



Antibiotic Use in Agriculture: Background and Legislation

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Summary

Public health experts have expressed concern about an increase in antibiotic resistance among sick patients. Such resistance has been linked to a number of causes, such as overuse of antibiotics by medical professionals and their patients, and their wide use for nontherapeutic (essentially nonmedical) purposes in food animals. Agricultural producers administer antibiotics in feed for some types of food-producing animals not only to treat and prevent diseases, but also to encourage growth and efficient use of feed rations. Some argue that nontherapeutic uses should be severely constrained and/or limited to drugs not associated with human medical treatments. Others oppose this approach, arguing that many animal production operations would not be commercially viable (and that the animals' health could be compromised) without the drugs' routine use, and/or that the linkage between such use and antimicrobial resistance lacks a strong scientific basis.

In the 111th Congress, companion bills (H.R. 1549, S. 619) have been introduced that would phase out the nontherapeutic use in food animals of seven specific classes of antibiotic drugs that can also be used to treat or prevent diseases and infections in humans. While not directly endorsing the bills, a top official of the U.S. Food and Drug Administration (FDA), which regulates animal drugs under the Federal Food, Drug, and Cosmetic Act, recommended in July 2009 that the phase-out of nontherapeutic uses of animal antibiotics be considered.

Some supporters of the bills have urged that they be incorporated into other pending legislation (for example, H.R. 2749, a food safety bill approved in June 2009 by the House Energy and Commerce Committee). Others, including some members of the House Agriculture Committee, have expressed strong opposition to the antibiotics bills and their inclusion in any food safety legislation.

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At Issue

Increased resistance of microbial pathogens to the various antimicrobial drugs developed to treat them is a widely recognized public health problem.¹ Most scientific and public health experts agree that the problem is linked to a number of causes, including over-prescription of antimicrobial drugs by medical practitioners, their misuse by patients, releases into the environment, and—at the root of all of these reasons—the ability of the pathogens themselves to evolve and adapt rapidly.

Another reason for resistance can be the use of antimicrobials or, more specifically, antibiotics, in food-producing animals. However, stakeholders disagree on the extent of agriculture’s contribution to the problem and on the strength of scientific evidence of such a linkage.

A number of bills have been introduced in recent years aimed at curtailing agricultural uses of medically significant antibiotics, but none have been enacted. The issue is again being debated in the 111th Congress, where new bills (H.R. 1549, S. 619) are pending. Top officials of the U.S. Food and Drug Administration (FDA) weighed in on the debate in July 2009 by expressing support in concept for phasing out nontherapeutic (essentially, nonmedical) uses of antimicrobials in food animal production. Whether a bill will advance beyond the hearing stages remains to be seen, however; many, including those with large agricultural constituencies, oppose these bills.

Current Legislative Proposals

Companion bills to restrict the use of medically significant antibiotics in food animals were introduced in the House and Senate on March 17, 2009, as H.R. 1549 by Representative Slaughter and S. 619 by Senator Reid (for Senator Kennedy). These bills, the Preservation of Antibiotics for Medical Treatment Act of 2009 (PAMTA), are similar in title and purpose to bills introduced but not enacted in the 110th Congress (H.R. 962, S. 549), the 109th Congress (H.R. 2562, S. 742), the 108th Congress (H.R. 2932, S. 1460), and the 107th Congress (H.R. 3804, S. 2508).

The currently pending bills (H.R. 1549, S. 619) would amend the key FDA authorizing law—the Federal Food, Drug, and Cosmetic Act (FFDCA, 21 U.S.C. 301 et seq.)—to require the Secretary of Health and Human Services (HHS, under which FDA is located) to withdraw, within two years, the approval of any “nontherapeutic use” in food-producing animals of a “critical antimicrobial animal drug.” Such action would be required unless the Secretary determines, in writing, that the holder of an approved application (i.e., the drug’s sponsor) has demonstrated, or a risk analysis has found, “that there is a reasonable certainty of no harm to human health due to the development of antimicrobial resistance that is attributable in whole or in part to the nontherapeutic use of the drug.” The HHS Secretary also would be required to refuse a new application for a critical antimicrobial animal drug if the sponsor failed to demonstrate the same “reasonable certainty” standard.

¹ The term “antimicrobial” refers broadly to drugs that act against a variety of microorganisms, including bacteria, viruses, fungi, and parasites. The term “antibiotic,” or “antibacterial,” refers to a drug that is used to treat infections caused by bacteria. Antibiotics are, therefore, types of antimicrobial drugs. The issues discussed in this report involve principally, but not exclusively, antibiotic drugs. The terms “antibiotic” and “antimicrobial” are often used interchangeably in policy discussions, and in this report.

