

TREADING THE PATH OF LEAST RESISTANCE:

**FDA'S REGULATION OF THE SUBTHERAPEUTIC USE OF
ANTIBIOTICS IN ANIMAL AGRICULTURE, 1970-2015**

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ABBREVIATIONS

AAFCO	Association of American Feed Control Officials
AFIA	American Feed Industry Association
APHIS	Animal and Plant Health Inspection Agency
AVMA	American Veterinary Association
BVM	Bureau of Veterinary Medicine (renamed Center for Veterinary Medicine)
CDC	Centers for Disease Control and Prevention
CVM	Center for Veterinary Medicine (formerly Bureau of Veterinary Medicine)
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
FD&C	Federal Food, Drug, and Cosmetics Act
FSIS	Food Safety Inspection Service
GAO	Government Accountability Office (formerly General Accounting Office)
GFI	Guidance for Industry
GRAS	Generally Recognized as Safe
IOM	Institute of Medicine of the National Academy of Sciences
NARMS	National Antimicrobial Resistance Monitoring System
NAS	National Academy of Sciences
NRDC	Natural Resources Defense Council
OTA	Office of Technology Assessment
PAMTA	Preservation of Antibiotics for Medical Treatment Act
USDA	U.S. Department of Agriculture
VMAC	Veterinary Medical Advisory Committee of the Food and Drug Administration
WHO	World Health Organization

INTRODUCTION

The American food system presents a complex intersection of some of the most critical environmental and health concerns of the modern day, creating unique challenges for regulators. Regulatory bodies face a complicated and ever-evolving system in which the public health impact and economic stakes are high — a system that must be carefully balanced when responding to new evidence of risk. Nevertheless, regulation of the food system remains understudied by political scientists.

The challenges and complexities of the food system are no more evident than in the animal feed industry, where ingredients are grown, rendered, manufactured, and processed by a diverse and geographically dispersed set of producers, and combined with pharmaceuticals designed to promote growth, increase feed efficiency, and prevent disease in food-producing animals. Some of these pharmaceuticals are added to medicated feeds at the mills and distributed to farmers by feed companies, while others are available for livestock producers to purchase over the counter and add to feed premixes, or via prescription by a veterinarian. Because many feed ingredients and recipes are considered proprietary information, little information is available to those outside the industry regarding the origin and composition of animal feed. Efforts to regulate animal feed ingredients are complicated not only by the complexity of the industry and the feed itself, but also by the diverse set of political and regulatory actors involved.

This paper examines the regulatory challenges posed by the food system by taking an in-depth look at the regulatory history behind a component of animal feed that has faced intense scientific and political scrutiny for decades: the routine use of subtherapeutic doses of antibiotic drugs. This paper pieces together the U.S. Food and Drug Administration's (FDA) regulation of the use of antibiotics in animal feed over more than forty years, beginning with the

commercialization of the first antibiotic feed supplement and early concerns about antibiotic resistance, and ending with FDA's most recent regulatory action on this issue in 2015. A longitudinal case study of this subject allows for a thorough examination of FDA's behavior on a single issue over time, and tells the story of a practice that has garnered a great deal of attention by politicians, scientists, industry actors, regulators, and the press at times, but which has largely been told in bits and pieces. By developing this case historically, this paper sheds light on the key factors that affect FDA decision-making, focusing on how FDA weighs the costs and benefits of an action based on internal and external pressures, and how the agency decides to substitute actions that are more informal or formal based on this cost/benefit calculus. I examine in close detail the significant moments in FDA's decision-making in order to analyze the influence of various stakeholders, as well as the political and budgetary costs of a potential action, on the agency at these crucial points. Studying the agency's shifting calculus over the course of several decades allows us to draw conclusions about how FDA makes decisions in this complex political, regulatory, and scientific landscape. Analysis of this case indicates that FDA's ability to regulate the food system is severely constrained by its need to limit political and budgetary costs by responding to the needs of a diverse set of stakeholders, leading to long delays in addressing health risks, such as antibiotic resistance. These conclusions have important implications for those who wish to stimulate or prevent agency action on this issue or others; a deeper understanding of the factors that motivate FDA's behavior can allow stakeholders to more effectively influence regulatory outcomes.

This paper is divided into four chapters. The first supplies the context for the case study by providing background on the animal feed industry and its regulation, including FDA's statutory authority to regulate animal feed and veterinary pharmaceuticals, as well as the

responsibilities of other agencies participating in animal feed regulation. The second chapter addresses theories of regulatory behavior and explains the theoretical framework of agency decision-making that will be employed in the examination of the case. The third chapter delves into the regulatory history of the use of subtherapeutic levels of antibiotics in animal feed, applying the theory from chapter two to analyze FDA's decision-making on the issue over the past several decades. The fourth chapter summarizes the conclusions that can be drawn from the case and the lessons that can be learned about how and why FDA and other agencies make regulatory decisions in the context of complex political, economic, and scientific environments.

CHAPTER 1: REGULATION IN CONTEXT: ANIMAL FEED AND ITS REGULATORY ENVIRONMENT

FDA's regulation of the subtherapeutic use of antibiotics in animal feed takes place in a larger context that poses many challenges for the agency. The food system comprises many complicated industries and actors, particularly in the realm of food animal production and the animal feed industry. This context is further complicated by the patchwork regulatory structure in which the food system is situated. This chapter aims to place the ensuing case in the broader context of the complex food system FDA must navigate by providing background about the animal feed industry and its regulation.

The Animal Feed Industry

The study of animal feed poses many challenges for researchers, mostly due to the lack of publicly available information on feed ingredients, formulation, and sales. Little data is collected at the local, state, or federal level regarding the details and proportions of ingredients in different

feed formulations, and virtually no chemical or biological testing is done on the finished products.¹ As a result, information on feed content is incomplete, and relies on previous studies and the limited data available.

One reason for the paucity of information surrounding animal feed is that much of the specific data on types and amounts of ingredients is considered proprietary information of the feed industry. The U.S. feed industry is a major supplier of animal feed globally, producing 173 million metric tons of feed in 2014, which represents 17 percent of the total global feed production.² The animal agriculture industry as a whole contributed \$371 billion to GDP and 1.98 million jobs in 2013, making it a major player in the U.S. economy.³ The animal pharmaceutical industry, which manufactures a wide range of products for agricultural use, including feed-grade antibiotics, is also a powerful economic force. In 2010, these companies sold \$6.8 billion in total animal health products in the U.S. alone.⁴ Many of the top animal pharmaceutical producers are owned by the biggest players in the pharmaceutical industry as a whole, including Novartis, Bayer, and Merck.⁵ The animal pharmaceutical industry is represented by the Animal Health Institute, which has been an active player in the regulatory battle over animal antibiotics for decades.

In the U.S., the feed industry is represented by the American Feed Industry Association (AFIA), with more than 75 percent of commercial feed in the U.S. produced by its members.⁶ The industry comprises a number of different types of suppliers, including rendering plants,

¹ Amy R. Sapkota et al., “What do we feed to food-production animals? A review of animal feed ingredients and their potential impacts on human health,” *Environmental Health Perspectives* 115.5 (2007): 667.

² International Feed Industry Federation, *International Feed Industry Federation Annual Report, 2014/15*.

³ American Feed Industry Association, “Feed Industry Statistics.” <http://www.afia.org/feedindustrystats>.

⁴ Animal Health Institute, “Industry Statistics: Animal Medicines by the Numbers.” <http://www.ahi.org/about-animal-medicines/industry-statistics/>.

⁵ Animal Health Institute, “Member Organization.” <http://healthyanimals.org/members/>.

⁶ International Feed Industry Federation, *International Feed Industry Federation Annual Report, 2014/15*.

grain elevators, farmers, distillers, and non-food industries.⁷ Feed is produced primarily in three types of facilities: commercial plants that produce feed for sale, integrated operations that produce feed for their own animals, and cooperative facilities owned jointly by farmers to produce feed for their animals.⁸ In 2015, the FDA reported that there were 6,012 total feed mills in the U.S., with 1,005 facilities producing medicated feed.⁹ Raw ingredients for commercial mills come from a variety of different sources, typically purchased through brokers who procure ingredients from farmers, elevators, and processors.¹⁰ Because of the fragmented and varied nature of industry players, it is difficult to gather accurate information on ingredient sourcing and processing.

Over the past several decades, the animal feed industry has changed dramatically, largely related to the industrialization of animal agriculture as a whole. The driving factor of these changes has been an economic motivation to bring animals used for human food up to the desired weight as quickly and inexpensively as possible.¹¹ Because feed costs are a huge portion of most livestock operations' overall expenditures, there are significant incentives to bring down the cost of feed. In the poultry industry, for example, feed costs make up nearly 70 percent of total broiler production costs, making feed efficiency a central concern.¹² Innovation in feed ingredients and feeding practices, as well as the availability of scientifically formulated feed products, have improved feed efficiency dramatically over the past several decades. The concentration and intensification of animal agriculture as a whole has led to several structural

⁷ Johns Hopkins Center for a Livable Future. *Feed for Food-Producing Animals: A Resource on Ingredients, the Industry, and Regulation* by Lisa Y. Lefferts, Margaret Kucharski, Shawn McKenzie, and Polly Walker (Baltimore, MD 2007), 4.

⁸ *Ibid.*

⁹ "Feed Industry Statistics." <http://www.afia.org/feedindustrystats>.

¹⁰ Johns Hopkins Center for a Livable Future. *Feed for Food-Producing Animals*, 5.

¹¹ *Ibid.*

¹² David Wallinga, *Playing Chicken: Avoiding Arsenic in Your Meat*, Institute for Agriculture and Trade Policy (2006): 11.

trends in the feed industry in recent years, including increased production of feed concentrates and a trend towards larger, more integrated plants.¹³ The trend of consolidation in livestock production has been mirrored by a concentration in feed production both geographically and economically, with a large number of acquisitions and mergers occurring in the past two decades as the industry shifted away from the smaller, decentralized operations of the 1970s and 1980s.¹⁴ By 2003, the top three feed manufacturers in U.S. made up 20 percent of the market.¹⁵ Increased concentration has been accompanied by vertical integration, particularly in the poultry industry, where major firms often have massive, in-house feed mills inside their concentrated feeding operations.¹⁶

Another significant trend in the industry is the increased use of antibiotics and other growth-promoting substances in feed, which is driven by economic incentives to increase feed efficiency and is linked more broadly to the intensification and concentration of livestock operations over the past few decades. Because livestock operations have become increasingly confined, producers face increased risk of pathogens that can spread through a large number of hosts at a rapid pace due to the crowding and the presence of animal waste in these facilities.¹⁷ As a result, it has become common practice to administer antibiotics for disease prevention, often at subtherapeutic levels.¹⁸ Though the line between therapeutic and subtherapeutic doses of antibiotics is not always clear, subtherapeutic use refers to the administration of antibiotics at a dosage less than that which would be required to treat disease. Antibiotics have also become common feed ingredients for poultry, swine, and cattle to increase feed efficiency and promote

¹³ Johns Hopkins Center for a Livable Future. *Feed for Food-Producing Animals*, 6.

