

SUPERBUGS V. WONDER DRUGS
FDA GUIDANCE FOR INDUSTRY #213'S NEGATIVE IMPACT TO SMALL PRODUCERS
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I. INTRODUCTION

The use of antibiotics in food animal industries carries both risks and benefits to human and animal health.¹ Perhaps the biggest risk is the rise of antimicrobial resistance; that is, the evolution of so-called superbugs—bacteria pathogens that are resistant to multiple antimicrobial compounds.² According to Centers for Disease Control estimates, antimicrobial resistant infections affect nearly two million people per year, resulting in more than twenty thousand deaths.³ The goal (and expectation) of banning antibiotic use from food animal production is to decrease the prevalence of antimicrobial resistance and to prevent negative implications for human medicine.⁴

This paper begins with a brief overview of the use of antibiotics in the food animal

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¹ Alan G. Mathew et al., *Antibiotic Resistance in Bacteria Associated with Food Animals: A United States Perspective of Livestock Production*, 4 *FOODBORNE PATHOGENS AND DISEASE* 115, 128 (2007).

² CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. DEP'T OF HEALTH AND HUMAN SERVICES, *ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES* 5 (2013) [hereinafter *CDC REPORT*] (“Antimicrobial resistance is one of our most serious health threats.”); Randall Singer in *Antibiotic Resistance—the Interplay Between Antibiotic Use in Animals and Human Beings*, 3 *THE LANCET: INFECTIOUS DISEASES* 47, 47 (Jan. 2003) (“[A]ntibiotic resistance is fast escalating into a global health crisis.”); Frank Moller Aarestrup et al., *Effect of Abolishment of the Use of Antimicrobial Agents for Growth Promotion on Occurrence of Antimicrobial Resistance in Fecal Enterococci from Food Animals in Denmark*, 45–7 *ANTIMICROBIAL AGENTS AND CHEMOTHERAPY*, 2054, 2054 (July 2001) (“[M]ultiple antimicrobial resistance is now one of the serious concerns of the new millennium.”).

³ *CDC REPORT*, *supra* note 2, at 6. Several strains of bacteria found in food animals are now on the CDC's second and third tiers of threats to human health. *Id.* at 7.

⁴ Carol Cogliani et al., *Restricting Antimicrobial Use in Food Animals: Lessons from Europe*, 6 *MICROBE*, 274, 275 (2011).

industry and the rise of antibiotic resistant bacteria.⁵ A summary of the United States Food and Drug Administration’s recent actions follows.⁶ This article concludes that FDA Guidance for Industry #213 (“GFI 213”) lacks a system of enforcement to create meaningful change, and may have the unintended effect of squeezing small producers out of the food animal production market, thereby compounding the problems stemming from heavy reliance on animal antibiotics.⁷

II. BACKGROUND

A. Antibiotic Use in Food Animals

Antibiotics have been hailed a wonder drug since the contents of Alexander Fleming’s Petri dish proved to be penicillin, the wonder drug that saved thousands of lives.⁸ Since then, many classes of antimicrobial products have been approved for use in food animals.⁹ Large-scale production farms require careful disease management—often including regular antibiotic treatment—due to high-density animal populations.¹⁰ In food animal production, antibiotics are used for four main reasons:

1. Treating sick animals (“therapeutic use”);
2. Short-term treatment of diseased and healthy animals to prevent the spread of current infection (“metaphylaxis”);
3. Preventive treatment at times of heightened risk (“prophylactic use”);
4. Improving feed utilization and production (“growth promotion”).¹¹

Non-therapeutic uses of antibiotics are an essential part of industrialized food-animal production, allowing for shorter weaning periods and increased animal density in production facilities,

⁵ See *infra*, Part II.

⁶ See *infra*, Part III.

⁷ See *infra*, Part V.

⁸ 2 JOHN W. SCHLICHTER, PATENT LAW: LEGAL AND ECONOMIC PRINCIPLES § 13:21 (2d ed.).

⁹ Mathew et. al., *supra* note 1, at 115.

