Antibiotics in Animal Feeds: Short-Term Economics v. Long-Term Health

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INTRODUCTION

The use of antibiotics in animal feed is an area of intensely heated debate, and the temperature, after fluctuating over the years since 1973, is again on the rise. In the context of safety considerations associated with the use of drugs in food producing animals, there are two separate, distinct issues: (1) drug residues in meat, milk, and eggs, and; (2) the effect of using antibacterial drugs at subtherapeutic levels on the development of drug resistance in intestinal bacteria, and resistance transfer between these bacteria.

The first issue has received extensive treatment by the Food and Drug Administration (FDA) and the United States Department of Agriculture (USDA) through drug metabolism studies, the development of adequate withdrawal times before slaughter and proper labeling. The parameters of this issue are essentially settled, and this article discusses it only briefly. A significant portion of this article, however, is devoted to the second issue as it represents the central area of controversy in the field of food and drug law. Also, the full ramifications and inherent future costs of the continued use of antibiotics in animal feeds are unknown.

This article begins with an examination of the related regulations and their historical development to date. The above issues are then analyzed in the context of countervailing medical, economic, and social considerations. The analysis concludes with a discussion of the current law as it affects these issues and the potential consequences if that law is not changed.

FEDERAL LEGISLATION

The pertinent federal legislation applicable to the use of antibiotics in food animals is contained in volumes nine[1] and twenty-one[2] of the Code of Federal Regulations. As any cursory examination of these regulations will evidence, a complete examination or analysis of all the related sections is beyond the scope and ambitions of both this article and the most conscientious layman. Thus, the analysis focuses on the law as it generally relates to antibiotics in animal feeds and where applicable specific code sections are noted.

Historical Development

The use of antibacterial drugs of subtherapeutic levels[3] in animals feed dates to approximately 1950.[4] The benefits of such use were originally discov-

1. 9 C.F.R. §§ 1-199 (1986); 9 C.F.R. §§ 200 *et seq.* (1985).
2. 21 C.F.R. §§ 500-599 (1985).
3. "Subtherapeutic" refers to dosage levels lower than those necessary to cure disease. Wirth, *FDA Flip-Flops on Antibiotic Hazard*, 25 ENV'T. 4 (June 1983).
4. 43 Fed. Reg. 3032 (1978) (to be codified at 21 C.F.R. pt. 558) (proposed January 20, 1978) (never adopted) (supplementary information) [hereinafter cited 43 Fed. Reg.].

ered by accident,[5] however, the use of the drugs have since been justified for growth promotion, improved feed efficiency, and disease prevention.[6] Antibiotics for use in animal feed were initially regulated under the Federal Food, Drug, and Cosmetic Act.[7] A monograph system for regulating these products differently than the private licensing system for new drugs was created because of their unknown chemical structures and complex manufacturing processes.[8] Any antibiotic residues in food of animal origin were subsequently regulated by provisions of the act dealing with misbranding and adulteration.[9] Thus, the only way an antibiotic would fall under FDA regulation was if it was manufactured and/or sold under an improper name or as impure.

In 1958, regulation of the residues was transferred to a different section of the United States Code and a premarket approval system for any companies interested in marketing antibiotics was also established.[10] Under this system, the pioneer drug manufacturer was required to submit all the basic safety and effectiveness data related to the drug to the FDA which promulgated a regulation "establishing standards of identity, strength, quality, and purity and the requirements for packaging and labeling which the product must meet."[11] In order for any other company to manufacture and/or market the same drug product, the FDA Commissioner's approval, based solely upon a demonstration that the drug meets the regulation's requirements, is required.[12] The Commissioner, however, has the discretion under the Food, Drug, and Cosmetic Act to "exempt by regulation any drug or class of drugs from the certification requirement when he concludes that certification is unnecessary for the manufacture of the drugs."[13] The Commissioner exercised this power twice in the early 1950's and exempted from the certification requirement antibiotics for use in animal feeds and antibiotics for use as animal drugs by publication in the Federal Register.[14]

The final legislative change related to the use of antibiotics in animals came with the Animal Drug Amendments which "consolidated the provisions of the [Food, Drug, and Cosmetic] act then dealing with the premarket approval of drugs intended for use in animals . . . , to more efficiently and effectively regulate these articles. . . ."[15] This legislative change, however, had the

5. *Id.* (animals were fed discarded products from a fermentation process originally used to manufacture chlorotetracycline).