¹⁴ *Ibid.*; Vincent Amanor-Boadu and Kara Ross, *Industry Trend Report: Animal Feed Manufacturing*, (May 2011).

¹⁵ Johns Hopkins Center for a Livable Future. *Feed for Food-Producing Animals*, 6.

¹⁶ *Ibid.*

¹⁷ Ellen K. Silbergeld, Jay Graham, and Lance B. Price, "Industrial Food Animal Production, Antimicrobial Resistance, and Human Health." *Annual Review of Public Health* (2008) 29: 153.

¹⁸ Sapkota et al. (2007): 667.

growth.¹⁹ Modern livestock feed typically contains several other ingredients specifically targeted at growth promotion and feed efficiency, including metal compounds such as organoarsenicals in poultry feed.²⁰ According to the feed industry, the inclusion of these ingredients in feed has been a major factor in the significant improvements in feed efficiency that have occurred over the past fifty years.²¹

While ingredients targeted at improving feed efficiency have cut costs for livestock producers by reducing the amount of feed they need to purchase to achieve the same growth results, the feed industry has also looked to new sources of protein, roughage, and nutrients to cut costs. As a result, waste from various other industries as well as from animals has become an increasingly important component of animal feed.²² The use of waste byproducts, often referred to as “recycling,” has long been a practice of commercial feed production,²³ but trends in animal agriculture have driven feed producers to rely on rendering products, animal waste, and byproducts from a variety of industries as ingredient sources.²⁴ The use of animal waste has been driven in part by the intensification of animal agriculture, as confined operations can no longer only rely on local croplands to absorb the large quantities of waste produced by these facilities. Thus, producers have seen the use of waste in animal feed as an economical alternative to its use as fertilizer.²⁵ The following section provides a more detailed discussion of these “recycled” ingredients.

Recent trends in the animal feed industry are linked to the intensification of animal agriculture over the past several decades. Demand for commercial feed blends and faster growth

¹⁹ Silbergeld et al. (2008): 153.

²⁰ Sapkota et al. (2007): 665.

²¹ Johns Hopkins Center for a Livable Future. *Feed for Food-Producing Animals*, 6.

²² Johns Hopkins Center for a Livable Future. *Feed for Food-Producing Animals*, 7.

²³ Sarah Muirhead, “Structure of Feed Industry Has Evolved to Meet Needs of Producers, Consumers; From a User of By-products to a Science-based Industry,” *Feedstuffs* 75.34 (2003): 14.

²⁴ Johns Hopkins Center for a Livable Future. *Feed for Food-Producing Animals*, 7.

²⁵ *Ibid.*

have led to a feed industry that is more concentrated economically and geographically than at any other time over the past century, and feed is formulated by combining a careful balance of ingredients to optimize feed efficiency and growth promotion. Understanding these trends in feed production and animal agriculture is critical to appreciating the challenges facing agencies charged with regulating this complex and evolving industry.

An Overview of Animal Feed Ingredients

Animal feed is formulated using a wide range of ingredients from diverse sources, and little official information is collected on the nature and amounts of these ingredients. Part of the challenge in regulating this industry lies in the complexity of animal feed formulation. This section will provide a basic overview of the types of ingredients used in modern animal feed to provide context for an analysis of how ingredients are regulated.

Figure 1 provides a summary of the major sources of ingredients for animal feed and gives several examples, though it is not a comprehensive list. Most substantial ingredients are of either plant or animal origin, though they are derived from a wide variety of sources. Many ingredients are byproducts of commercial production in other industries, which poses challenges for regulators seeking to understand risk pathways. For example, distiller grain byproducts from corn ethanol fuel production are widely used in animal feed, and often contain the antibiotics used in ethanol production to manage bacterial outbreaks in fermentation vats, according to FDA testing.²⁶ Because distiller grains are not recognized from a regulatory perspective as a source of antibiotics in animal feed, they are not considered when determining the types of allowable dosages of antibiotics placed directly in feed. Similar concerns related to pesticide and drug residues accompany the use of wastes from other industries.

²⁶ Center for Food Safety, *Factory Farms: Antibiotics in Distiller Grains*, (2013).

Figure 1: Overview of Animal Feed Ingredients²⁷

Origin	Types of Ingredients
Plant	<ul style="list-style-type: none"> • <i>Grains</i> (corn, sorghum, wheat, barley, oats); • <i>Forage</i> (Alfalfa meal and hay); • <i>Grain by-products</i>, including distiller grains, brewer's yeast, corn gluten, etc.; • <i>Processed meals and cakes</i>, such as from soybean, peanut, canola, cottonseed; • <i>Miscellaneous</i> (dried fruit pulp, molasses, almond hulls and ground shells, banana peels).
Animal	<ul style="list-style-type: none"> • <i>Rendered animal protein</i> (from slaughtered animals or other dead or diseased animals), including meat by-products, hydrolyzed poultry feather, meat and bone meal, blood meal, unborn calf carcasses, ensiled paunch; • <i>Animal Waste</i> (dried poultry litter, dried ruminant waste, dried swine waste); • <i>Marine by-products</i> (fish meal, fish oil, fish liver and glandular meal); • <i>Dairy products</i> (dried cow milk, casein, whey products);
Mixed	<ul style="list-style-type: none"> • <i>Fats and oils</i> (animal fat, vegetable oil, hydrolyzed fats); • <i>Restaurant food waste</i> (edible food waste, including plate waste, collected from restaurants, dairies, and cafeterias); • <i>Contaminated or adulterated food</i> (food originally intended for humans that has become adulterated with rodent, roach, or bird excreta and that has been heat-treated to destroy pathogenic organisms);
Other (mineral, microbial, or synthetic)	<ul style="list-style-type: none"> • <i>Antibiotics</i> • <i>Non-protein nitrogen</i> (urea, anhydrous ammonia); • <i>Polyethylene plastic</i> in pellet form (used as roughage substitute); • <i>Minerals</i> (including mineral mixes) and <i>vitamins and vitamin-containing oils</i> (shark oil, cod liver oil); • <i>Probiotics</i> (direct-fed microorganisms, such as <i>Aspergillus niger</i>, <i>Bacillus subtilis</i>, <i>Bifidobacterium animalis</i>, <i>Enterococcus faecium</i>, yeast) and <i>enzymes</i> (lipase, pepsin); • <i>Flavors</i> (aloe vera gel, ginger, capsicum, fennel) • <i>"Generally recognized as safe" (GRAS) ingredients</i> • <i>Neutraceuticals and other dietary supplements</i>

The use of ingredients of animal origin adds another layer of complexity for regulators, as this provides an additional pathway for potentially unrecognized or unwanted substances in feed. Drugs or other ingredients used under certain circumstances for a particular animal could

²⁷ Information adapted from Sapkota et al. (2007) and Johns Hopkins Center for a Livable Future, *Feed for Food Producing Animals* (2007).

get into the feed of another if that substance is present in the animal matter used in its feed, whether it accumulates in the animal's body or is excreted in its waste. Additionally, poultry feed is often spread or spilled on the floor of feeding operations, such that it becomes mixed with the litter that is later used in feed for other animals. The complexity of sources and ingredients used in modern feed formulation presents many challenges for regulators in determining which substances are present and assessing the various pathways in which controlled substances could enter feed.

Federal Regulation

The regulation of animal feed in the U.S. involves a number of federal, state, and industry actors. FDA is the primary agency at the federal level charged with animal feed regulation, but a number of other federal agencies, state officials, and industry groups carry out regulatory activities as well. In order to understand the factors that affect FDA's regulatory actions, it is critical to understand the regulatory context in which FDA operates. This section aims to provide an overview of the regulatory landscape for animal feed and identify any gaps or overlaps in this system.

The Federal Food, Drug, and Cosmetic (FD&C) Act charges FDA with regulating animal feed ingredients and additives, and this responsibility is handled by FDA's Center for Veterinary Medicine (CVM).²⁸ Animal feed and feed ingredients are regulated as foods, food additives, or drugs based on the properties and the claims made about the product.²⁹ Feed or feed ingredients regulated as "food" are considered safe, and thus do not require pre-market approval.³⁰ This category includes ingredients such as grains and hays, as well as some

²⁸ Federal Food, Drug, and Cosmetic Act, 21 U.S.C. ch. 9 (1938).

²⁹ Johns Hopkins Center for a Livable Future, *Feed for Food-Producing Animals*, 8.

³⁰ *Ibid.*

adulterated human food. Feed ingredients classified as drugs under the Act face more rigorous regulation. A feed ingredient is classified as a drug based on its intended use, which is determined based on claims made about that product on the product's approved label.³¹ Ingredients that claim to prevent, treat, cure, or mitigate disease, or affect the structure or function of the body (including increasing leanness, growth, or efficiency of gain) are considered drugs under the Act.³² Because this designation is based solely on claims made about the product, ingredients that contain drug residues but are not intended for such a purpose are not classified as drugs. As a result, feed ingredients such as distiller grains, which often have significant traces of antibiotics, are regulated as "food" and not seen as a source of a drug that is more restrictively regulated.

Under section 512(a)(1) of the FD&C Act, FDA must approve all new animal drugs before they can be marketed. In order to approve a new animal drug use, FDA must make a determination of safety based on a weighing of risks and benefits, and establish that there is a "reasonable certainty of no harm" with regard to food produced from treated animals under the intended conditions of use.³³ Section 512(d)(1)(B) explicitly prohibits FDA from approving a drug use if the evidence "does not show that such drug is safe for use."³⁴ If new evidence becomes available after approval that indicates that the drug use is not safe, FDA is required to notify the sponsor, provide opportunity for a hearing, and, if the sponsor fails to provide

³¹ Johns Hopkins Center for a Livable Future, *Feed for Food-Producing Animals*, 8.

³² U.S. Food and Drug Administration, Center for Veterinary Medicine, "General Review and Enforcement Policies: Regulating Animal Foods with Drug Claims," in *Center for Veterinary Medicine Program Policy and Procedures Manual* (1998).

³³ Michael R. Taylor, "Re: Docket No. FDA-2009-P-0594," U.S. Food and Drug Administration, September 30, 2013.

³⁴ *Ibid.*

sufficient evidence of safety at this hearing, FDA must issue an order withdrawing approval for that drug use.³⁵

Ingredients not classified as food or drugs are regulated as feed additives unless the ingredient is generally recognized as safe (GRAS).³⁶ Approved food additives have met the criteria for safety based on a review of available scientific evidence, and are subject to limited regulation.³⁷ A substance may be considered GRAS if it has been commonly used in feed prior to January 1, 1958 or based on an evaluation of available scientific evidence by experts.³⁸ The FDA does not publish a full list of approved feed additives or GRAS ingredients, but the most complete list can be found in the Association of American Feed Control Officials (AAFCO) Official Publication.³⁹

In addition to approving and regulating feed ingredients, the FDA also regulates all drug use in animals producing food for human consumption, inspects feed mills producing medicated feed, and monitors labeling and marketing materials.⁴⁰ The FDA can carry out its regulatory activities by using a number of tools, including formal rulemaking, adjudication, and informal guidance. As in many of their other regulatory areas, the FDA has increasingly relied on informal guidance to carry out its regulatory activities in animal feed in recent years. While informal guidance has several advantages for the FDA, particularly its relatively low cost compared to rulemaking or adjudication and the greater flexibility it allows, it is non-binding and thus does not carry the force and effect of law in the way that more formal procedures do.⁴¹

³⁵ Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §512(e)(1) (1938).