¹⁰ *Id.*

¹¹ *Id.* at 116.

among other economic benefits to producers and consumers.¹² It is also important to note that while subtherapeutic uses generate the most controversy, drugs used on food animals for therapeutic treatments are identical to those used in human medicine,¹³ and superbugs that are resistant to human drug therapies should be of special concern.

B. Antibiotic Resistance

Drug resistance in bacteria is a form of natural selection: in simple terms, antibiotics kill those bacteria that are not resistant, and the remaining resistant bacteria multiply.¹⁴ While antimicrobial resistance may have its roots in nature, the concern is that the wide use of antibiotics in humans and animals increases the selection pressure to levels beyond what nature exerts, thereby speeding the evolutionary process of the superbugs.¹⁵ Because selection is a natural response, bacteria will begin to resist any antibiotic drug to which it is exposed¹⁶—that is, both human and animal consumption of antibiotics leads to an increase in the prevalence of resistant bacterial strains.

Reports suggesting links between antibiotic use in livestock and increased resistance

¹² Henrik Wegener, *Antibiotic Resistance—Linking Human and Animal Health* in IMPROVING FOOD SAFETY THROUGH A ONE-HEALTH APPROACH 331, 332 (2012). *See also* Mathew et al., *supra* note 1, at 123–26 (discussing the various uses of each type of treatment in the swine, dairy and beef cattle, and poultry industries).

¹³ Mark Casewell, et al., *The European Ban on Growth-Promoting Antibiotics and Emerging Consequences for Human and Animal Health*, J. OF ANTIMICROBIAL CHEMOTHERAPY 159, 160 (2003).

¹⁴ *See* CDC REPORT, *supra* note 2, at 14 (displaying simplistic graphic representations of how resistance happens and spreads). Bacteria have been developing resistance to antibiotics as long as the wonder drugs have been around. MARYN MCKENNA, SUPERBUG: THE FATAL MENACE OF MRSA 7 (2010).

¹⁵ Mathew et. al., *supra* note 1, at 117–18; BRIDGING THE GAP BETWEEN ANIMAL HEALTH AND HUMAN HEALTH 13 (Nov. 2013) [hereinafter BRIDGING THE GAP] (applying the media term “superbug” to methicillin-resistant *S. aureus* and vancomycin-resistant *S. aureus*).

¹⁶ CDC REPORT, *supra* note 2, at 12. *See* page 28 of the CDC Report for a timeline of the rise of resistance following the introduction of new antibiotics. *Id.*

were published as early as 1951.¹⁷ However, early efforts to understand the risk that resistance in animals posed to human health came to differing conclusions.¹⁸ The transfer of antibiotic resistance from animals to humans is a complex issue that is difficult to assess for many reasons.¹⁹ This short summary should be considered a very high level overview, not a comprehensive explanation of the scientific phenomena at work.

III. FDA GUIDANCE

While the FDA convened a task force to study the risk of feed-based antibiotics as early as the 1960s,²⁰ the agency has appeared slow to react to the recommendations the task force published in 1972.²¹ Among those recommendations were to (1) prohibit the use of feed-based animal antibiotics unless the drugs met FDA safety standards, and (2) reserve several specific drugs (including penicillin and tetracycline) for therapeutic uses only.²² The following year, the FDA stated its intent to withdraw approval for all subtherapeutic use of feed-based antibiotics unless drug companies submitted conclusive proof that such uses were safe to man and animal.²³ Approximately twenty interested parties requested hearings, which the FDA Commissioner

¹⁷ See, e.g., M.P. Starr & D.M. Reynolds, *Streptomycin Resistance of Coliform Bacteria from Turkeys Fed Streptomycin*, 41 AM. J. PUB. HEALTH 1375 (1951).

¹⁸ See NETHERTHORPE COMMITTEE, REPORT OF THE JOINT COMMITTEE ON ANTIBIOTICS IN ANIMAL FEEDING 7 (1962) (concluding no evidence of risk to humans); *Select Committee on Science and Technology Seventh Report*, PARLIAMENT, <http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/081vii/st0706.htm> (last visited Apr. 2, 2014) (summarizing at Box 6 the 1969 Swann Report findings that nontherapeutic levels of antibiotic treatment pose a hazard to both human and animal health).