6. Guest, *Status of the FDA's Program on the Use of Antibiotics in Animal Feeds*, 31 FOOD DRUG COSM. L.J. 54 (1976).

7. Act of July 6, 1945, § 507(c), Pub. L. No. 139, 59 Stat. 463 (amending the Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 717, 52 Stat. 1040).

8. 43 Fed. Reg., *supra* note 4, at 3032.

9. *Id.* (citing the Food Additives Amendment of 1958, Pub. L. No. 85-929, 72 Stat. 1784).

10. 43 Fed. Reg., *supra* note 4, at 3032.

11. *Id.*

12. *Id.*

13. *Id.*; Act of July 6, 1945, § 507(c), Pub. L. No. 139, 59 Stat. 463 (amending the Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 717, 52 Stat. 1040).

14. 43 Fed. Reg., *supra* note 4, at 3032 (citing 16 Fed. Reg. 3647 (April 28, 1951) and 18 Fed. Reg. 2335 (April 22, 1953) for animal feeds and animal drugs respectively. These exemptions are now set out in 21 C.F.R. §§ 510.510 and 510.515 (1985)).

15. 43 Fed. Reg., *supra* note 4, at 3032 (citing the Senate Committee on Labor and Public Wel-

adverse effect of placing the manufacturing of antibiotics for animal use under the same private licensing system applicable to new drugs.[16] To effectuate this vast increase in workload, the Animal Drug Amendments were passed which allowed "all prior approvals for the use of drugs in animals and animal feeds to continue in effect and be subject to change in accordance with the provisions of the basic act as amended."[17] Thus, the impact of this legislation was to award any person or company who had legally marketed antibiotics under the old regulations prior to the Animal Drug Amendments of 1968 the equivalent of an approved new animal drug application (NADA).[18] Consequently, pre-1968 uses of antibiotics in animals and animals feeds were given the "benefit of the doubt" in that such uses were treated as having met the higher safety and effectiveness standards required for NADA's by the private licensing system when in fact antibiotics had been exempted from the certification requirement by the FDA Commissioner under the old public monograph system.[19]

The remainder of the regulatory background on antibiotics used in animals and animal feeds is best described as stagnation of overall objectives and results masked by intensive and extensive study and debate so characteristic of all bureaucratic activities.[20] With one exception, the FDA has not been successful in securing Congressional approval of any FDA promulgated regulations affecting antibiotic use since the 1968 Animal Drug Amendments.[21] The lone successful regulation was a final order of the FDA Commissioner on February 25, 1976 withdrawing all approved NADA's held by individuals who had not complied with an earlier order requiring the filing of commitments to study the safety and effectiveness of antibiotics produced or marketed by such individuals.[22] Thus, only those products listed in particular sections of volume twenty-one of the Code of Federal Regulations can be legally marketed today.[23]

FDA's Position

The examination of every regulatory or procedural step the FDA has taken in the antibiotic-animal drug area from 1970 to date would add little to this article except length. However, some highlights during this time frame

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fare, Animal Drug Amendments of 1968, S. REP. No. 1308, 90th Cong., 2d Sess. (1968) (the new section created was 21 U.S.C. § 360(b)).

16. 43 Fed. Reg., *supra* note 4, at 3032 (citing *Hearing on S. 1600 and H.R. 3639 Before the Subcomm. on Health of the Senate Comm. on Labor and Public Welfare*, 90th Cong., 2d Sess. (1968)).

17. 43 Fed. Reg., *supra* note 4, at 3032.