The bills would define a “critical antimicrobial animal drug” to be one that “is intended for use in food-producing animals” and is composed wholly or partly of “any kind of penicillin, tetracycline, macrolide, lincosamide, streptogramin, aminoglycoside, or sulfonamide,” or “any other drug or derivative of a drug that is used in humans or intended for use in humans to treat or prevent disease or infection caused by microorganisms.”

With respect to such drugs, the bills would define the term “nontherapeutic use” as “any use of the drug as a feed or water additive for an animal in the absence of any clinical sign of disease in the animal for growth promotion, feed efficiency, weight gain, routine disease prevention, or other routine purpose.”

H.R. 1549 was the subject of a hearing in the House Rules Committee.² Neither the House nor the Senate version otherwise advanced during the first session of the 111th Congress. Supporters have considered seeking to attach the bills to pending food safety or health reform legislation, but have not done so at this time.³

Another antimicrobial resistance bill, the “Strategies to Address Antimicrobial Resistance Act” (STAAR, H.R. 2400, introduced May 13, 2009, by Representative Matheson), takes a different approach to the issue of antimicrobial resistance. H.R. 2400 would apply broadly to all antimicrobials and to a variety of uses, including in human health care, not just to antimicrobials used in food animals. The bill, which had been introduced in the 110th Congress as H.R. 3697, would establish an Antimicrobial Resistance Office within the HHS Secretary’s office as well as a public health advisory board to channel advice and expertise on the issue, and would reauthorize a number of antimicrobial resistance programs authorized in a previous law that have since expired, among other things.⁴ The bill has not advanced.

Administration Views

The Obama Administration has not taken a position on the PAMTA or STAAR bills, but HHS officials have suggested that a phase-out of the use of antimicrobials for growth promotion and/or feed efficiency may be considered. “Eliminating these uses will not compromise the safety of food,” an FDA official told Congress in July 2009. Noting that the agency’s current statutory authority for withdrawing a new animal drug approval “is very burdensome,” he stated that any proposed legislation should “facilitate the timely removal of nonjudicious uses of antimicrobial drugs in food-producing animals.”⁵

At the same time, he added, FDA believes that some antimicrobial uses for disease prevention “are necessary and judicious to relieve or avoid animal suffering and death.” However, he noted a

² U.S. Congress, House Committee on Rules, *H.R. 1549—Preservation of Antibiotics for Medical Treatment Act of 2009*, 111th Cong., 1st sess., July 13, 2009.

³ See, for example, Ben Moscovitch, “Lawmaker, Stakeholders Try Rallying Support for Animal Antibiotic Ban,” *FDA Week*, December 4, 2009.

⁴ This paragraph is based in part on material in a CRS congressional distribution memo, “Comparison of Selected Bills in the 110th Congress Regarding Animal Drug Use and Antimicrobial Resistance,” dated June 9, 2008, by Sarah A. Lister, Specialist in Public Health and Epidemiology.

⁵ Joshua M. Sharfstein, FDA Principal Deputy Commissioner of Food and Drugs, July 13, 2009, testimony before the House Committee on Rules; and Linda Tollefson, FDA Assistant Commissioner for Science, June 28, 2008, testimony before the Senate Committee on Health, Education, Labor, and Pensions.

number of factors that should be considered in weighing the need for such a use and stated that “FDA also believes that the use of medications for prevention and control should be under the supervision of a veterinarian.”⁶ In practical terms, this would mean that animal antimicrobials that are currently available over the counter would no longer be, although whether a prescription would be needed in all situations remains unclear.⁷

Use of Antibiotics in Agriculture⁸

Types of Use

Antibiotics are used in food-producing animals for three major reasons, according to HHS’s Centers for Disease Control and Prevention (CDC).⁹ First, they are used in high doses for short periods of time to treat sick animals. Second, they are used—also in high doses for short periods of time—to prevent diseases during times when animals may be more susceptible to infections (for example, after weaning, or during transport). This use “usually involves treating a whole herd or flock, which increases the likelihood of selecting for organisms that are resistant to the antibiotic.” Finally, “antibiotics are commonly given in the feed at low doses for long periods to promote the growth of cattle, poultry, and swine. In the 1950s studies showed that animals given low doses of antibiotics gained more weight for a given amount of feed than untreated animals. Exactly how this occurs is still greatly unknown.”¹⁰

Animal drugs may be administered either by injecting them directly or by mixing them into feed and water. The latter method may be viewed as more efficient when treating large groups of animals, and it is the only feasible approach for some species such as poultry and fish.¹¹

Citing USDA survey data from 1999, McEwen and Fedorka-Cray observed that approximately 83% of feedlots administered at least one antibiotic for disease prevention or growth promotion, including control of liver abscesses, accelerated weight gain, and prevention of respiratory disease outbreaks. Other feedlot uses were for a variety of individual animal or group treatments such as for diarrhea and pneumonia. Cow-calf producers, however, used antimicrobials relatively little. Milk replacers to feed veal calves could contain antimicrobials for disease prevention;

⁶ Sharfstein testimony.