³⁶ “Animal Food & Feeds: Ingredients & Additives,” U.S. Food and Drug Administration.
<http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/IngredientsAdditives/default.htm>.

³⁷ Determination of Food Additive Status, 21 C.F.R. §570.38.

³⁸ Eligibility for classification as generally recognized as safe (GRAS), 21 C.F.R. §570.30.

³⁹ U.S. Food and Drug Administration, *Memorandum of Understanding between the United States Food and Drug Administration and the Association of American Feed Control Officials*, MOU 225-07-7001 (2015).

⁴⁰ Johns Hopkins Center for a Livable Future, *Feed for Food-Producing Animals*, 9.

⁴¹ KM Lewis, “Informal Guidance and the FDA,” *Food and Drug Law Journal* 66.4 (2011):507-50.

FDA's choice of regulatory tools and a weighing of their costs and benefits will be discussed more fully in subsequent chapters.

Several other federal agencies are also involved in issues related to animal feed. The U.S. Department of Agriculture (USDA) is not directly charged with regulating animal feed, but its regulatory activities involving livestock and poultry often have an impact on feed. The USDA monitors both imported and domestic animals and animal products as part of its mandate, through the USDA Food Safety Inspection Service (FSIS) and the USDA Animal and Plant Health Inspection Service (APHIS), both of which can involve animal feed. USDA regulations were particularly important in the animal feed industry during the early 2000s, when there was concern about Bovine Spongiform Encephalopathy in cattle and the potential for this disease to be spread through animal feed.⁴² The USDA's Agricultural Research Service also conducts many activities relevant to animal feed, particularly looking at feed contaminants and the use of antimicrobials.⁴³ While much of this research is relevant to the FDA's regulatory activities, interagency coordination on animal feed has often proved challenging.

The U.S. Environmental Protection Agency (EPA) is also involved in the regulation of animal feed, primarily through its jurisdiction over pesticide use and waste management. The EPA sets tolerances and tests residues for pesticides used in crops for animal feed, including antimicrobial pesticides.⁴⁴ However, an animal feed containing an animal drug is not considered a pesticide, and is solely regulated by the FDA.⁴⁵ The EPA is also charged with regulating environmental and public health concerns related to Animal Feeding Operations (AFOs),

⁴² Johns Hopkins Center for a Livable Future, *Feed for Food-Producing Animals*, 9.

⁴³ *Ibid.*

⁴⁴ U.S. Environmental Protection Agency, "Pesticide Registration: Data Requirements," <http://www.epa.gov/pesticide-registration/data-requirements>.

⁴⁵ U.S. Environmental Protection Agency, "What is a Pesticide?" in *U.S. EPA Label Review Manual* (2014), 3.

including waste management and feeding practices.⁴⁶ In partnership with USDA, EPA has published guidelines for AFOs, including strategies for feed management practices to reduce the amount of nutrients in manure and regulations for feed mills that are integrated into AFOs.⁴⁷

Though FDA has primary responsibility for animal feed and its ingredients, USDA and EPA both play important roles in this area. From a stakeholder perspective, all three agencies are involved in various stages of the production and use of animal feed, and the feed and livestock industries must interact with regulators from all three agencies. Additionally, because research on issues related to animal feed, as well as residue testing on animal feed and human food products, is spread among different agencies, inter-agency coordination to handle both overlaps and gaps in regulatory activity remains a challenge that affects FDA actions in this area.

State Regulation

States are also involved in the regulation of animal feed in partnership with federal agencies and industry organizations. State feed officials are members of the AAFCO, though their activities vary based on state regulation. State officials may review animal feed through product registration or licensing, and some states also have labeling requirements that feed manufacturers must meet.⁴⁸ States and FDA officials also monitor and inspect feed mills, and the AAFCO has developed a model feed safety program development guide that is used by officials in various states to create and manage a feed safety program.⁴⁹ State and federal coordination is largely accomplished through the AAFCO, which works with both the FDA and state regulatory bodies.

⁴⁶ U.S. Environmental Protection Agency, “Animal Feeding Operations (AFOs): Regulations, Guidance, Policy, and Funding,” <http://www.epa.gov/npdes/animal-feeding-operations-afos-regulations-guidance-policy-and-funding>.

⁴⁷ U.S. Department of Agriculture and U.S. Environmental Protection Agency, *Unified National Strategy for Animal Feeding Operations* (Washington, DC 1999).

⁴⁸ Johns Hopkins Center for a Livable Future, *Feed for Food-Producing Animals*, 10.

⁴⁹ *Ibid.*

Industry Activities

Industry organizations and initiatives have played a significant role in animal feed regulation, particularly due to the complex and technical nature of many of the industry's practices and products. Industry groups both organize the diverse set of actors in animal feed production, including commercial and integrated feed manufacturers, ingredient suppliers, and equipment manufacturers, and coordinate partnerships with FDA, USDA, and state regulators.⁵⁰ This section will provide a brief summary of a few major actors as they relate to regulatory activities, though it is by no means a comprehensive list.

The AFIA has played a major role in developing industry guidelines for safe feed production, as well as in coordinating with regulators and advocating for industry interests at the federal and state levels. The AFIA developed the "Safe Feed/Safe Food" certification program for feed manufactures, ingredient suppliers, integrated producers, meat producers, and feed purchasers that contains many guidelines related to record-keeping, product tracing, and facility management and is widely used in the industry.⁵¹ The AFIA also helps manufacturers and consumers understand FDA regulations and AAFCO Good Management Practices, and develops guides for industry actors to help them adapt to changes in regulation, including the implementation of the Food Safety Modernization Act of 2011.⁵²

Other industry groups are also active in developing voluntary guidance and certification programs in partnership with regulators and researchers. The Animal Protein Producers Industry, for example, developed a third-party certification program to help manufacturers meet FDA requirements on animal proteins used in feed, as well as a salmonella testing, education, and

⁵⁰ American Feed Industry Association, "About," <http://www.afia.org/about>.

⁵¹ Johns Hopkins Center for a Livable Future, *Feed for Food-Producing Animals*, 11; American Feed Industry Association, "Safe Feed/Safe Food Certification Program," <http://safefeedsafefood.org/main/home.cfm>.

⁵² American Feed Industry Association, "Industry Regulations," <http://www.afia.org/industryregs>.

reduction program in partnership with several land-grant universities, USDA, and FDA.⁵³ State associations, most notably in California, have developed similar quality assurance and training programs for feed producers.⁵⁴

International Regulatory Activities

Because there is considerable variation in animal feed regulation throughout the world, particularly when it comes to drugs allowable in animal feed, the U.S. participates in some international activities related to animal feed to facilitate trade. The Codex Alimentarius Commission (CAC), an international group that regulates food standards, develops guidelines for various aspects of food production that are recognized under international trade agreements.⁵⁵ The U.S. participates in the CAC, but does not necessarily follow the practices outlined by the commission. In the realm of animal feed, the CAC has several subsidiary bodies that deal with feed safety and feeding practices, most notably the Ad Hoc Intergovernmental Codex Task Force on Animal Feeding, the Codex Committee on Residues of Veterinary Drugs in Food, and the Codex Committee on Food Additives and Contaminants.⁵⁶ These groups have published various codes addressing the development of feed safety systems for food-producing animals, feed contaminants, and antibiotic use, though feed practices in the U.S. deviate from these guidelines in many ways. In 2004, the CAC adopted a code stating that antibiotics should not be used in animal feed for growth promotion purposes without a public health safety assessment, though the details of such an assessment were left to individual countries.⁵⁷ The World Health Organization and the Food and Agriculture Organization have also taken action on animal feed in the past,

⁵³ Johns Hopkins Center for a Livable Future, *Feed for Food-Producing Animals*, 10-11.

⁵⁴ *Ibid.*

⁵⁵ Johns Hopkins Center for a Livable Future, *Feed for Food-Producing Animals*, 11-12.

⁵⁶ *Ibid.*

⁵⁷ World Health Organization and Food and Agriculture Organization of the United Nations, Codex Alimentarius Commission, *Code of Practice on Good Animal Feeding* (Rome 2004), 3.

particularly during the Bovine Spongiform Encephalopathy outbreaks.⁵⁸ Because the U.S. is a large exporter of animal feed, international regulation has the potential to play a significant role in influencing U.S. policy.

Conclusion

Animal feed regulation in the U.S. is characterized by a number of federal, state, and international actors that deal with a diverse group of stakeholders. The regulatory landscape is most complex in areas where there are visible public health concerns, especially in dealing with the use of antimicrobials in feed. As the primary federal agency charged with regulating animal feed and its ingredients (including animal pharmaceuticals), FDA is responsible for leading any action on animal feed production or use, but faces challenges in coordinating with other federal agencies involved in animal agriculture, as well as state officials and industry groups. As a result, the regulatory landscape influences FDA action, affecting the information available to FDA, the pressure FDA faces to act on a particular issue, and the flexibility and constraints on this action.

CHAPTER 2: HOW DOES FDA DECIDE? A THEORETICAL FRAMEWORK FOR AGENCY BEHAVIOR

In deciphering and explaining FDA behavior, two key questions must be addressed. First, how does FDA decide when to take regulatory action on a particular issue, and what are the various factors that affect this decision? Second, when it does decide to act, how does the agency determine which regulatory action to take at a given time? In order to answer these two questions, we must first address FDA's objective function.

⁵⁸ Johns Hopkins Center for a Livable Future, *Feed for Food-Producing Animals*, 12.

The objective function represents the agency's ultimate motivation, which drives its behavior. Prominent models of agency behavior assume a number of different functions, and no single objective function has emerged in the literature on agency decision-making. An approach focusing on managerial discretion assumes that agencies seek to maximize their budgets,⁵⁹ while public interest theory would assume that agencies seek to maximize the welfare of regulatory beneficiaries.⁶⁰ The "congressional dominance" theory, which first became prominent during the mid-1980s, sees an agency's primary objective as the optimization of the preferences of congressional committees that oversee the agency.⁶¹ Another theory prominent among political economists of the Chicago school assumes the agency is "captured" by the regulated industry, and thus its function is to maximize the industry's preferences.⁶²

Each of these theories, however, limits the agency by assuming it responds to only one set of interests based on its predetermined objective, which neglects other potential pressures influencing its behavior. The external signals model of agency behavior, first presented by Joskow,⁶³ later developed by Magat, Krupnick, and Harrington⁶⁴ and applied extensively to FDA's behavior by Olson,⁶⁵ allows for the possibility that agency officials respond to all the preferences posited by these theories. In the external signals theory, an agency's function is to

⁵⁹ Jean-Luc Migué, Gérard Bélanger, and William A Niskanen, "Toward a General Theory of Managerial Discretion," *Public Choice* 17.1 (1974): 27–47.