18. *Id.*

19. *Id.*

20. *See generally*, 43 Fed. Reg., *supra* note 4, at 3032-36; Sun, *Use of Antibiotics in Animal Feed Challenged*, 225 SCI. 144, 144-46 (Oct. 12, 1984).

21. *Id.*

22. 43 Fed. Reg., *supra* note 4, at 3033.

23. 21 C.F.R. §§ 520, 522, 524, 526, 529 (new animal drugs for animal use) (1985); 21 C.F.R. § 558 (new animal drugs for use in animal feed) (1985); U.S. DEP'T OF AGRIC., FOOD SAFETY AND INSPEC. SERV., *Compound Evaluation and Analytical Capability Annual Residue Plan section 4.A.1.* (1985) [hereinafter cited as *Compound Evaluation*].

are important in examining the FDA's general stance on the issues and how erosion of that stance may ultimately affect the resolution of those issues. In 1970, after reviewing a report issued by the Swann Committee,[24] the FDA Commissioner established the United States Task Force on Antibiotics in Feeds to comprehensively review the safety and efficacy of using antibiotics in animals feeds.[25] The Task Force's principal conclusions were as follows:[26]

> (1) The use of antibiotics and sulfonamide drugs, especially in growth promotant and subtherapeutic amounts, favors the selection and development of single and multiple antibiotic resistant and R-plasmid-bearing bacteria.[27]
>
> (2) Animals which have received either subtherapeutic and/or therapeutic amounts of antibiotic and sulfonamide drugs in feeds may serve as a reservoir of antibiotic resistant pathogens and nonpathogens. These reservoirs of pathogens can produce human infections.
>
> (3) The prevalence of multiresistant R-plasmid-bearing pathogenic and nonpathogenic bacteria in animals has increased and has been related to the use of antibiotics and sulfonamide drugs.
>
> (4) Organisms resistant to antibacterial agents have been found on meat and meat products.
>
> (5) There has been an increase in prevalence of antibiotic and sulfonamide resistant bacteria in man.
>
> (6) The Task Force also identified three areas of primary concern: human health hazards, animal health hazards, and antibiotic effectiveness; and it established guidelines to measure whether use of any antibiotic or antibacterial agent in animal feed presents a hazard to human and animal health.

From 1972, when the Task Force conclusions were received, until 1977, the FDA "aggressively pursu[ed] the public health issues surrounding animal feed uses of antibiotics."[28] In 1977, the FDA tried to ban the use of penicillin and tetracycline in animal feed, but the interest groups lobbying Congress had sufficient strength to defeat the proposal.[29] Thus, even though the FDA had studied the safety issues and drawn its conclusions, Congress directed more studies be done.[30]

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24. A committee formed by the British government to study an outbreak of resistant infectious diarrhea among cattle in the 1960's in Great Britain. The committee concluded "subtherapeutic use of antibiotics in animal feeds presented a definite health risk and should be restricted." Wirth, *supra* note 3, at 5.
25. *Id.*
26. 43 Fed. Reg., *supra* note 4, at 3032-33.
27. R-Plasmids are small lengths of DNA that are separate from the bacterial chromosome. These R-plasmids carry transferable drug resistance genes as well as the capacity to reproduce themselves. Plasmids may determine resistance to more than one antibiotic, and resistance to several antibiotics is common. Moreover, plasmids can transfer from one bacteria to another and from nonpathogenic to pathogenic strains. . . . [T]he R-plasmid-bearing bacteria interchange among animals, man, and the environment. The potential for harm increases as the R-plasmid reservoir increases because the probability of R-plasmid transfer to pathogens increases.

Id. at 3035.
28. Wirth, *supra* note 3, at 5.
29. Sun, *supra* note 20, at 144.
30. Wirth, *supra* note 3, at 5.