¹⁹ Wegener, *supra* note 12, at 334.

²⁰ Antibiotic and Sulfonamide Drugs in Animal Feeds, 37 Fed. Reg. 2444 (proposed Feb. 1, 1972). The task force included specialists from industry and universities as well as the Food and Drug Administration, the National Institutes of Health, the U.S. Department of Agriculture, and the Center for Disease Control. *Id.*

²¹ Natural Res. Def. Council, Inc. v. U.S. Food & Drug Admin., 884 F. Supp. 2d 127, 132 (S.D.N.Y. 2012).

²² Antibiotic and Sulfonamide Drugs in Animal Feeds, 37 Fed. Reg. 2444 (proposed Feb. 1, 1972).

²³ Antibiotic and Sulfonamide Drugs in the Feed of Animals, 38 Fed. Reg. 9811, 9813 (Apr. 20, 1973) (codified at former 21 C.F.R. § 135.109; renumbered at 21 C.F.R. § 558.15).

granted, stating that public hearing dates would be set “as soon as practicable.”²⁴ That date has not yet come.²⁵ Instead, at the direction of congress, the FDA sought further research,²⁶ which culminated in industry guidance that sparked opposition by several advocacy organizations.²⁷

C. FDA GFI 209

The FDA published a draft of guidance 209 in 2010.²⁸ The final guidance published in 2012 (“GFI 209”) includes a brief summary of sixteen public health reports and eleven peer-reviewed scientific studies on the effect of antibiotics used in food animal production.²⁹ This voluntary guidance recommended two specific principles regarding what the FDA considers “judicious use” in animals.

The first principle states that medically important antibiotics should be limited to uses necessary for ensuring animal health.³⁰ Antibiotics used purely for production purposes are deemed as injudiciously used.³¹ The FDA was careful to state that this did not preclude the use of feed- and water-based delivery of medications used for the treatment, control, or prevention of particular diseases, so long as the administration of such drugs was subject to veterinary

²⁴ Natural Res. Def. Council, 884 F. Supp. 2d at 134 (quoting Penicillin and Tetracycline in Animal Feeds Hearing, 43 Fed.Reg. 53827–53828 (Nov. 17, 1978)).

²⁵ *Id.* at 135.

²⁶ *See generally, id.* (summarizing the results of several studies).

²⁷ *Id.* In May of 2011, the Natural Resources Defense Council, the Center for Science in the Public Interest, Food Animal Concerns Trust, Public Citizen, and the Union of Concerned Scientists, Inc. sued to compel the FDA to withdraw approval for subtherapeutic uses of penicillin and tetracycline in food animal production. *Id.* FDA also published GFI 152 Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern in 2003 to assess resistance as a part of the new drug approval process.

²⁸ FOOD AND DRUG ADMINISTRATION, U.S. DEP’T OF HEALTH AND HUMAN SVCS, GUIDANCE FOR INDUSTRY #209: THE JUDICIOUS USE OF MEDICALLY IMPORTANT ANTIMICROBIAL DRUGS IN FOOD-PRODUCING ANIMALS (2012) [hereinafter GFI 209].

²⁹ *Id.* at 5–17.

³⁰ *Id.* at 21. The FDA defines “medically important” drugs as those important to therapeutic treatments in human medicine. *Id.* at 3 fn. 1.

³¹ *Id.*

oversight.³²

Veterinary oversight is the second principle.³³ While the guidance recognizes that this oversight is likely to vary widely throughout the industry, it sets no expectations beyond that veterinarians should be a part of the decision-making process.³⁴ In some cases, veterinarians may be brought in to diagnose and treat sick animals directly, but in others the veterinarians will simply make periodic consultative visits.³⁵ The availability of large animal veterinarians may play a significant role in whether and how this guidance is implemented.³⁶

The guidance specifically states that when considering whether preventive treatment is justified, veterinarians may consider “the client’s production practices and herd health history.”³⁷ Under these loose guidelines, the same veterinarian may prescribe treatment to Producer A, whose herd has a history of infection, but withhold treatment at Producer B, a similarly situated producer with the same production practices but slightly better herd health history. Two veterinarians could also come to differing conclusions as to whether Producer A’s historical practices justify the use of preventive antibiotics.