⁷ See, for example, “New Administration First to Let FDA Take Strict Stance on Antibiotics,” *FDA Week*, July 24, 2009. Some antimicrobials approved for use in food animals may be purchased over the counter by producers. Other require greater oversight, including veterinary prescriptions with varying requirements, depending on the drug, its intended use, and stipulations associated with its approval.

⁸ Portions of this report are adapted from out-of-print CRS Report RL30814, *Antibiotic Resistance: An Emerging Public Health Issue*, by Donna U. Vogt and Brian A. Jackson. Another source is Government Accountability Office (GAO, then called the General Accounting Office), *Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals* (GAO-04-490), April 2004.

⁹ Antibiotics also are used in plant agriculture, primarily sprayed in orchards as a prophylactic treatment for diseases. Although use data are somewhat limited, this use appears to be limited. Source: Anne K. Vidaver, “Uses of Antimicrobials in Plant Agriculture,” *Clinical Infectious Diseases*, 2002:34, Supplement 3, pp. S107-S110.

¹⁰ CDC, “Antibiotic Resistance 101,” posted on its web page, “Get Smart: Know When Antibiotics Work on the Farm,” at http://www.cdc.gov/narms/get_smart.htm.

¹¹ Scott A. McEwen and Paula J. Fedorka-Cray, “Antimicrobial Use and Resistance in Animals,” *Clinical Infectious Diseases*, 2002:34, Supplement 3, pp. S93-S106.

lactating dairy cattle could receive antimicrobial injections to treat or prevent mastitis. Poultry were administered antimicrobials to treat, control, or prevent a number of problematic diseases such as necrotic enteritis (an intestinal infection) and *E. coli* infections; several types were also approved and widely used mainly for growth promotion and feed efficiency in broilers, egg layers, and turkeys. For swine, antimicrobial use was mainly in feed at relatively low concentrations for growth promotion or disease prevention, particularly after weaning. Swine received antimicrobials either individually or in feed to treat or prevent pneumonia, bacterial diarrhea caused by such organisms as *E. coli* and *Clostridium perfringens*, swine dysentery, and ileitis.¹²

Table I. Examples of Antibiotics Commonly Used in Animals
(feedlot cattle, swine, broiler chickens)

| Antibiotic Class | Animal Use | Human Medicine Importance |
|--------------------------------------|---|---------------------------|
| Cephalosporin (3 rd gen.) | disease treatment in cattle and swine | critical |
| Fluoroquinolone | disease treatment in cattle | critical |
| Penicillins | disease treatment in cattle; growth, disease treatment in swine | high |
| Macrolide | disease treatment and prevention in cattle; growth, disease treatment and prevention in swine | critical |
| Phenicol | disease treatment and prevention in cattle | not |
| Sulfonamide | growth in swine | not |
| Tetracycline | disease treatment and prevention in cattle; growth, disease treatment and prevention in swine | high |
| Lincosamide | disease treatment in swine | high |
| Pleuromutilin | growth in swine | not |
| Polypeptide | growth in swine; growth promotion, disease prevention in chickens | not |
| Streptogramin | growth, disease prevention in chickens | high |
| Carbadox | growth in swine | not |
| Bambermycin | growth, disease prevention in chickens | not |

Source: Adapted from GAO, *Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals*, Appendix V. Rankings of human medicine importance are GAO's, based on FDA determinations.

Notes: With regard to human medicine importance, FDA ranks antibiotics as "critically important" ("critical" in the above table), "highly important" ("high" in the table), or "important." The ranking is based on five criteria from the most important (it is used in treating pathogens that cause foodborne disease) to the least important (there is difficulty in transmitting resistance across genera and species). See the discussion under "Regulatory Approach" later in this report.

Long-term, low-dose treatments may serve as a prophylactic against diseases, particularly where animals are housed in large groups in close confinement facilities. Such facilities are very widely

¹² McEwen and Fedorka-Cray.

used in commercial swine, poultry, and egg production and are increasingly being adopted in the dairy and beef cattle industries. On the one hand, animal confinement facilities provide for closer and more cost-effective management of animals, protection from the elements and predators, and increased biosecurity (protection from outside pathogens, whether unintentionally or intentionally introduced). On the other hand, the concentrated nature of such agricultural operations means that a disease, if it occurs, can spread rapidly and become quickly devastating—increasing the need to rely on antibiotics as a preventive measure.