The first such study completed was a literature review done by the National Academy of Sciences (NAS) in 1980.[31] Even though "the NAS report conceded that it was difficult if not impossible to design a perfect study on this issue," it rigorously examined all the existing studies finding defects in each one.[32] The NAS study concluded that "the available evidence did not prove the existence of a health risk from the subtherapeutic use of antibiotics in animals feeds."[33] Thus, the NAS study recommended further study, and the FDA complied.[34] While the NAS study and the FDA's position may appear contradictory, the only real difference is in who has the burden of proof.[35] The NAS study placed the burden on the FDA while the FDA placed the burden "squarely on industry to show that the existing uses were safe, a standard that industry was and continues to be unable to meet."[36] The justification for the FDA's position is its governing statute, "which demands that the agency resolve public health questions on the side of safety."[37] Given the fact that Congress created the FDA and its governing statute, it seems odd that action on Congress' part should not have occurred with the information then known by the FDA. In fact, affirmative action on Congress' part did not occur until 1980 when two Congressmen drafted a bill that "would have explicitly required [the] FDA to regulate subtherapeutic uses of antibiotics in animal feeds."[38] The bill, however, died in committee and the FDA has since begun to erode its own position.[39]

After President Reagan was elected, industry asked the FDA formally to abandon its 1977 proposals to ban penicillin and tetracycline.[40] The FDA refused in February, 1983, stating that it "[did] not have any less concern at present about the safety issues."[41] Surprisingly, however, on the same day the FDA "proposed relaxing its standards to allow *new* animal feed uses of penicillin and tetracycline," in direct contravention of its governing statute and its tough policy stance since 1973.[42] Thus, this unexpected reversal by the FDA leaves not only the agency's credibility but also the future direction of the law in the antibiotics-animal area uncertain.

ANALYSIS

As stated in the introduction, there are two major issues in the area of safety considerations and the use of antibiotics in food producing animals. The first, drug residues in meat, milk, and eggs, is relatively well defined and

31. *Id.*
32. *Id.*
33. *Id.* at 42.
34. *Id.* at 5.
35. *Id.* at 42.
36. *Id.*
37. *Id.*
38. *Id.* Congressmen John Dingell (D-Mich.) and Henry Waxman (D-Calif.) introduced the bill.
39. *Id.* at 42.
40. *Id.*
41. *Id.*
42. *Id.*

settled. Briefly, the residue testing program is established by the FDA and administered by the USDA.[43] At present, the USDA program tests for residues of over 100 compounds in food of animal origin on a rotating basis.[44] Critics of the residue program argue that existing tests for residues should be improved and new tests for chemicals not now tested developed.[45] While these are valid concerns, of major importance to this issue and especially to the second, is the fact that "[t]here is no system for tracing animals with violative levels of residue back to their production point."[46] Thus, it is often difficult if not impossible to find the exact source of the residue contamination as well as the concrete link from antibiotics in animal feed directly to the injured human consumer of the food product.

The second issue, the effect of using subtherapeutic levels of antibiotics on the development of drug resistant bacteria in animals and resistance transfer between these bacteria in animals and man, is much less quantifiable in terms of potential costs or hazards. But, the fact that the risks of harm or potential hazard is less quantifiable in dollars and cents should not affect anyone's judgment, much less that of the FDA given its governing statute. That governing statute "demands that the [FDA] resolve public health questions on the side of safety."[47] Neither does the FDA's governing statute permit consideration of economic factors in resolving questions affecting public health.[48] Thus, the inability to *quantifiably* calculate the long-term health risks or side-effects to both animals and humans of continued subtherapeutic antibiotic use in animals does not justify the FDA's failure to ban or at least severely restrict such uses, especially in light of its governing statute. Furthermore, the *possibility* that potential health hazards exist is *alone* sufficient for the FDA to propose and Congress to pass a ban. With the probability increasing that potential health hazards or risks of harm to humans exist from subtherapeutic antibiotic use, the FDA cannot maintain its present position without making a mockery of its governing statute.

It is a documented fact that the overuse and abuse of antibiotics in human disease treatment has decreased the effectiveness of such drugs.[49] Penicillin, when first used, was nearly 100% effective against bacteria causing pneumonia and hospital-related infections; now it is much less so.[50] Tetracycline and pen-

43. *Compound Evaluation, supra* note 23, at § 2.1.

44. *Id.* at § 4.A.1-A.3.