D. FDA GFI 213

In December of 2013, the FDA published a draft of a follow-up guidance targeted at sponsors of new animal drugs.³⁸ GFI 213 distinguished over-the-counter drugs (for which

³² *Id.*

³³ *Id.* at 22.

³⁴ *Id.* (recognizing geographic location, availability of large animal veterinarians, and other constraints as factors that will contribute to inconsistencies in application).

³⁵ *Id.*

³⁶ *See id.* (recognizing the “significant practical implications” for the food animal and veterinary industries and soliciting comments pertaining to how this guidance can be promoted so that voluntary adoption does occur).

³⁷ *Id.* at 21.

³⁸ FOOD AND DRUG ADMINISTRATION, U.S. DEP’T OF HEALTH AND HUMAN SVCS, GUIDANCE FOR INDUSTRY #213: NEW ANIMAL DRUGS AND NEW ANIMAL DRUG COMBINATION PRODUCTS, ADMINISTERED IN OR ON MEDICATED FEED OR DRINKING WATER OF FOOD-PRODUCING ANIMALS:

adequate directions for use by lay persons can be written) from those requiring veterinarian oversight (designated as prescription or veterinary feed directive).³⁹ This guidance calls for a voluntary three-year phase-out plan for antibiotics used for production purposes; the necessary changes require updated regulations concerning the criteria of veterinary supervision and related administrative procedures.⁴⁰

GFI 213 addresses the issue of judicious preventive use of antibiotics using the same specific examples presented in GFI 209.⁴¹ However, the guidance also lists several other factors that veterinarians consider in determining the appropriateness of an approved drug.⁴² Additionally, it states veterinarians should also consider the evidence of effectiveness of such treatment, whether the use is consistent with accepted practices, whether the use is linked to a particular cause of disease, whether such use is targeted to animals at risk of developing a specific disease, and whether any other reasonable alternatives for intervention exist.⁴³ This wide range of factors does little to ensure standard treatments throughout the industry.⁴⁴

IV. ANALYZING THE LIKELY OUTCOME OF GFI 213

GFI 213 leaves the door wide open for veterinarians to continue prescribing antibiotics for uses that are currently in practice. Without additional intervention tactics, decreasing one of the prevalent uses of antibiotics may not decrease total antibiotic consumption.⁴⁵ Because therapeutic antibiotics used in animals are identical to those used in human treatments, increasing

RECOMMENDATIONS FOR DRUG SPONSORS FOR VOLUNTARILY ALIGNING PRODUCT USE
CONDITIONS WITH GFI #209 (2013) [hereinafter GFI 213].

³⁹ *Id.* at 4.

⁴⁰ *Id.* at 6–10.

⁴¹ *Id.*

⁴² *Id.* (listing mode of action, distribution of the drug in particular tissues, length of time of effective drugs levels).

⁴³ *Id.*

⁴⁴ *See infra*, Part IV.

⁴⁵ Cogliani, et al., *supra* note 4, at 276 (increased need for therapeutic treatment kept total level of antibiotics used at the same level as before the ban).

the food animal industry's reliance on therapeutic drugs may prove more dangerous to human health than continued reliance on prophylactic treatments from drug classes that have little overlap with human treatments. Decreasing preventive antibiotics without a corresponding upswing in the necessity for therapeutic treatments requires other changes in animal husbandry.

A. A. Focus on Eliminating Conditions Requiring Preventive Antibiotics

Antibiotics are used in food animal production in order to prevent disease in crowded and unsanitary conditions even where none of the animals are exhibiting symptoms of disease.⁴⁶ Animal welfare in the European Union suffered following the withdrawal of growth promoters due to the prophylactic effects of this type of treatment.⁴⁷ Controlling the spread of infectious diseases without prophylactic antibiotics requires improved hygiene and infection control.⁴⁸ GFI 209 specifically allows this use of antibiotics with veterinary oversight.⁴⁹ If veterinarians are allowed to prescribe antibiotics in these situations, it is unlikely that the use of preventive antibiotics in large farms will decrease. Studies have shown that the difference in management practices on organic farms results in lower prevalence of common diseases found on

⁴⁶ CARMEN CORDOVA, NATURAL RESOURCES DEFENSE COUNCIL, PLAYING CHICKEN WITH ANTIBIOTICS: PREVIOUSLY UNDISCLOSED FDA DOCUMENTS SHOW ANTIBIOTIC FEED ADDITIVES DON'T MEET THE AGENCY'S OWN SAFETY STANDARDS 2 (2014).