Antibiotics work by interfering with some part of the necessary biological mechanisms of bacteria to kill them directly or to halt their growth. They are broadly divided into classes based on their chemical structures and modes of action. Classes include a “lead” antibiotic as initially discovered, and modified versions of it, including improvements designed to overcome developing resistance to it. (See **Table 1.**) After penicillin was first clinically tried in the 1930s (and mass-produced in the 1940s), antibiotic development and usage in both animal and human populations, generally of the same types of drugs, grew steadily. By the 1950s antibiotics came into even wider use as livestock growth promoters.¹³

Amount of Use

Reliable data on total U.S. antibiotic use do not appear to be publicly available. A 2001 report by the Union of Concerned Scientists (UCS), a science-based advocacy organization, stated that 24.6 million pounds of antibiotics were used for nontherapeutic purposes in food animals annually. The organization asserted that this represented 70% of all antibiotics produced in the United States in one year.¹⁴ Others including the Animal Health Institute (AHI), which represents companies that market animal drugs and other animal health products, counter that the UCS figures are based on questionable assumptions and estimates (in part, because no publicly reliable data appear to have been developed). Also, the UCS counts in the total such substances as ionophores, which are used as growth promoters in animals but have never been used in human medicine, AHI has noted.¹⁵

UCS includes disease prevention in its definition of nontherapeutic use along with growth promotion. Others have taken issue with this definition. The American Veterinary Medical Association (AVMA) has argued: “The term ‘non-therapeutic’ has no meaning in federal regulation or common usage. The FDA approves antimicrobials for four purposes: disease treatment, disease prevention, disease control, and growth promotion/feed efficiency. The FDA does not approve antimicrobials for ‘non-therapeutic’ uses.”¹⁶ The last AHI survey of its members reported that 87% of the antibiotics used in all animals (including nonfood animals such as pets) were for disease treatment, control, and prevention.¹⁷ A policy statement on antibiotic usage by the American Public Health Association (APHA) asserts that as much as 40% of all antibiotics

¹³ CDC, “Landmarks in Antibiotic Use,” posted on its web page, “Get Smart: Know When Antibiotics Work on the Farm,” at http://www.cdc.gov/narms/get_smart.htm.

¹⁴ Union of Concerned Scientists, *Hogging It: Estimates of Antimicrobial Abuse in Livestock*, January 2001.

¹⁵ AHI, e-mail communication, July 20, 2009.

¹⁶ Christine Hoang, DVM, MPH, AVMA, September 25, 2008, testimony before the House Agriculture Subcommittee on Livestock, Dairy, and Poultry.

¹⁷ AHI, e-mail communication, July 20, 2009.

used in the United States are added into feeds to promote efficient growth, but no source is provided for this figure.¹⁸

Seeking more useful data, lawmakers included a provision in the Animal Drug User Fee Amendments of 2008 that requires drug sponsors to submit an annual report to the HHS Secretary for each approved antimicrobial drug that is sold or distributed for use in food-producing animals. The annual report must contain such details as the amount of the active ingredient and the quantities distributed domestically and exported. The Secretary is required to make summaries of the information available to the public. The first annual report for currently approved antibiotics must be submitted no later than March 31, 2010.¹⁹

Citing data inadequacies, Representative Slaughter on September 21, 2009, asked the Government Accountability Office (GAO) to examine these questions:

- What data exist on the types and quantities of antibiotics used in food animals and on the purposes for which they are used?
- What further data do USDA, FDA, and CDC believe are needed to assess and mitigate the risks to humans from antibiotic use in animals and what efforts are underway or are needed to collect these data?
- To what extent is USDA monitoring food animals and meat for the emergence of antibiotic-resistant strains of pathogens, such as *E. coli*, *Campylobacter*, *Salmonella*, and *Listeria*?
- How effectively is FDA overseeing industry compliance with currently approved animal antibiotics and uses for these antibiotics?
- What is FDA's plan and time frame for reevaluating the antibiotics (and antibiotic uses) that it has approved for animals?
- What efforts have USDA, FDA, and CDC taken to assess the human health risks related to antibiotic use in animals, and what have the assessments shown?²⁰

Public Health Concerns

Approximately 2 million people acquire bacterial infections each year in U.S. hospitals alone. Approximately 90,000 die as a result, and 63,000, or 70%, of these deaths are from infections resistant to one or more antimicrobial drugs.²¹ Antimicrobial resistance is a natural phenomenon associated with use of antimicrobial drugs and began to be recognized soon after penicillin was

¹⁸ APHA, "Antibiotic Resistance Fact Sheet," accessed July 21, 2009, at <http://www.apha.org/advocacy/reports/facts/advocacyfactantibiotic.htm>.