⁶⁰ Michael Hantke-Domas, "The Public Interest Theory of Regulation: Non-Existence or Misinterpretation?" *European Journal of Law and Economics* 15.2 (2003): 165–94.

⁶¹ Terry M. Moe, "An Assessment of the Positive Theory of 'Congressional Dominance,'" *Legislative Studies Quarterly* 12.4 (1971): 475–520.

⁶² George J. Stigler, "The Theory of Economic Regulation," *The Bell Journal of Economics and Management Science* 2.1 (1971): 3–21.

⁶³ Paul L. Joskow, "Inflation and Environmental Concern: Structural Change in the Process of Public Utility Price Regulation," *Journal of Law & Economics* 17.2 (1974): 291–328.

⁶⁴ Wesley A. Magat, Alan J. Krupnick, and Winston Harrington (1986), *Rules in the Making: A Statistical Analysis of Regulatory Agency Behavior*. Washington, DC: Resources for the Future.

⁶⁵ Mary Olson, "Substitution in Regulatory Agencies: FDA Enforcement Alternatives." *Journal of Law, Economics, and Organization* 12.2 (1996): 376–407; Mary Olson, "Agency Rulemaking, Political Influences, Regulation, and Industry Compliance," *Journal of Law, Economics, and Organization* 15.3 (1999): 573–601.

maximize positive feedback from external sources in order to maintain its autonomy.⁶⁶ By avoiding negative feedback and seeking positive feedback from a wide variety of external stakeholders, the agency ensures that it has the political support necessary to take a given action among the relevant groups that would otherwise be able to create “hassles” for the agency and decrease its autonomy.⁶⁷

In explaining and predicting when an agency⁶⁸ decides to act and which action it chooses to take, the external signals model focuses on the tradeoffs that the agency faces, accounting for positive and negative feedback from various external groups as well as the budgetary costs of agency actions. Instead of assuming, based on a narrow objective function, that the agency responds only to feedback from a particular stakeholder group, this model allows for a more dynamic decision-making process in which the agency reacts to diverse and changing feedback. Under the external signals model, the agency is engaged in a continuous process of weighing positive feedback from external stakeholders against the political costs of negative feedback from other outside groups, as well as the budgetary costs of the various regulatory actions they are able to take.⁶⁹ Because the preferences of external groups shift and the political environment is constantly evolving, an agency’s calculus regarding a particular issue changes over time, providing opportunities for substitution of one regulatory action for another.⁷⁰ For example, if the agency receives a substantial amount of negative feedback that outweighs any positive feedback on a given regulatory action, political costs of taking that action are high. As a result, the agency may not wish to spend a great deal of budgetary resources to take the action,

⁶⁶ Olson (1996).

⁶⁷ *Ibid.*

⁶⁸ Here, the use of “agency” refers to FDA, but this theory has been applied to other federal bureaucratic agencies as well.

⁶⁹ Olson (1996).

⁷⁰ *Ibid.*

particularly if it requires procedural steps that consume substantial time and resources. Instead, it may choose not to take the action, to postpone the action, or to substitute the action for another that is less formal and resource-intensive, and perhaps that will draw less negative political feedback. Because this model allows for the agency to change its behavior on a particular issue over time, given shifting costs and benefits, the external signals model is better suited for a longitudinal case study of agency behavior than other, more static models.

Political costs, defined as negative feedback from external stakeholders, can come from a variety of actors and provide resistance for the agency in several ways. In the case of animal pharmaceutical regulation by FDA, the pharmaceutical companies tend to resist any additional restrictions or regulation, as this can disrupt their operations or, in the most extreme case, permanently take their product off the market. The food animal production industry, which includes cattle, swine, and poultry producers as well as a variety of other related agricultural interests, also tends to resist regulation of pharmaceuticals for food-producing animals, though their response is often affected by the current practices they employ. For example, while large swine producers might oppose regulation of a drug they use widely in feed for disease prevention, small producers might have different management practices that effectively prevent disease without the drug, and they also might not be able to afford a medicated feed premix. As a result, small producers would have an advantage if the drug were restricted or banned. Furthermore, if the regulation is limited to a drug used only in swine production, then poultry and cattle producers might not resist the regulation, as an increase in the price of pork could give them an advantage in the market. Nevertheless, if new regulation sets a precedent for restrictions on a broad class of drug uses or indicates a shift towards more active intervention in the industry by FDA, food animal producers are likely to collectively oppose the action. Industry actors can

apply pressure to FDA through Congress, but they can also exert influence directly by expressing preferences formally and informally during the rulemaking process.⁷¹

Regulatory beneficiaries and their advocates can also be a source of political costs. In the case of antibiotic regulation in food-producing animals, consumers and groups that advocate for public health, the environment, and public interest or consumer issues can create political costs when they believe FDA is not adequately protecting human health. These groups are also able to provide political benefits in the form of positive feedback to offset the political costs created by those opposed to regulation. These groups tend to be at their most powerful when there is a lapse in regulation that causes a “scandal” and gains media attention, as FDA is likely to respond quickly to avoid reduced autonomy in the future. However, advocates for regulatory beneficiaries tend to be at a disadvantage when it comes to organization and resources for legal challenges and lobbying.⁷²

Though Congress can sometimes act as an independent source of political costs and benefits, more often Congress acts as a conduit for concerns of other stakeholders to be transmitted to FDA. If stakeholders provide negative feedback that garners attention, Congress is able to apply pressure on their behalf through oversight of FDA and in the appropriations process, by threatening to cut FDA’s budget or allocating funds for a specific purpose in order to direct FDA action. Negative feedback can also lead to procedural constraints or legal challenges, which are undesirable for FDA because they consume resources that could otherwise be used to carry out the agency’s goals.

⁷¹ Susan Webb Yackee, “Sweet-Talking the Fourth Branch: the Influence of Interest Group Comments on Federal Agency Rulemaking,” *Journal of Public Administration Research and Theory* 16.1 (2006): 103–24.

⁷² Compared to the incentives for a regulated entity to get involved in the rulemaking process or the development of guidance, the marginal benefit of a change in policy for any one regulatory beneficiary is much lower, and the costs of organizing are high (see Lewis (2011) at 70-71). However, in the case of regulating subtherapeutic antibiotic use in animals, these groups were not always at a disadvantage in organization and coordination, which helped them exert influence more effectively.

Budgetary costs can be increased by procedural and legal challenges driven by negative feedback, but they also factor independently into FDA's decision-making. Formal rulemaking is guided by statutes that contain extensive procedural requirements, including scientific evaluation, an economic impact study, advanced notice of proposed rules, public comment periods, opportunities for hearings, and ultimately an evidentiary hearing before an administrative law judge. These procedures, along with the adjudication and enforcement proceedings that come along with formal rulemaking, consume time and budgetary resources, making formal rulemaking an expensive undertaking for the agency. Stakeholders are also able to hold up the rulemaking process at various stages by requesting additional hearings or evidence, submitting substantive comments that FDA must evaluate and address, or by challenging the final decision. These challenges make the prospect of formal rulemaking even more daunting for an agency with limited resources, as they can consume FDA's manpower and funding for years. The threat of legal action from the regulated industry has also become an increasingly strong deterrent from formal rulemaking over the last few decades.⁷³ However, the advantage of formal rulemaking is that it creates binding rules that are legally enforceable.

FDA can also employ informal regulatory actions, such as guidance documents, which are much less costly because they do not require the extensive procedures and opportunities for public comment mandated by the formal rulemaking process.⁷⁴ This also makes them more flexible, as FDA is able to respond more quickly to changes in technology or scientific

⁷³ Lewis (2011), 61-64.

⁷⁴ Under FDA's "Good Guidance Practices," which were codified in the Food and Drug Administration Modernization Act of 1997, the agency created additional opportunities for public participation in the creation of guidance documents, adding notice-and-comment periods for guidance documents that discuss changes in policy or interpretation, or cover controversial issues. However, unlike the formal rulemaking notice-and-comment requirements, FDA does not have to respond to comments and instead must only review them. Though public participation in the creation of guidance documents has increased, to the advantage of the regulated industry, informal guidance documents remain significantly less burdensome for the agency than formal rulemaking (see Lewis (2011) for a more detailed explanation).

understanding. However, these actions are nonbinding and thus unenforceable.⁷⁵ The budgetary costs of an action play a significant role in FDA's decision to initiate regulatory action and in determining whether they will take formal or informal measures. Changing feedback can incentivize FDA to substitute one type of action for another.⁷⁶

Another key factor that is not incorporated into the external signals theory, but which plays a central role in the story of animal antibiotics regulation, is the availability and strength of the scientific evidence. Because the FD&C Act requires FDA to evaluate scientific evidence regarding the safety of a drug as part of its regulatory duties, science places a constraint on agency action, and can be used as a tool by other stakeholders to delay or force action. The establishment of strong scientific evidence is a prerequisite for FDA to move forward with formal rulemaking, as the agency does not wish to waste resources attempting to overcome the procedural hurdles if the action will ultimately be blocked by a scientific challenge. Like external signals from stakeholders, the body of scientific evidence evolves over time, which can change FDA's calculus.

Because the focus of this paper is FDA behavior, the strategies and decision-making of external stakeholders, including Congress, are not analyzed extensively and a complete examination of their behavior is beyond the scope of this paper. Additionally, though the motivations of individuals within FDA (including political appointees that change with each administration and may advance their own agendas) likely play a role in shaping FDA's behavior, here we examine the agency as a single entity and do not analyze the role of internal politics. The present goal is to understand how external signals affect FDA's decision-making.

⁷⁵ Guidance documents were previously binding for the agency under a rule enacted by FDA in 1977. However, the agency rescinded this decision in 1992, making all guidance nonbinding for FDA and the regulated agency (see Lewis (2011) at 30).

⁷⁶ Olson (1996).

Future research on the topic should consider evaluating the impact of internal actors and changing presidential administrations as an additional factor affecting FDA's regulatory behavior in the food system.

The next chapter takes up a longitudinal case study of FDA's regulation of subtherapeutic antibiotic use in animal agriculture in the years between 1970 and 2015. By piecing together the key moments in FDA's regulatory record on this issue, this paper builds a comprehensive history of how FDA allowed the drugs to become incorporated into animal feeding practices, and subsequently dealt with the human health hazard posed by the emerging threat of antibiotic resistance. In telling this history, trends in FDA's behavior are identified and explained through an analysis of the external signals the agency was receiving at the time. A longitudinal study of a single issue provides a unique opportunity to see how FDA's behavior changed over time, as the political environment evolved and the balance of costs and benefits shifted.