45. Remarks of Carol Tucker Foreman, Pres., Foreman & Company, Before the Food and Drug Law Institute, Hyatt Regency Hotel, Washington, D.C., p. 2 (Dec. 12, 1984) (copy on file at S.D.L. REV. OFFICE [hereinafter cited as Foreman]).

46. *Id.*

47. Wirth, *supra* note 3, at 42.

48. *Id. See* Foreman, *supra* note 45, at 4 (on the economic side of the issue, "[t]he costs of salmonella alone have been estimated at about $1 billion annually in medical care, hospital costs, and lost work."). *See also* Franklin, *Drug Resistance Link from Animal to Man*, 126 SCI. NEWS 127 (Aug. 25, 1984) (two to four million salmonella infections are reported annually in the U.S.—between 1,000 and 2,000 of those patients die).

49. *Those Overworked Miracle Drugs*, TIME 63 (Aug. 17, 1981).

50. *Id.*

icillin, the two most common antibiotic animal feed additives,[51] now have a failure rate of more than twenty percent against some strains of gonorrhea, a disease they cured in the past.[52] This is just one example of the diminishing effectiveness of antibiotics.

The reasons behind the overuse and abuse of antibiotics are varied. Part of the problem comes from doctors who casually prescribe antibiotics for everything, including acne and the common cold.[53] Another part is due to people taking antibiotics without doctor's orders or prescription.[54] The problem is even worse in Third World countries where doctors routinely distribute stronger antibiotics with toxic side effects for simple infections.[55] But limiting antibiotic use by prescription or even restricting prescription use further would solve only half the problem as over forty percent of all antibiotics produced in the United States are added to animal feed.[56] Antibiotics in animal feed today represents a $250 million a year industry, or nearly fifteen million pounds of antibiotics added to forty-two million tons of animal feed.[57] Antibiotics are estimated to be fed to 100% of turkeys, at least 30% of chickens, 80% of swine and veal calves, and 60% of feedlot beef cattle.[58]

There are several other "given" factors in the antibiotic-animal equation that tend to skew it more like an inequality in favor of the FDA ban. Scientists have known for more than twenty years that routinely feeding subtherapeutic levels of penicillin or tetracycline to animals encourages the development of resistant strains of bacteria in those animals.[59] Animals and humans can exchange drug-resistant bacteria.[60] The proportion of bacteria resistant to one or more drugs is increasing whether sampled from humans or natural bodies of water.[61] For example, in 1967 only 0.8% of salmonella bacteria isolated in hospitals were resistant to six or more antibiotics compared with 9.2% in 1975.[62] Finally, "a majority of [the] outbreaks of drug-resistant salmonella in the United States during the past decade could be traced to animal food sources. The fatality rate as a result of these infections was twenty-one percent higher than for disease caused by salmonella strains that responded to conventional antibiotics."[63] Also, the incidence of drug-resistant salmonella and "immune-suppressed individuals" is increasing.[64]

The increased cost of meat production which opponents of the FDA ban

51. *Whose Drugs are They, Anyhow?*, CONSUMER REP. 170 (Mar. 1985).
52. *Those Overworked Miracle Drugs, supra* note 49.
53. *Id.; An Antibiotic That Threatens More Than Germs*, PREVENTION 32 (May 1982) (use of tetracycline by an adult caused intracranial hypertension resulting in headaches and permanent vision impairment).
54. Seligmann & Glass, *Overdoing on Antibiotics*, NEWSWEEK 77 (Aug. 17, 1981).
55. *Id.; Those Overworked Miracle Drugs, supra* note 49.
56. Seligmann & Glass, *supra* note 54.
57. Sugarmann, *The Salmonella Strain*, 68 CONSUMERS' RESEARCH MAG. 31, 33 (July 1985).
58. Franklin, *Drug Resistance Link From Animal to Man*, 126 SCI. NEWS 127 (Aug. 25, 1984).
59. *Whose Drugs are They, Anyhow?, supra* note 51.
60. *Health Hazards of Drugs in Animal Feed*, 115 SCI. NEWS 422 (June 30, 1979).
61. *Id.*
62. *Id.*
63. Foreman, *supra* note 45, at 4.
64. *Id.*

strongly tout is also unpersuasive. The USDA study cited estimated cost increases of $15 million to $3.5 billion.[65] Notably, however, this study assumed the loss of *all* antibiotics used in animal feeds.[66] The FDA ban only seeks to remove penicillin and tetracycline from use in animal feed—the two most common antibiotics used in human treatment for which viable substitutes exist for use in animal feeds.[67]