¹⁹ Section 105 of P.L. 110-316, signed into law August 14, 2008. Other proposals in the 110th Congress would have provided for more extensive data requirements. See CRS Report RL34459, *Animal Drug User Fee Programs*, by Sarah A. Lister.

²⁰ The letter was posted on the Representative's website and accessed September 30, 2009, at http://www.louise.house.gov/index.php?option=com_content&view=article&id=1306:slaughter-asks-gao-for-additional-data-on-antibiotic-use-in-animals&catid=41:press-releases&Itemid=109. See also the discussion in the next section on the work of the existing National Antimicrobial Resistance Monitoring System for Enteric Bacteria.

²¹ Sharfstein testimony; Tollefson testimony.

first used. However, strains that acquire an ability to survive a drug and to multiply have been subject to wider scientific study.²² According to the CDC:

Bacteria become resistant to antibiotics through several mechanisms. Through their ability to share genetic information, bacteria can transfer resistant genes to one another. Some bacteria develop the ability to neutralize an antibiotic before it can do them harm, others can rapidly pump the antibiotic out, and still others can change the antibiotic attack site so it cannot affect the function of the bacteria. In addition, bacteria that were at one time susceptible to an antibiotic can acquire resistance through mutation of their genetic material or by acquiring pieces of DNA that code for the resistance properties from other bacteria. The DNA that codes for resistance can be grouped in a single easily transferable package called a plasmid. Bacteria can become resistant to many antimicrobial agents because they can acquire multiple antibiotic resistant plasmids.²³

Antimicrobial use in animals has contributed to the emergence of antimicrobial-resistant microorganisms but is by no means the only cause. Many scientists believe that the misuse and overuse of antimicrobials in human medicine have greatly accelerated antimicrobial resistance. Physicians may prescribe the drugs too frequently or for the wrong reasons (e.g., prescribing antibiotics to treat viral infections, which do not respond to the drugs). Patients may not complete their prescribed courses of an antimicrobial, making it more likely the surviving microbes will develop resistance.²⁴ Sometimes, antimicrobials are used as preventive measures, for example, before surgeries to ward off infections or prior to travel to avert traveler's diarrhea. Hospital medical staff appear to contribute to resistance through improper sanitary practices like inadequate hand washing or instrument cleaning.

Another route of resistance is the release of antibiotics into the environment (e.g., through runoff from farm waste). Studies have found that some pharmaceuticals, including antibiotics, are not completely used in human or other animal bodies and can be passed into the sewage system, where treatment does not break them down completely. Significant concentrations of certain drugs have been reported in drinking water, for example. Testimony presented in 2008 to a Senate committee cited several studies that found antimicrobial-resistant bacteria in groundwater sampled near hog farms.²⁵

Many foodborne bacteria that can cause disease in humans, such as *Salmonella*, *Campylobacter*, and strains of *E. coli* including O157:H7, are found in the intestinal tracts of healthy food-producing animals like swine, poultry, and cattle. According to FDA, "When an animal is treated with an antimicrobial drug, a selective pressure is applied to all bacteria exposed to the drug. Bacteria that are sensitive to the antimicrobial are killed or put at a competitive disadvantage, while bacteria that have the ability to resist the antimicrobial have an advantage and are able to grow more rapidly than the more susceptible bacteria."²⁶ Resistant bacteria can then be transferred to the human population through either direct contact with the animals or through

²² See, for example, J. F. Acar and G. Moulin, "Antimicrobial resistance at farm level," *Rev. sci. tech. Off. int. Epiz.*, 2006, 25(2), 775-792.

²³ CDC, "Antibiotic Resistance 101."

²⁴ Sharfstein testimony.

²⁵ Jay P. Graham, Research Fellow at the Johns Hopkins Bloomberg School of Public Health, June 28, 2008 testimony before the Senate Health, Education, Labor, and Pensions Committee.

