antibiotic resistance.⁹⁶ Certain harmful bacteria may become resistant against nano-silver. In addition, because of the type of resistance mechanism developed, the harmful bacteria could develop resistance to 50% of currently used antibiotics.⁹⁷

Demonstrated under laboratory conditions, silver resistance can be induced and "is most easily developed in bacteria with already documented resistance mechanisms to antibiotics, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), enterobacteria with production of extended spectrum beta-lactamases (ESBL), multiresistant *Pseudomonas aeruginosa*."⁹⁸

Thomas O'Brien of Harvard Medical School states that, "antimicrobial-resistance genes and their genetic vectors, once evolved in bacteria of any kind anywhere, can spread indirectly through the world's interconnecting commensal, environmental, and pathogenic bacterial populations to other kinds of bacteria anywhere."⁹⁹ The widespread introduction of nano-silver into consumer products could thus contribute significantly to the spread of antibiotic resistance throughout the world. Uncertainties about silver and resistance prompted Swedish pharmacies to stop selling band-aids containing silver in April 2006.¹⁰⁰

⁹⁶ See generally Sass, Jennifer, *Nanotechnology's Invisible Threat: Small Science, Big Consequences*, NRDC ISSUE PAPER at 3(May 2007).

⁹⁷ Melhus, A, *Silver threatens the use of antibiotics*, Unpublished manuscript, (on file with author) (2007).

⁹⁸ *Id.*

⁹⁹ O'Brien, Thomas F., *Emergence, Spread, and Environmental Effect of Antimicrobial Resistance: How Use of an Antimicrobial Anywhere Can Increase Resistance to Any Antimicrobial Anywhere Else*, 34 CLINICAL INFECTIOUS DISEASES S3, S78-84 (2002).

¹⁰⁰ Sandquist, Anna, *Swedish Pharmacies Ban Silver Band-Aids*, 3 MILJOAKTUELLT (April 2006).