⁴⁷ Casewell et al., *supra* note 13, at 160 (stating that the withdrawal of bacitracin as a growth promoter for poultry led to problems requiring drug therapy in both Denmark and France, because clostridial necrotic enteritis is suppressed by growth promoting bacitracin). While the total use of antibiotics across Europe has decreased following the bans, there were substantial increases in the use of therapeutic antibiotics following bans of growth promoters. *Id.* (from 1999 to 2000, sale of therapeutic antimicrobials in the EU increased from 383 to 437 metric tonnes; from 1996 to 2001 in Denmark the sale of therapeutic antibiotics increased from 48 to 94 tonnes); Robin Bywater in *Antibiotic Resistance—the Interplay Between Antibiotic Use in Animals and Human Beings*, 3 THE LANCET: INFECTIOUS DISEASES 50 (Jan. 2003).

⁴⁸ Wegener, *supra* note 12, at 344.

⁴⁹ GFI 209, *supra* note 28, at 21 n. 5 (“[D]isease prevention involves the administration of an antimicrobial drug to animals, none of which are exhibiting clinical signs of disease, in a situation where disease is likely to occur if the drug is not administered.”).

conventional farms.⁵⁰ If the overcrowded and unsanitary conditions were eliminated, the need for the current level of preventive treatments should also decrease.⁵¹ Therefore, addressing the conditions in which food-producing animals are raised would likely be more effective in decreasing antibiotic consumption than GFI 213.

B. Negative Impact to Small Producers

GFI 213 specifically states that “if a veterinarian determines, based on the client’s production practices and herd health history, that cattle being transported or otherwise stressed are more likely to develop a certain bacterial infection, preventively treating these cattle . . . would be considered a judicious use.”⁵² Large corporations will be able to (1) staff veterinarians to prescribe at will, and (2) simply rebrand current prophylactic use as metaphylaxis. Smaller producers may be squeezed out of the market because they are unable to pay for the increased veterinarian oversight. Other economic issues that should be examined in more depth include the profit margins on preventive antibiotics and the current cost-savings realized by using less expensive feed in conjunction with growth promoters.⁵³

Additionally, current industry practices sometimes require the use of antibiotics in emergency outbreak situations—for small producers in remote areas, waiting to consult with a

⁵⁰ See, e.g. M. Pol & P.L. Ruegg, *Treatment Practices and Quantification of Antimicrobial Drug Usage in Conventional and Organic Dairy Farms in Wisconsin*, J. DAIRY SCI. 249–61 (2007) (summarizing the prevalence and defined daily dose treatments per cow on conventional and organic dairy farms).

⁵¹ Another factor to consider is that the complete absence of antibiotic treatments also may not directly correlate with the prevalence of resistance—resistant pathogens have been found in dairy cattle treated with antibiotics, but similar resistance levels have been shown among cows on organic farms (where use of antibiotics is restricted). M. Roesch, et al., *Comparison of Antibiotic Resistance of Udder Pathogens in Dairy Cows Kept on Organic and on Conventional Farms*, J. DAIRY SCI. 989–97 (2006).

⁵² GFI 213, *supra* note 38, at 21.

⁵³ See Wegener, *supra* note 12, at 341–42 (discussing the effects of limiting prescribers’ profits from the sale of antibiotics and the possible benefits of taxing growth promoters).

veterinarian may lead to otherwise preventable animal disease and mortality.⁵⁴ The evidence provided by the European Union ban suggests that a blanket ban on growth promoters leads to a decrease in animal production.⁵⁵ Increased production costs are felt most strongly by small producers, who are more likely to be able to provide individualized care for animals. Since crowding and confinement are a result of the increased size of U.S. livestock farms,⁵⁶ and these conditions require antibiotics to effectively control or prevent the spread of diseases, squeezing out small producers seems contrary to the aim of any regulation related to decreasing the amount of antibiotics used in the food animal industry.