²⁶ FDA, Center for Veterinary Medicine (CVM), *Judicious Use of Antimicrobials for Swine Veterinarians*, and *Judicious Use of Antimicrobials for Poultry Veterinarians*, <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/default.htm>.

consumption of improperly handled food from them. FDA “believes that human exposure through the ingestion of antimicrobial resistant bacteria from animal-derived foods represents the most significant pathway for human exposure to bacteria that have emerged or been selected as a consequence of antimicrobial drug use in animals.”²⁷

According to FDA, an estimated 80% of the estimated 2.5 million annual human cases of illness from campylobacteriosis are foodborne, and 95% of the 1.4 million annual human cases from non-typhoidal salmonellosis are foodborne. When the bacteria are also resistant to antimicrobial drugs, public health can be compromised. For example, despite regulatory restrictions on the use of two FDA-approved fluoroquinolone products, ciprofloxacin-resistant *Campylobacter* were found in 20% of retail chicken product samples. Further, molecular subtyping showed an association between resistant strains of bacteria found in chicken products and in human cases of campylobacteriosis.²⁸

In 1996 the CDC began a new effort to collect antimicrobial resistance data in collaboration with FDA and the U.S. Department of Agriculture (USDA). The effort, the National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria, is charged with monitoring antimicrobial resistance among foodborne bacteria isolated from humans. The most recent published report includes surveillance data for 2006 for clinical non-Typhi *Salmonella*, *Salmonella* ser. Typhi, *Shigella*, *Campylobacter*, and *E. coli* O157 isolates.²⁹ The NARMS reported that:

- 19.6% (160 out of 816) of *Campylobacter* isolates were resistant to the fluoroquinolone ciprofloxacin, compared with 12.9% (28 out of 217) in 1997;
- 2.7% (60 out of 2,184) of non-Typhi *Salmonella* isolates were resistant to the quinolone nalidixic acid, compared with 0.4% (5 out of 1,324) in 1996;
- 3.6% (79 out of 2,184) of non-Typhi *Salmonella* isolates were resistant to the third-generation cephalosporin ceftiofur, compared with 0.2% (2 out of 1,324) in 1996;
- 54.0% (175 out of 324) of *Salmonella* ser. Typhi isolates were resistant to the quinolone nalidixic acid, compared with 19.2% (32 out of 167) in 1999.

FDA has observed that “[d]efinitive answers about the safety of antimicrobial use in animals remain scientifically challenging, but more information is accumulating that raises concerns about food safety.” The agency also cited earlier studies from the Netherlands, the United Kingdom, and Spain indicating temporal relationships between ciprofloxacin-resistant *Campylobacter* and approval of fluoroquinolones for food-producing animals, for example.³⁰

²⁷ FDA, *Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern*, Guidance for Industry #152, October 23, 2003, p. 3.

²⁸ *Judicious Use of Antimicrobials for Swine Veterinarians*, and *Judicious Use of Antimicrobials for Poultry Veterinarians*. In 2005, FDA withdrew its approval of Baytril, a fluoroquinolone related to the human drug Cipro, in poultry (which it first proposed to do in 2000), after it concluded that the drug played a role in promoting antibiotic resistance among *Campylobacter* infections in humans. See <http://www.fda.gov/AnimalVeterinary/SafetyHealth/RecallsWithdrawals/ucm042004.htm>.

²⁹ Data can be accessed at <http://www.cdc.gov/NARMS/>.

³⁰ *Judicious Use of Antimicrobials for Swine Veterinarians*, and *Judicious Use of Antimicrobials for Poultry Veterinarians*.

Others believe that the scientific evidence regarding the relationship between animal antibiotics use and human health risk is subject to differing interpretations. The AVMA, while acknowledging the need for prudent use of such drugs, has called such evidence “limited and conflicting.”³¹ The organization and others argue that leveling a ban on those now in use, particularly before conducting additional studies and risk-based evaluations, would be detrimental to both animal and human health.

The AVMA and others have pointed to the experience in Europe, where the European Union (EU) phased out antimicrobials for animal growth promotion as of January 1, 2006.³² Among EU members, Denmark implemented a voluntary ban on the use of antimicrobials for growth promotion in 1998 and a mandatory ban in 2000. This ban, which was not extended to the use of these drugs for control and treatment of disease, “has not resulted in significant reduction of antibiotic resistance patterns in humans. It has, however, resulted in an increase in disease and death in swine herds and an increase in the use of antimicrobials for therapeutic uses in swine herds that discontinued the use of antibiotic growth promoters,” according to the AVMA.³³

Such observations are based on data published in annual reports on the antimicrobial situation by the Danish government.³⁴ Others have offered differing interpretations of the data. The Pew Environment Group reported that an updated assessment of the impacts of Denmark’s ban shows that although therapeutic use of antibiotics increased slightly after the ban, it has leveled off since 2003, and total antibiotic consumption has decreased significantly. The assessment also shows limited if any long-term effects on overall productivity in the swine herd, and a decrease in antimicrobial resistance has followed reduced use.³⁵

Meanwhile, the United States is participating with other member countries in a Codex Alimentarius Commission Ad Hoc Intergovernmental Task Force on Antimicrobial Resistance aimed at helping to develop guidelines to assess human health risks associated with the presence of antimicrobial resistant agents transmitted through food and feed. Codex, which established the task force in 2006, is the international standards body for food safety. The United States in September 2009 submitted its comments on proposed draft guidelines to be discussed at an October 2009 task force meeting in Korea.³⁶

³¹ AVMA, “Judicious Therapeutic Use of Antimicrobials,” accessed July 21, 2009, at <http://www.avma.org/issues/jtua/default.asp>.