CHAPTER 3: A REGULATORY HISTORY OF THE SUBTHERAPEUTIC USE OF ANTIBIOTICS IN ANIMAL FEED

Antibiotics in Animal Feed: The Early Years

FDA's long history with antibiotics in animal agriculture began in 1949 at a tetracycline manufacturing plant owned by American Cyanamid Corporation, located on the Pearl River just outside New York City.⁷⁷ In these early years of mass antibiotic production, only about five percent of the tetracycline grown on grain mashes could be extracted, and the waste was dumped into the river. After noticing that the fish swimming downriver from the plant were larger than average, a biochemist named Thomas Jukes set out to experiment on animals in the lab. Jukes

⁷⁷ Shannon Brownlee, "A LOOK at . . . Antibiotics in the Food Chain." *The Washington Post*, May 21, 2000.

discovered that after being fed this mash, chicks grew 20 percent faster than those without the antibiotic supplement, and pigs, turkeys, and dairy calves in later experiments showed remarkable responses to the drugs as well.⁷⁸

Jukes's finding was hailed as a "spectacular discovery" that farmers and scientists alike believed would hold great significance "for the survival of the human race in a world of dwindling resources and expanding populations."⁷⁹ Enthusiastic pharmaceutical companies raced to market this new discovery, and antibiotic feed supplements intended to improve growth and feed efficiency in a variety of food-producing animals were commercialized one year later, in 1950.⁸⁰ Researchers soon found that the antibiotics that promoted growth and increased feed efficiency also prevented and controlled disease in large groups of animals, which allowed farmers to keep animals confined indoors for longer periods with lower risk of fatal outbreaks.⁸¹ As producers faced increased pressure to meet rising demand, the subtherapeutic use of antibiotics became widespread practice, creating the conditions for the confined, large-scale operations that dominate modern animal agriculture.

Not long after antibiotics became a common tool in animal agriculture, scientists and policymakers were becoming concerned about the problem of antibiotic resistance. By the early 1960s, the scientific community was beginning to examine the occurrence and mechanisms of the development and transfer of resistance in bacteria, looking at antibiotic uses in human medicine as well as animal husbandry.⁸² After an outbreak of food poisoning in United Kingdom

⁷⁸ *Ibid.*; Thomas H. Jukes, "Antibiotics in Animal Feeds and Animal Production," *Bioscience*, 22.9 (1972): 526–534.

⁷⁹ William L. Lawrence, "'Wonder Drug' Aureomycin found to Spur Growth 50%," *New York Times*, Apr 10, 1950.

⁸⁰ U.S. Department of Agriculture, Economic Research Service, *Briefing Paper: Food and Drug Administration Proposal to Restrict the Use of Selected Antibiotics at Subtherapeutic Levels in Animal Feeds*, by Clark R. Burbee, Robert Lenahan, and George Allen, ERS-662 (Washington, DC, 1977).

⁸¹ R.H. Gustafson and R.E. Bowen, "Antibiotic Use in Animal Agriculture," *Journal of Applied Microbiology* 83 (1997): 531–541.

⁸² Gerald B. Guest, "Status of FDA's Program on the Use of Antibiotics in Animal Feeds," *Journal of Animal Science* 42.4 (1976): 1052–57.

that was caused by the spread of *Salmonella typhimurium* in dairy calves to humans, the British government appointed the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (often referred to as the Swann committee) to study the subtherapeutic use of antibiotics in animal feed.⁸³ In November of 1969, the Swann committee presented its report to the British Parliament, which highlighted the potential human health hazard of the development of antibiotic resistance in bacteria in farm animals. This conclusion was reached after the committee found that most cases of nontyphoidal *Salmonella* infection in humans were transmitted through food, with farm animals as a significant source.⁸⁴ The Swann committee recommended that animal antibiotics be separated into two classes: a “therapeutic” category, which would include tetracyclines and penicillins, among others, would only be permitted for therapeutic uses under a veterinary prescription, while those in the “feed” category would not be subject to such restrictions.⁸⁵ In March of 1971, the British government carried out the recommendations of the Swann Report.⁸⁶

FDA’s Science Advisory Committee reviewed the Swann Report and recommended that the Commissioner of Food and Drugs establish a task force to study the use of antibiotics in animal agriculture.⁸⁷ In April of 1970, the Commissioner created FDA’s Task Force on the Use of Antibiotics in Animal Feeds, which included ten specialists on infectious disease and animal science from several agencies, including FDA, Centers for Disease Control (CDC), USDA, and the National Institutes of Health (NIH), as well as five consultants from universities and the

⁸³ U.S. Department of Agriculture, Economic Research Service (1977), 5.

⁸⁴ Frank M. Calia and Morton I. Rapoport, “The Use of Antibiotics in Animal Feeds,” *JAMA* 229.9 (1974): 1212–12.

⁸⁵ U.S. Department of Agriculture, Economic Research Service (1977), 5.

⁸⁶ Guest (1975).

⁸⁷ U.S. Congress, House of Representatives, Committee on Interstate and Foreign Commerce, *Antibiotics in Animal Feed: Hearings on H.R. 7285, Before the Subcomm. on Health and the Environment*, 96th Cong., 2nd sess., 1980, 429 (Testimony of Lester Crawford, Director of Bureau for Veterinary Medicine).

animal production and pharmaceutical industries.⁸⁸ The task force focused on three areas of concern for its investigation: the human health hazard, the animal health hazard, and the efficacy of antibiotics in growth promotion.⁸⁹ Two years later, the task force reported that it found that “the use of low-level antibiotics in animal feed for growth promotion and/or disease prophylaxis poses a potential danger to man.”⁹⁰ This hazard was based on their conclusion that antibiotic use may promote both an increase in the reservoir of pathogenic bacteria in animals, and the development of resistance that can often be transferred to other bacteria and transmitted to man.⁹¹ Though the task force was not able to determine if a direct link existed between subtherapeutic antibiotic use in animals and disease in man, they nevertheless recommended that antibiotics be categorized such that certain types could be reserved for human treatment, and thus limited in agricultural uses.⁹² The task force’s report contained safety and effectiveness guidelines and recommended that FDA prohibit antibiotics used in human medicine from being added to feed for growth promotion or disease prevention if the antibiotics failed to meet the proposed guidelines.⁹³

In April of 1973, FDA took up the task force’s recommendations and published a Statement of Policy and Interpretation Regarding Animal Drugs and Medicated Feeds, in which FDA declared that it would withdraw any antibiotic-containing compounds unless the drug’s sponsors submitted data that established the product’s safety and effectiveness.⁹⁴ FDA required sponsors to complete these studies under the criteria established by the task force and submit

⁸⁸ *Ibid.*; Guest (1975).

⁸⁹ Calia and Rapoport (1974).

⁹⁰ U.S. Congress, House of Representatives, Committee on Interstate and Foreign Commerce, *Antibiotics in Animal Feed: Hearings Before the Subcomm. on Oversight and Investigations*, 95th Cong., 1st sess., 1977, 79 (Donald Kennedy, Commissioner of Food and Drug Administration).

⁹¹ Guest (1975).

⁹² U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1977, 9 (Gregory Ahart, Director of Human Resources Division, General Accounting Office).

⁹³ *Ibid.*

⁹⁴ Guest (1975), 1054.

data within two years to prove safety and efficacy.⁹⁵ Reporting on the progress of this project and FDA's current regulatory standpoint in 1975, Gerald Guest, who would become the director of FDA's Bureau of Veterinary Medicine the following year, emphasized that future safety and efficacy considerations would be more demanding given the "present climate," and said that FDA expected to make decisions on continued uses of certain antibiotics in feed by the following year.⁹⁶

FDA's early actions to assess the risks of antibiotic use in animal feed were prompted largely by the growing concern about antibiotic resistance within the scientific community, as well as by the policy changes in Great Britain as a result of the Swann Report, which garnered international attention. Between 1960 and 1970, the use of antibiotics in animal feeds increased six fold, and the practice had become a major topic of conversation in scientific and public health circles.⁹⁷ Still, rather than taking swift action to protect against potential human health hazards like the British, FDA's behavior at this stage was characterized by careful and deliberate information-gathering from scientific and industry experts on the task force in order to ensure a defensible basis for future action. In October 1973, just after the FDA had released its new policy adopting the task force's recommendations, the World Health Organization (WHO), which had created a working group specifically to study the use of antibiotics in animal feed, recommended that antibiotics with therapeutic value not be used for growth promotion.⁹⁸ In acting on the task force's conclusions, FDA took its first step towards actual regulation of animal feed antibiotics, which soon gained the attention of the pharmaceutical and animal production industries, as well as Congress.

⁹⁵ *Ibid.*; Calia and Rapoport (1974).

⁹⁶ Guest (1975).

⁹⁷ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1977, 4 (Testimony of Gregory Ahart, Director, Human Resources Department, General Accounting Office).

⁹⁸ *Ibid.*

FDA Proposes Withdrawals for Penicillin and Tetracyclines

In June 1975, FDA created a subcommittee of the National Advisory Food and Drug Committee that was tasked with reviewing the evidence that had been submitted by pharmaceutical companies in response to FDA's 1973 regulation, as well as other scientific evidence related to antibiotic resistance and the subtherapeutic use of antibiotics in animal feed. The subcommittee reviewed data on the use of tetracyclines, penicillin, and sulfaquinoxaline in animal feed, and submitted recommendations to the parent committee that would place significant limits on subtherapeutic uses of these three antibiotics. According to the subcommittee's recommendations, all growth promotion and feed efficiency uses of penicillin would be discontinued, and penicillin could only be used for disease prevention where there were no effective substitutes available. The subcommittee also called for the termination of growth promotion and feed efficiency uses of tetracyclines where substitutes were available. For disease prevention, uses of both sulfaquinoxaline and tetracyclines were to be limited to periods with the greatest threat of animal disease.⁹⁹ If adopted, these regulations would be the most significant restrictions on animal feed antibiotic use since their commercialization began 25 years before.

The National Advisory Food and Drug Committee, FDA's broad policy advisory committee, voted on January 24, 1977 to accept the subcommittee's recommendations on penicillin and sulfaquinoxaline, but rejected their recommendations on tetracyclines. Instead, the committee voted to recommend to FDA that tetracyclines remain available for growth promotion and disease prevention uses without restriction.¹⁰⁰ Though there was no formal statement from the committee on why this portion of the recommendation was reversed, an official from the U.S.

⁹⁹ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1977, 6 (Testimony of Gregory Ahart, Director, Human Resources Department, General Accounting Office).

¹⁰⁰ *Ibid.*

General Accounting Office (GAO, later renamed the Government Accountability Office) who investigated FDA's actions on this issue said the committee was primarily concerned about such restrictions on tetracyclines due to their economic benefit to livestock production and the lack of effective substitutes available.¹⁰¹

Four months later, on April 15, 1977, FDA announced its decision to place restrictions on subtherapeutic animal feed uses of penicillin, tetracyclines, and sulfaquinoxaline in accordance with the subcommittee's original recommendations.¹⁰² FDA initiated formal rulemaking proceedings to enact these restrictions, issuing a notice of opportunity for hearing in the Federal Register in August of 1977 for its proposal to withdraw approval for all animal feed uses of penicillin. This notice was shortly followed by another notice for its proposal to withdraw approval for certain subtherapeutic uses of tetracyclines.¹⁰³ FDA stated that the grounds for withdrawal were that the drug uses had not been shown to be safe for human health under the requirements of the FD&C Act, and that there was also a lack of substantial evidence for the effectiveness for therapeutic use of penicillin.¹⁰⁴

After FDA's initial gathering and analysis of the evidence on the risk of antibiotic resistance associated with subtherapeutic use in animal feed, the agency initiated strong action in the form of formal rulemaking proceedings to implement the recommendations it received from the scientific community. By the time it announced the proposal to withdraw approval for subtherapeutic uses of penicillin and certain uses of tetracyclines, its actions were supported by

¹⁰¹ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1977, 14 (Testimony of Gregory Ahart, Director, Human Resources Department, General Accounting Office).