Furthermore, the opponents of the FDA ban argue that no direct link between antibiotics in animal feed and drug-resistant, illness-causing bacteria in humans exists.[68] Conclusive studies, however, now exist. The most persuasive, by Scott Holmberg, traced eighteen severe salmonella infections in four midwestern states to hamburger processed from a single cattle herd in southeastern South Dakota which was fed low doses of chloretetracycline as a growth promoter.[69] Opponent's major criticism of this study was that Holmberg never found an actual piece of infected meat from the cattle herd.[70] Arguably, however, there is no way anyone could have found an actual tainted piece of meat from the South Dakota cattle herd, given the time lapse from the time of slaughter to the on-set of human consumption and illness.[71] Indeed, according to Philip Frappaolo, "[Holmberg's] study is as good as you can do . . . you don't get much better empirical evidence than this study."[72] The FDA even acknowledges "that the scientific documentation is now much more definite than in 1980. . . ."[73]

CONCLUSION

The use of antibiotics in animal feeds is likely to continue indefinitely into the future even though strong scientific, medical, social and rational considerations exist for at least limiting their use. The trade-off is between immediate economic benefits-profits to drug manufacturers, and unquantifiable future health risks for both humans and animals. While in the field of economics it

65. Franklin, *supra* note 58.

66. Foreman, *supra* note 45, at 5; Sun, *supra* note 20, at 145.

67. *Id.*

68. Sun, *supra* note 20, at 145.

69. Sun, *In Search of Salmonella's Smoking Gun*, 226 SCI. 30, 30-32 (Oct. 5, 1984). *See also*, Holmberg, Osterholm, Senger & Cohen, *Drug-Resistant Salmonella From Animals Fed Antimicrobials*, 311 New Eng. J. of Med. 617-22 (Sept. 6, 1984). The study used a new scientific technique called "genetic fingerprinting" to match a "penicillin-and tetracycline-resistant strain of salmonella" which infected 18 people. Sugarmann, *supra* note 57, at 33.

70. Sun, *supra* note 69, at 32 (although a "plasmid profile from the suspect beef [would have] clinched the investigation," the isolate taken by Holmberg "from the sample from the dead dairy calf was persuasive.").

71. *See* Sugarmann, *supra* note 57 at 31; Holmberg, Osterholm, Senger & Cohen, *supra* note 69 at 619-20. Symptoms of salmonellosis take up to 72 hours to appear, and the time frame involved from date of slaughter until the meat even reached retail outlets was more than one week. Sugarmann, *supra* note 57, at 31; Holmberg, Osterholm, Senger & Cohen, *supra* note 69, at 619-20.

72. Telephone interview with Philip Frappalo, Director of Voluntary Compliance and Hearing Development in the Office of New Animal Drug Evaluation, Washington, D.C. (January 1986). *See also* Sun, *supra* note 20, at 145 (Dr. Lester Crawford, Director of the FDA's Center for Veterinary Medicine, agrees stating, "[t]his study is about as good as we're going to get. I don't see how we can get any better information.").

73. Wirth, *supra* note 3, at 42.

may be true that "in the long-run, we are all dead," in the area of antibiotics and animals, farmers, as well as society in general could all benefit from a more responsible and responsive FDA and government. Congress' inaction and the FDA's reversal in policy regarding penicillin and tetracycline use in animal feed represents all too clearly and tragically what can happen when short-run economics and short-sighted special interest politics are allowed to influence rational decision making processes.

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