³² This phase-out is delineated under Article 11 of European Parliament and Council Regulation No. 1831/2003, on additives for use in animal nutrition, at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:268:0029:0043:EN:PDF>.

³³ Lyle Vogel, DVM, MPH, DACVM, AVMA, June 24, 2008, testimony before the Senate Health, Education, Labor, and Pensions Committee.

³⁴ The most recent report is DANMAP 2007—Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. DANMAP is the Danish acronym for the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme. The annual reports can be accessed at <http://www.danmap.org/>.

³⁵ Robert P. Martin, Senior Officer of the Pew Environment Group and former Executive Director of the Pew Commission on Industrial Farm Animal Production, July 13, 2009 testimony before the House Rules Committee. Martin’s testimony states that these new findings recently had been presented to a producers conference in Kansas by a Danish health official and would be published later in 2009 in the Journal of the AVMA.

³⁶ For information and links, see the FSIS September 9, 2009, news release “Public Meeting to Address Agenda Items for the 3rd Session of the Codex Ad Hoc Intergovernmental Task Force on Antimicrobial Resistance,” at http://www.fsis.usda.gov/News_&_Events/NR_090909_01/index.asp.

Regulatory Approach

The FDA's Center for Veterinary Medicine (CVM) is responsible for regulating the manufacture and distribution of drugs and food additives for all animals, including food animals, under authority of the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended.³⁷ CVM approves new animal drugs, using criteria similar to those in the approval process for human medicines, with the intent of ensuring their safety and effectiveness.

Generally, animal drug approval, including for antimicrobials, is conducted under two processes. The first process involves the submission by the drug's manufacturer or sponsor of an application for an investigational new animal drug (INAD) exemption to conduct pre-approval clinical trials. The second process is the new animal drug application (NADA) review. The review includes the evaluation not only of its safety and effectiveness for the intended animal, but also, for a food animal, its safety to humans who might consume food from the animal. Among the required tests for an animal drug not required for a human one is how much time is necessary for drug residues to leave the animal's body (withdrawal time), to ensure that antibiotic residues are not in food products made from it. A new animal drug product cannot be marketed without NADA approval.³⁸

The FDA issued in October 2003 a guidance document reflecting its "current thinking" regarding its assessment of the safety to humans of antimicrobial animal drugs.³⁹ *Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern* (Guidance #152) focuses specifically on food safety, and in particular on the risk that foodborne pathogens that contaminate these products will be resistant to antimicrobial drugs that were used in the food-producing animal. The guidance does not address other effects of antimicrobial animal drug use, such as from environmental runoff, or the question of antimicrobial residues that may be present in the food products. The latter hazard is addressed in several other FDA guidance documents.

An assessment of the potential public health effects of the use of antimicrobial animal drugs is challenging in at least three ways. First, drug sponsors cannot readily explore potential public health effects of animal drugs through premarket clinical trials, as the trials are not conducted on humans. Second, antimicrobial resistance is a hazard that sometimes develops only after an antimicrobial drug is approved and becomes widely used; it is not necessarily a hazard that exists and can be studied during the approval process. Third, the causal pathways by which uses of an antimicrobial animal drug may lead to antimicrobial resistance in microbial pathogens, and thereby cause or worsen human illness, are often poorly understood, or may be difficult to document because relevant data are not available. Guidance #152 is the agency's effort to clarify, for drug sponsors, its approach to these challenges, using qualitative risk assessment.

³⁷ Primary authority is at FFDCA § 512 [21 U.S.C. 360(b)].

³⁸ FFDCA § 512(d), regarding review of animal drug applications, provides grounds for denying approval, including tests that show the drug is unsafe, or the determination that there is insufficient information as to whether the drug is safe. Applicable regulations are at 21 CFR 514.1(b)(8). For a fuller explanation of the approval process, see Appendix B of CRS Report RL34459, *Animal Drug User Fee Programs*, by Sarah A. Lister.

³⁹The following discussion of Guidance #152 is adapted from material prepared in 2008 by Sarah A. Lister, CRS Specialist in Public Health and Epidemiology. The guidance document can be viewed at this FDA web page: <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf>.