¹⁰² U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1977, 6 (Testimony of Gregory Ahart, Director, Human Resources Department, General Accounting Office).

¹⁰³ U.S. Food and Drug Administration, Notice, "Penicillin-Containing Premixes, Opportunity for Hearing," *Federal Register* 42, no. 168 (August 30, 1977): 43772; U.S. Food and Drug Administration, Notice, "Tetracycline (Chlortetracycline and Oxytetracycline)-Containing Premixes; Opportunity for Hearing," *Federal Register* 42, no. 204 (October 21, 1977): 56264.

¹⁰⁴ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1977, 6 (Testimony of Gregory Ahart, Director, Human Resources Department, General Accounting Office).

recommendations from the Swann committee, the FDA task force, the WHO, and the agency's advisory subcommittee, as well as many other scientific organizations that had spoken on the issue. By waiting to take action until the evidence had piled up in its favor, FDA positioned itself strongly to defend against any attacks on its position. At the same time, FDA had yet to experience any vocal opposition from industry or Congress on this issue, lowering the political barriers to action. With overwhelming support from the recommendations of numerous independent scientific bodies and muted backlash thus far, FDA decided to initiate formal regulatory action to address antibiotic use in animal agriculture.

Congress Intervenes to Block FDA Action

Immediately after publishing its proposal to withdraw approval for uses of penicillin and tetracyclines in 1977, FDA faced the strong backlash it had anticipated from industry and Congress, which constrained the regulatory options available to the agency. Less than a month after FDA published its notice, the Subcommittee on Oversight and Investigation of the House Commerce Committee held the first of what would eventually turn into many Congressional hearings on antibiotics in animal feed.¹⁰⁵ During the hearing, FDA Commissioner Donald Kennedy was questioned extensively about FDA's decision-making process on animal antibiotics, which some critics argued was too hasty and unsupported by sufficient evidence, while others questioned FDA for not acting earlier and more decisively. Rep. Henry Waxman, a Democrat from California, questioned Kennedy about why FDA did not act several years earlier when many had deemed the evidence sufficient, and suggested that FDA consider using its "imminent hazard" powers to avoid lengthy delays in the regulatory process. At the same time, Republican members and those representing rural districts emphasized the economic costs of

¹⁰⁵ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1977.

restricting subtherapeutic uses of antibiotics and urged the agency to delay action until more direct evidence was presented.¹⁰⁶ Those who opposed FDA's position focused on the fact that no direct link between a human illness and the subtherapeutic use of antibiotics in animal feed had been established. They argued that without determining this direct link, it would be unwise to move forward with proposals to restrict the use of drugs that were beneficial to American farmers and consumers.

Examining FDA testimony in Congressional hearings provides a unique opportunity to hear directly from FDA officials on how agency decisions are made, a process that tends to be somewhat opaque to the public. Kennedy's testimony in the 1977 hearing provided a strong public statement that FDA considered the hazard of antibiotic use in animal feed to be significant, and that there was "not any doubt...on the grounds of evidence" about the transfer of resistant microorganisms from livestock animals to humans working with the animals or their meat.¹⁰⁷ When criticized for moving slowly to regulate this hazard, Kennedy also explained why FDA must proceed cautiously:

"In defense of my colleagues, I would like to say that one of the real important questions here is if the evidence is good enough for us to write a document that will stand up. We know we are going to be challenged on actions like this. If we cannot make a strong case, it is often a poor expenditure of our resources."¹⁰⁸

Kennedy's statement summarizes several of the key factors playing into FDA's calculus regarding whether, when, and how to act when regulating a complex and controversial issue. As FDA's careful and deliberate process during the 1970s indicates, FDA knew that it would face challenges to its attempts to regulate antibiotics in animal feed, even though it had not

¹⁰⁶ *Ibid.*

¹⁰⁷ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1977, 87 (Donald Kennedy, Commissioner of Food and Drugs).

¹⁰⁸ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1977, 77 (Donald Kennedy, Commissioner of Food and Drugs).

experienced serious opposition up to this point. Because formal rulemaking is extremely resource-intensive, Kennedy was aware that FDA must have the strongest possible case backed by convincing evidence before proceeding to avoid wasting time, money, and manpower on a rule that could be blocked by Congress or successfully challenged in court by the industry. In delaying action until their position was supported not only by the Swann Committee, the WHO, and their own task force, but also by the recommendations of the advisory committee that reviewed data submitted by the drugs' sponsors, Kennedy hoped the agency's case for rulemaking was strong enough to overcome opposition.

In the first Congressional hearing on antibiotics in animal feed, FDA's position was supported by testimony from representatives of CDC, GAO, and from the only microbiologist called as witness in the hearing, but the agency faced challenges on several other fronts. While members of Congress that represented agricultural and pharmaceutical interests questioned the evidentiary basis of FDA's proposed action, USDA's Economic Research Service (ERS) published a briefing paper in September of 1977 that highlighted the substantial economic benefits of subtherapeutic antibiotic use in feed, which they acknowledged "must be weighed against the theoretical risks" of creating resistant bacteria.¹⁰⁹ The ERS report based its evaluation on a total ban of all subtherapeutic uses of antibiotics, which was much more restrictive than the FDA proposals, but nevertheless concluded that FDA's proposed action "could have a significant impact upon the efficiency of production of cattle, swine, and poultry." FDA was being opposed not only by another federal agency that was involved in the regulation of food and agriculture, but also by the American Veterinary Medical Association (AVMA), which at this point was

¹⁰⁹ U.S. Department of Agriculture, Economic Research Service (1977).

recommending the continued use of subtherapeutic antibiotics in animal feed.¹¹⁰ Nevertheless, during the hearing, Kennedy assured Representative Waxman and others that he had “communicated [his] own sense of urgency” about the current proposals to withdraw approval for certain subtherapeutic uses of penicillin and tetracyclines to FDA staff and the Office of General Counsel, and said that the issue was “receiving all the priority attention that I believe it can receive, stretching our resources as far as they will go.”¹¹¹

Over the course of the next year, FDA continued to push forward with its proposals. In January of 1978, the agency published a third proposal to further restrict the sale of feed premixes containing penicillin and tetracyclines to FDA-approved feed manufacturers and to farmers only under the order of a veterinarian.¹¹² During March and April of that year, FDA held three informal public hearings on the third proposal and ultimately decided to delay going forward with the distribution controls until the outcome of the first two proposals on animal feed antibiotics was known.¹¹³ The agency had also received numerous requests from drug sponsors for hearings on the proposals to ban subtherapeutic use of penicillin and restrict subtherapeutic use of tetracyclines, and planned to hold a formal evidentiary hearing as it continued to move forward in the rulemaking process.¹¹⁴

However, before FDA could take this step, Congress intervened to block FDA’s proposed actions. In September of 1978, Congress allocated \$250,000 for a comprehensive study of the issue of antibiotics in animal feed to be carried out by the National Academy of Sciences (NAS), and prohibited FDA from moving forward on its current proposals, as well as from taking any

¹¹⁰ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1977, 88 (Donald Kennedy, Commissioner of Food and Drug Administration).

¹¹¹ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1977, 84.

¹¹² U.S. Food and Drug Administration, Proposed Rule, “New Animal Drugs for Use in Animal Feeds: Animal Feeds Containing Penicillin and Tetracycline,” *Federal Register* 42, no. 14 (January 20, 1978): 3032.

¹¹³ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 431 (Lester Crawford, Director, Bureau of Veterinary Medicine).

¹¹⁴ *Ibid.*

additional action to restrict antibiotic use in animals, until the NAS study could be completed.¹¹⁵ Specifically, Congress asked the NAS to study the human health effects of the subtherapeutic use of penicillin and tetracyclines in animal feeds, to review the existing epidemiological data, and to provide recommendations for future research.¹¹⁶ Congress requested that the NAS provide insight into the feasibility of additional epidemiological studies that could potentially begin to establish the direct link between human illness and the subtherapeutic use of antibiotics.

This move struck a blow to FDA's progress on this issue, indicating that Congress was sympathetic to the arguments from the animal production industries and pharmaceutical companies, which claimed that the existing evidence was not sufficient to justify FDA's proposals. With little choice in the face of direct instruction from Congress, the agency announced in November of 1978 that it would delay the formal hearing on the current proposals until the completion of the NAS study, which was expected in March of 1980.¹¹⁷

1978-1980: FDA, Industry, Congress, and the Battle Over Uncertainty

Over the next two years, Congress mandated that other agencies undertake studies of the issue to add to the body of evidence as they awaited the release of the NAS report. In late 1978, USDA released a report on the economic effects of the proposed and potential restrictions on animal antibiotic use that had been commissioned by the Senate Committee on Agriculture, Nutrition and Forestry. Unlike USDA's prior economic impact study, this report undertook a more nuanced assessment of the effect of the proposed regulations, though it assumed that there

¹¹⁵ John Elliott, "Antibiotics in Feed Still OK," *JAMA* 242.14 (1979): 1464–64.

¹¹⁶ National Research Council, Committee to Study the Human Health Effects of Subtherapeutic Antibiotic Use, *The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds*, Report, Washington, DC: National Academies Press, 1980.

¹¹⁷ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 432 (Lester Crawford, Director, Bureau of Veterinary Medicine).

were no available substitutes and no changes in management practices. Though USDA seemed to maintain its position in the report that low-level use of antibiotics in animal feeds was beneficial for producers and consumers, the study found that “the economic system would generally be quite resilient to a more restrictive policy on animal drug use.”¹¹⁸ In July of the following year, the Office of Technology Assessment (OTA) published a report, also commissioned by the Senate Agriculture Committee, that looked at the benefits and risks of antibiotic use in animal agriculture, the availability of substitutes for each category of drugs, the acceptable risks in the use of each category, and the options available to Congress to improve the regulation of drugs used in animal feed.¹¹⁹ Based on the analysis of scientists and experts from the pharmaceutical and animal agriculture industries that consulted on this report, OTA concluded that there was “no real disagreement over the overall conclusion that food animals are the source of some infections in humans and that the use of antibacterials in feed is one cause of the growing pool of drug-resistant pathogenic bacteria.”¹²⁰ The report found that it would be exceptionally difficult to prove every step of the causal chain linking a case of human illness to the use of antibiotics in livestock feed, but that “each step in the chain has been documented repeatedly.”¹²¹

Both the USDA and OTA reports seemed to lend support to FDA’s position, and provided additional evidence that the economic impact of FDA’s proposals would not be as dramatic as opponents had warned, especially given that OTA concluded that most antibiotics could be replaced by alternative drugs that had already been approved by FDA. On March 18, 1980, the National Research Council committee of the NAS released the results of their

¹¹⁸ U.S. Department of Agriculture, Economics, Statistics, and Cooperatives Service, “The Economic Effects of a Prohibition on the Use of Selected Animal Drugs,” September 1978.