V. CONCLUSION

To minimize resistance selection while applying antibiotic treatments requires the careful balancing of complicated scientific factors.⁵⁷ While in some cases withdrawing an antibiotic from production animals is linked to a decrease in antimicrobial resistance, other studies have shown inconclusive results or that withdrawing a particular antibiotic is not sufficient to decrease

⁵⁴ *Subterfuge: FDA's Phase Out of Antibiotics for Animal Growth Purposes Ineffective—Will Disadvantage Small Farmers*, CORNUCOPIA INSTITUTE, Jan. 31, 2014, <http://www.cornucopia.org/2014/01/subterfuge-fdas-phase-antibiotics-animal-growth-purposes-ineffective-will-disadvantage-small-farmers/#footnote1>.

⁵⁵ Casewell et al., *supra* note 13, at 161. Early studies in Sweden showed that a blanket ban of growth promoters led to unintended consequences both for animal welfare and farmers' bottom lines as animal mortality increased. *Id.* at 159. Pig production in both Sweden and Denmark showed a marked decrease following the respective bans on growth promoters; Swedish production had not recovered to previous national levels in sixteen years following the ban. *Id.* at 160.

⁵⁶ CORDOVA, *supra* note 46, at 3.

⁵⁷ Mathews, et al., *supra* note 1, at 122 (stating that “knowledge of the specific microbe biochemistry, structure, resistance mechanisms, mode(s) of transfer, population dynamics, and pharmacodynamics and pharmacokinetics” are required to set efficient treatment plans while minimizing resistance risks) (quoting F. Shojaee AliAbadi & P. Lees, *Antibiotic Treatment for Animals: Effect on Bacterial Population and Dosage Regimen Optimization*, 14 INT. J. ANTIMICROBIAL AGENTS, 307 (2000).). *See also* Cogliani et al., *supra* note 4, at 279 (stating that “behaviors may lead to important health consequences, albeit through a complex series of imperfectly understood steps”).

antimicrobial resistance.⁵⁸ Existing surveillance systems have concluded that it's fair to say that there is a "close relationship" between patterns of antibiotic usage and resistance among food animals and levels of resistance in the food supply and antibiotic resistance in human foodborne infections.⁵⁹

The FDA has responded to public health concerns by requesting more research on the safety of antibiotic treatments in food animals and implementing incremental changes to industry practices.⁶⁰ While the approach of making small changes is an appropriate way to encourage evolution in the American food animal industry, the voluntary guidelines contained in GFI 213 lack a means of ensuring industry compliance with the intent of the guidelines.⁶¹ The interests of small producers—as those most likely to be able to provide individualized medical care— should be weighted heavily; rather than creating additional veterinarian oversight processes, the conditions requiring preventive antibiotic therapies should be addressed as the primary means of ensuring a decrease in the overuse of and resistance to medically important antibiotics.⁶²

⁵⁸ Six years following the ban of growth promoters in the European Union, the resistance to some antibiotics decreased significantly, but resistance to at least two showed little change. Aarestrup et al., *supra* note 2, at 2057–58. *See also* Mathew et al., *supra* note 1, at 125 (stating inconclusive results in the poultry industry); A.S. Fairchild et al., *Effects of Orally Administered Tetracycline on the Intestinal Community Structure of Chicken and on Tet Determinant Carriage by Commensal Bacteria and Campylobacter Jejuni.*, 71 APPL. ENV. MICROBIOL., 5867–72 (2005) (tetracycline-resistant strains of *Enterococcus* and *E. coli* found both in birds exposed to the drug and those that were not). Further complicating the issue, in Denmark, antibiotic resistant *Campylobacter* steadily increased in humans after the ban of growth promoters, while the prevalence of resistant strains in animals decreased as expected. Casewell et al., *supra* note 13, at 160.

⁵⁹ Wegener, *supra* note 12, at 347.

⁶⁰ *See supra*, Part III.

⁶¹ *See supra*, Part IV.

⁶² *See supra*, Part IV.B.