Guidance #152 provides a step-wise approach that comports with international standards.⁴⁰ First, FDA recommends that drug sponsors submit a hazard characterization, providing basic information about the drug, its uses and mechanisms of action, mechanisms for the emergence of resistance in target and non-target microbes, the importance of the drug in human medicine, the state of scientific information and knowledge gaps about the drug and antimicrobial resistance, and related information. Based on the hazard characterization, FDA could potentially (1) provide more specific guidance regarding the conduct of the subsequent risk assessment; (2) determine that a risk assessment was not necessary to demonstrate the drug's safety; or (3) determine that such a demonstration was not likely to be made, and that the application was not likely to succeed.

Next, the three steps in the qualitative risk assessment are (1) a *release assessment* to estimate the probability that the proposed use of the antimicrobial new animal drug in food-producing animals will result in the emergence or selection of resistant bacteria in the animal; (2) an *exposure assessment* of the likelihood of human exposure to foodborne bacteria of human health concern through particular exposure pathways, in this case through foods of animal origin; and (3) a *consequence assessment* regarding the importance of the antimicrobial animal drug or its analogs in human medicine, though a sponsor may use alternate data if it believes it to be more current or otherwise superior. This process yields an FDA ranking of each antimicrobial drug according to its importance in human medicine, as "critically important," "highly important," or "important." Outputs are then to be integrated into an overall risk estimation, using a matrix provided in the guidance. The risk estimation would yield an overall assessment of the public health risk associated with the proposed conditions of use of the drug, ranked as high (Category I), medium (Category II), or low (Category III).

Guidance #152 says that an advisory committee may be convened to evaluate the applications of Category I and selected Category II antimicrobial animal drugs. The guidance then lays out a risk management strategy for approved antimicrobial animal drugs, noting that even a Category I classification would not necessarily result in the denial of approval, but would likely require appropriate (and perhaps more stringent) risk management steps. These steps may include limiting the conditions, including duration, of use; requiring veterinary supervision (versus, for example, over-the-counter marketing); prohibiting extra-label uses;⁴¹ and postmarket monitoring of microbial resistance to the drug, possibly through NARMS.

After Guidance #152 was published, FDA convened its Veterinary Medicine Advisory Committee (VMAC) in September 2006 to consider an application for cefquinome, an antibiotic to be used in beef cattle. The drug's sponsor presented its risk assessment according to the guidance, concluding that the proposed uses placed the drug in Category II (medium risk), and recommending that the drug be approved, with certain postmarket risk management steps. The

⁴⁰ FDA cites a 2001 method for antimicrobial risk analysis published by the Office of International Epizootics (OIE), the international animal health standard-setting and harmonization organization, of which the United States is a member.

⁴¹ "Extra-label use," which is similar to "off-label use" of drugs in humans, is defined by FDA (at 21 C.F.R. 530) as "[a]ctual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease and other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from labeled withdrawal time based on these different uses." Such use is by definition a prescription drug use, and is only permitted within the scope of a valid veterinarian-client-patient relationship. Extra-label use is limited to circumstances when the health of an animal is threatened by failure to treat; therefore, extra-label use to enhance production is prohibited.

VMA instead voted against approving the drug. FDA, which does not have to abide by the committee's recommendation, had not approved the drug as of December 2009.

The trajectory of the cefquinome application highlights the challenging and evolving regulatory approach to the safety of antimicrobial animal drugs. The drug's sponsor reached a conclusion of medium risk using guidance that it called conservative, leaning toward greater safety when evidence was insufficient. Consumer representatives asserted that the guidance should have given the drug a higher consequence risk ranking, which would have yielded a higher overall risk ranking.⁴² Industry representatives asserted that members of the committee strayed from the methodical constraints of the guidance in reaching their individual conclusions.

The FDA also has developed a series of species-specific educational materials for veterinarians based on 15 AVMA-developed "Guidelines for the Judicious Therapeutic Use of Antimicrobials." These guidelines range from employing where possible non-drug preventive strategies such as appropriate husbandry and hygiene to using the narrowest-spectrum antimicrobials whenever appropriate.⁴³ At its annual meeting on July 10, 2009, the AVMA House of Delegates reportedly voted to create a steering committee to reassess its policy regarding judicious use, a process that could take a year to complete.⁴⁴

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⁴² Martin of the Pew Environment Group stated in his House testimony that most animal antibiotics in nontherapeutic use were approved before the FDA began considering the resistance question, and that the agency has not established a schedule for reviewing existing approvals, even though Guidance #152 notes the importance of doing so.

⁴³ For details see <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/default.htm>.

⁴⁴ "AVMA votes to reassess antimicrobial policy," *Food Chemical News*, July 27, 2009.