¹¹⁹ U.S. Congress, Office of Technology Assessment, *Drugs in Livestock Feed* (Washington, DC: U.S. Government Printing Office, 1979).

¹²⁰ *Ibid.*

¹²¹ *Ibid.*

congressionally mandated study on antibiotics in animal feed, which both FDA and Congress had hoped would provide definitive conclusions regarding the existing scientific knowledge on the issue. However, after a year of studying the matter, the committee reported that the existing data regarding the possible human health effects of subtherapeutic antibiotic use in animals were inconclusive and that “insurmountable technical difficulties” prevented a comprehensive epidemiological study from being realized or even suggested.¹²² In the report, the NAS stated that the potential link between antibiotics in feed and human health effects has been “neither proven nor disproven.”¹²³ Although the authors emphasized in the following sentence that the lack of data “must not be equated with proof that the proposed hazards do not exist,” opponents of restrictions on antibiotic use in agriculture would quote those words for years to stymie FDA’s regulatory progress.¹²⁴

In anticipation of the NAS report, Congress had marked \$1.5 million in FDA’s budget for fiscal year 1980 to be used to carry out just the kind of “comprehensive” epidemiological study that the NAS had just deemed virtually impossible.¹²⁵ Congress had hoped the NAS report would provide a research framework for such a study, but instead the report essentially suggested that the type of research policymakers seemed to need in order to take decisive action on subtherapeutic uses of antibiotics in animals would not be feasible.¹²⁶ While the NAS report suggested that FDA and scientists could carry out studies that might strengthen the circumstantial evidence for a human health hazard or document various steps in the proposed

¹²² National Research Council, Committee to Study the Human Health Effects of Subtherapeutic Antibiotic Use (1980).

¹²³ *Ibid.*

¹²⁴ *Ibid.*

¹²⁵ Susan Walton, “FDA Stymied on Antibiotic Ban,” *BioScience* 30.5 (1980): 295–96.

¹²⁶ *Ibid.*

causal chain, it indicated that the direct link many were searching for might never been fully proven.

With FDA in no stronger a position to move forward with formal regulation of animal feed antibiotics than it had been before the NAS study, some in Congress moved to bolster the agency's position. On May 7, 1980, Rep. John Dingell, a Democrat from Michigan, introduced the Antibiotics Preservation Act with his cosponsor, Rep. Henry Waxman, who had been vocal during the 1977 hearing on the need for FDA to move swiftly on its proposed restrictions.¹²⁷ The Antibiotics Preservation Act proposed to amend Section 3(a)(1) of Section 507 of the FD&C Act to specifically require the Secretary of Health and Human Services to designate certain antibiotics that may not be used at subtherapeutic levels in animal feed within 180 days of the bill's enactment.¹²⁸ The FDA already had sufficient statutory authority to regulate such drugs if they were found to pose a hazard to human health. Nevertheless, Lester Crawford, the Director of the Bureau of Veterinary Medicine (BVM), said that the agency believed that "the bill's proposed statutory mechanism for limiting the subtherapeutic animal feed uses of antibiotics [would] assist FDA in removing these products from the marketplace" by giving them a clear mandate and more flexibility in the regulatory process.¹²⁹

In June of 1980, the Subcommittee on Health and the Environment of the House Commerce Committee, of which Rep. Waxman was chairman, held a hearing on the bill. During the hearing, the USDA representative called to testify said that the scientific evidence linking subtherapeutic antibiotic use in animals to the development of resistant strains of pathogenic

¹²⁷ Antibiotics Preservation Act, H.R. 7285, 96th Cong. (1980).

¹²⁸ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 7 (Rep. John Dingell).

¹²⁹ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 438 (Lester Crawford, Director of Bureau of Veterinary Medicine).

bacteria in humans remained “quite tentative.”¹³⁰ He stressed that where there existed such uncertainty about a potential risk, costs and benefits of new actions should be weighed. This feeling was echoed by Rep. Tim Carter, the ranking Republican on the subcommittee, who cited the NAS study to demonstrate that the evidence on the “postulated hazards to human health” was “far from clear.”¹³¹ Rep. Charles Rose, a Democrat from North Carolina who chaired the House Agriculture Subcommittee on Livestock and Grains and was considered a strong advocate for farmers, expressed the opposition to Dingell and Waxman’s bill shared by members from both parties who represented agricultural interests. Rep. Rose called the bill a “reaction to theoretical risks” that he considered hasty and unwise, and urged members of the subcommittee to proceed with greater caution when considering such a regulation.¹³² He reiterated the need to await more conclusive evidence before restricting “what has become a basic part of the meat industry’s effort to convert grain more efficiently into meat.”¹³³

Despite the suggested importance of this issue to the livestock industry, the National Pork Producers Council and the National Cattlemen’s Association declined to participate in the hearing.¹³⁴ Some postulated that livestock producers did not like that the Commerce Committee’s Subcommittee on Health and Environment was holding the hearing because it framed an agricultural issue as a health issue. However, the National Pork Producers Council explained their absence in a letter to the subcommittee that stated that the issue had already been considered by the House and Senate agriculture committees, as well as the House Agriculture

¹³⁰ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 472 (Howard Hjort, Director, Economics, Policy Analysis, and Budget, Department of Agriculture).

¹³¹ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 6 (Rep. Tim Carter).

¹³² U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 309-311 (Rep. Charles Rose).

¹³³ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 311 (Rep. Charles Rose).

¹³⁴ E. Marshall, “Health Committee Investigates Farm Drugs. Proposed Legislation Would Enable FDA to Ban the Use of Antibiotics in Animal Feeds,” *Science* 209.4455 (1980): 481–82.

Appropriations Subcommittee, all of whom had agreed with the livestock and pharmaceutical industries in opposing FDA's proposals.¹³⁵ The pork producers also suggested that the hearing would provide a "public platform for misguided activists to make unfounded charges" that would create "unfavorable publicity" for their products.¹³⁶ Representatives of the Animal Health Institute, the industry organization that represented veterinary pharmaceutical manufacturers, provided testimony that called into question the certainty of the scientific evidence on the risk to human health created by the subtherapeutic use of antibiotics in feed. In opposing Dingell's bill, they buttressed the position of the livestock and pharmaceutical industries, as well as many members of Congress representing agricultural districts.¹³⁷

Conversely, Crawford's testimony, representing the position of BVM and FDA as a whole, emphasized that the existing scientific evidence indicated a need for regulatory action. Crawford stated that "no one would disagree that continuous sub-therapeutic feeding of penicillin or tetracycline encourages the development of bacterial resistance," or that resistant infections are difficult to cure in humans.¹³⁸ Crawford dismissed the arguments of those who called for additional studies before moving forward with regulation, on the grounds that "what appears to be controversy is for the most part the contrivance of special interest groups."¹³⁹ He called the demand for more studies "the obvious gambit of the regulated industry," which had effectively postponed reforms for over a decade, and compared the "so-called controversy" over whether to limit subtherapeutic antibiotic use in feed to the Bastian-Pasteur debates of the nineteenth century. Just as those who opposed Pasteur were never able to accept germ theory,

¹³⁵ *Ibid.*

¹³⁶ *Ibid.*

¹³⁷ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 407-410 (Dr. William L. Hewitt); 414-416 (Eugene Lambert, Counsel, Animal Health Institute).

¹³⁸ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 455 (Lester Crawford, Director of Bureau of Veterinary Medicine).

¹³⁹ *Ibid.*

continuing to ask for more studies even after the evidence was clear, Crawford argued that those who did not support the agency's position at this point never would.¹⁴⁰ Crawford also pointed to a number of other controversial proposals in the past, such as water purification and milk pasteurization, where the government moved forward on public health measures despite the fact that there could be “no human experimentation and there were no bodies in the streets,” and saw the material reduction of human maladies as a result.¹⁴¹

During this 1980 hearing, FDA made its position clear: Congress should allow the agency to move forward with its proposals without further delay. However, FDA knew that there was interest in extending a “moratorium toward taking any final action” until the agency conducted the study that Congress had mandated in the 1980 appropriations bill.¹⁴² Crawford expressed FDA's frustration regarding their orders from Congress, given that the NAS study had concluded that “the study envisioned by the Congress was not attainable.”¹⁴³ Addressing a question from Rep. Waxman as to whether the agency believed regulatory action should be delayed until the completion of this study, Crawford said FDA was “in somewhat of a quandary because these studies would cost well over \$1 million and yet would not finally answer the regulatory questions.”¹⁴⁴ Based on the existing scientific evidence, the position of FDA and the administration was that subtherapeutic uses of penicillin and tetracyclines in animal feed should be prohibited.¹⁴⁵

¹⁴⁰ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 457 (Lester Crawford, Director of Bureau of Veterinary Medicine).

¹⁴¹ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 455 (Lester Crawford, Director of Bureau of Veterinary Medicine).

¹⁴² U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 472 (Lester Crawford, Director of Bureau of Veterinary Medicine).

¹⁴³ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 473 (Lester Crawford, Director of Bureau of Veterinary Medicine).

¹⁴⁴ *Ibid.*

¹⁴⁵ *Ibid.*

Nevertheless, FDA's proposals were ultimately at the mercy of Congress, which faced a difficult issue involving complex science, unavoidable uncertainties, and strong vested interests that held power on both sides of the aisle. The true question at this critical point in the summer of 1980 was not one of science, but one of policy. As Rep. Dingell expressed during his testimony, the issue at hand required policymakers to answer tough questions about the nature of proof and the appropriate course of action when the type of proof they desired was unattainable, and to decide for themselves when there existed sufficient data to justify action.¹⁴⁶ While members of Congress remained split on these questions, the agency to which Congress had delegated the authority to make such judgments had made its position clear: the scientific community had provided its recommendations that the subtherapeutic use of antibiotics in animal feed be limited, and the time for action had come.

Though FDA had found strong allies in Reps. Dingell and Waxman, the agency faced a formidable adversary in Rep. Jamie L. Whitten, a Democrat from Mississippi who served as the Chairman of the House Appropriations Committee.¹⁴⁷ Whitten was known as a staunch advocate for farmers and was sometimes referred to as the “permanent secretary of agriculture.”¹⁴⁸ It was Whitten who had led the charge to write a ban on FDA regulation of subtherapeutic animal antibiotic use in the appropriations bills for the previous two years.¹⁴⁹ American Cyanamid Corporation, a leading manufacturer of penicillin and tetracyclines used in animals, had also been an active opponent of regulation, so much so that Crawford, the director of BVM, called the corporation “the biggest obstacle” to FDA's regulatory efforts on this issue for more than eight

¹⁴⁶ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1980, 14 (Rep. John Dingell).

¹⁴⁷ Elizabeth Wehr, “Drugs Losing Punch in Humans: FDA [Food and Drug Administration], Dingell Seek Ban on Use of Antibiotics in Animal Feed,” *Congressional Quarterly Weekly Report* 38 (1980): 1880–81.

¹⁴⁸ *Ibid.*

¹⁴⁹ *Ibid.*

years.¹⁵⁰ A veterinarian for American Cyanamid’s animal drug division described how the company had spent “plenty” attempting to delay, and ultimately prevent, the FDA proposals from being carried out, both by lobbying Congress to stop the agency and by sending information to livestock farmers in the hopes they would join the opposition.¹⁵¹

Despite FDA’s efforts to persuade Congress to support their position in 1980, advocates for agricultural and pharmaceutical interests won the battle over subtherapeutic antibiotic use in animal feed in the short term. Whitten’s Agriculture Appropriations Subcommittee prohibited FDA action on the issue again in the fiscal year 1981 appropriations bill, leaving the agency powerless to move forward with its proposals.¹⁵² The Appropriations Committee noted that there were “significant data gaps that must be filled before an informed agency decision is made,” and stated that “FDA will be expected to hold in abeyance any implementation of its proposal” pending the results of the epidemiological study Congress had asked FDA to complete.¹⁵³ Disappointed by Congress’s intervention, Crawford was quoted saying the ban defied “almost universal agreement” among microbiologists and public health experts that the subtherapeutic use of antibiotics in animal feed was “foolhardy,” and he noted that “the Appropriations Committee is a strange, strange body of experts,” to be making such a determination.¹⁵⁴ FDA’s only hope of overcoming this prohibition lay with Dingell’s bill, which would have overridden the language in the appropriations committee’s report. Unfortunately for FDA, the Antibiotics Preservation Act did not make it out of committee.¹⁵⁵

¹⁵⁰ *Ibid.*

¹⁵¹ *Ibid.*

¹⁵² U.S. Congress, Senate, Committee on Appropriations, *Agriculture, Rural Development and Related Agencies Appropriations Bill, 1982*, 97th Cong., 1st sess., October 23, 1981, S. Rep. 97-248, 79.

¹⁵³ *Ibid.*

¹⁵⁴ Wehr (1980).

¹⁵⁵ “Congressional Record on H.R. 7285, Antibiotics Preservation Act.” U.S. Congress. <https://www.congress.gov/bill/96th-congress/house-bill/7285>.

The battle over FDA's proposals to restrict subtherapeutic use of antibiotics in feed from 1977 to 1980 provides an extreme example of how negative external feedback can lead to diminished agency autonomy. The animal agriculture and pharmaceutical industries provided strong negative feedback both directly to the agency as well as to Congress, allowing them to exert influence through two channels. Congress, hoping that the NAS study would provide an unequivocal answer to the regulatory questions at hand, intervened directly to postpone FDA action until the results were published. When the results of the NAS study did not provide the answers they sought, and instead casted doubt on the idea that such questions could ever be answered to Congress's satisfaction, FDA officials decided that the existing evidence was sufficient to justify moving forward with their proposals. Instead of deferring to agency decision-making and the regulatory process designated for dealing with such issues, Congress stepped in once again to exert control directly over FDA's behavior. Because FDA did not align its behavior with the feedback it received on its proposals to the satisfaction of external stakeholders, the agency's autonomy was significantly reduced by direct intervention from Congress.

Crawford, the director of BVM, expressed surprise and disappointment at the agency's inability to regulate what he deemed to be a hazard to human health that fell directly under FDA's statutory authority. While FDA's ability to act swiftly on subtherapeutic antibiotics in feed had been fettered first by its burdensome rulemaking procedures and then by the prospect of legal action from the pharmaceutical industry (which is perhaps why FDA moved slowly after its initial task force report), Crawford seemed most surprised by Congress's decision to place direct restrictions on FDA action through the appropriations process for three consecutive years. After

the passage of the 1981 agricultural appropriations bill that banned regulatory action on animal feed antibiotics, Crawford commented, “It’s the god-damnedest thing I’ve ever seen.”¹⁵⁶

1981-1985: New Scientific Evidence Renews the Debate

Though FDA was unable to proceed with its proposals to restrict subtherapeutic uses of penicillin and tetracyclines in animal feed, the agency moved forward to carry out the epidemiological study for which Congress had allotted money in 1981. FDA contracted with the Seattle-King County Department of Health to carry out an epidemiological study of *Salmonella* and *Campylobacter* in meat products in the community and their link to human disease, hoping that the results would provide additional evidence to answer the lingering technical questions that were standing in the way of regulatory action.¹⁵⁷ As this study was being completed, several other studies were published that made significant breakthroughs in the technical obstacles standing in the way of the proposals. The results of these studies weakened the argument that a direct link between subtherapeutic antibiotic use in animals and human illness could not be proven, and strengthened FDA’s position significantly.

In July of 1982, the *New England Journal of Medicine* published a study authored by Thomas O’Brien along with a number of prominent microbiologists and public health researchers that examined the transfer of antibiotic resistance among *Salmonella* bacteria.¹⁵⁸ The study used a technique that extracted the genetic material that codes for resistance, called plasmids, from bacteria taken from animals and humans, and found that the plasmids were often

¹⁵⁶ Wehr (1980).

¹⁵⁷ U.S. Congress, House of Representatives, Committee on Science and Technology, *Antibiotic Resistance: Hearing before the Subcommittee on Investigations and Oversight*, 98th Cong., 2nd sess., December 18 and December 19, 1984, 81 (Lester Crawford, Director, Center for Veterinary Medicine).

¹⁵⁸ T.F. O'Brien et al., “Molecular Epidemiology of Antibiotic Resistance in *Salmonella* From Animals and Human Beings in the United States,” *New England Journal of Medicine* 307.1 (1982): 1-6.

identical. This finding indicated that bacteria from animals and humans extensively share the genetic material that codes for resistance.¹⁵⁹ Because the plasmids provided a unique “fingerprint” that they could identify, researchers were able to link a bacterium-plasmid combination that was found to be endemic in cattle in 20 states to an outbreak that infected 26 persons caused by the same bacterium-plasmid combination, which showed characteristics of a foodborne infection.¹⁶⁰ This study provided much-needed concrete evidence to support the theory that resistant bacteria in animals can be spread to humans.

Two years later, Scott D. Holmberg of the CDC authored two key studies that further supported this link. In August of 1984, Holmberg and a team of CDC researchers reported that the majority of drug-resistant *Salmonella* outbreaks in the U.S. over the past decade were traced to animal food sources, and that patients with drug-resistant *Salmonella* infections had a significantly higher fatality rate than those infected with drug-responsive strains of the bacteria.¹⁶¹ A month later, Holmberg was the lead author of a study published in the *New England Journal of Medicine* that carefully investigated cases of antibiotic-resistant *Salmonella newport* infections among 18 people in the Midwest, and traced each case back to hamburger from a South Dakota beef cattle herd that had been fed subtherapeutic chlortetracycline for growth promotion.¹⁶² The authors concluded that the study “demonstrates that antimicrobial-resistant organisms of animal origin cause serious human illness, and emphasizes the need for more prudent use of antimicrobials in both human beings and animals.”¹⁶³ The findings of the *S. newport* study provided perhaps the most conclusive evidence yet for the direct link between

¹⁵⁹ *Ibid.*

¹⁶⁰ *Ibid.*

¹⁶¹ S. Holmberg et al., “Animal-to-Man Transmission of Antimicrobial-Resistant *Salmonella*: Investigations of U.S. Outbreaks, 1971-1983,” *Science* 225.4664 (1984): 833–35; Sun, Marjorie. “Use of Antibiotics in Animal Feed Challenged.” *Science* 226.4671 (1984): 144–46.

¹⁶² S. Holmberg et al., “Drug-Resistant *Salmonella* from Animals Fed Antimicrobials,” *New England Journal of Medicine* 311.10 (1984): 617-622.

¹⁶³ *Ibid.*

subtherapeutic antibiotic use in livestock and human illness that many had sought as a prerequisite to FDA regulation. Together with the CDC report on the *Salmonella* outbreak and the O'Brien study, Holmberg's research gave those pushing for progress on FDA's proposals renewed hope that Congress and the industry would allow the agency to move forward.¹⁶⁴

Lester Crawford, director of the renamed Center for Veterinary Medicine (CVM) at FDA, said that the *S. newport* study was "about as good as we're going to get," and that he "[didn't] see how [FDA] can get any better information."¹⁶⁵ According to Crawford, the findings of these studies were consistent with CVM's preliminary review of the Seattle-King epidemiological study that FDA had commissioned, but when Holmberg's study was published in September of 1984, the Seattle-King study was still under evaluation at the agency.¹⁶⁶ Others who had studied the issue were also enthusiastic about the new evidence. Raoul Stallones, chairman of the 1980 NAS study that had been unable to prove or disprove the existence of such a connection between human illness and subtherapeutic antibiotic use in animals, said the Holmberg study was "as close as one can get to a direct link." Stallone commented that had the Holmberg and O'Brien studies been available during NAS's evaluation, the committee "might not have been as blasé about antibiotics" as they were.¹⁶⁷

Some opponents of FDA's proposals denied that the recent studies were as significant as many were making them out to be, while others changed tacks and focused on alternative arguments to avoid regulation. Commenting on the *S. newport* study, a vice president at the Animal Health Institute, which represented animal drug manufacturers, said the authors had taken "a great leap in logic" to come to the conclusion that that the *S. newport* was of animal

¹⁶⁴ Sun, "Use of Antibiotics in Animal Feed Challenged."

¹⁶⁵ *Ibid.*

¹⁶⁶ *Ibid.*

¹⁶⁷ *Ibid.*

origin and that there was “not a shred of evidence” to suggest that the bacteria could not have come from other foods.¹⁶⁸ Many representing the views of livestock producers, including the American Farm Bureau Federation, acknowledged that the new studies had undermined their arguments that the scientific evidence was unable to show a direct link, and instead emphasized the economic costs to both farmers and consumers should FDA move forward with restrictions on subtherapeutic antibiotic use.¹⁶⁹

The Seattle-King study, which was the final report Congress had required FDA to complete before the agency was permitted to revisit its proposals, was released in November of 1984, and addressed a much narrower, but critical, question that had hitherto been unanswered in the breakthrough studies of the early 1980s.¹⁷⁰ The Seattle-King study was designed to help answer the question of how much human illness was caused by the consumption of bacteria from animal products, which was critical in helping policymakers understand the scope and magnitude of the risk and determine if restrictions were justified.¹⁷¹ The researchers found that of all the cases of diarrheal illness among residents of Seattle-King County, half were caused by the consumption of bacterially contaminated chicken. They also discovered that one in four chickens sold was contaminated by bacteria, primarily *Salmonella* and *Campylobacter jejuni*.¹⁷² Additionally, the Seattle-King study determined that 30 percent of *C. jejuni* from animal and human sources were resistant to tetracycline, which at the time was fed to approximately 30 percent of poultry in the U.S.¹⁷³

¹⁶⁸ Sun, “Use of Antibiotics in Animal Feed Challenged,” 145.

¹⁶⁹ *Ibid.*

¹⁷⁰ Sun, “New Study Adds to Antibiotic Debate” (1984)

¹⁷¹ *Ibid.*

¹⁷² *Ibid.*

¹⁷³ *Ibid.*

Bolstered by significant new evidence that pointed to the human health hazards of subtherapeutic antibiotic use in animals, FDA presented the new studies to Congress at a hearing before the House Subcommittee on Investigations and Oversight of the Committee on Science and Technology in December of 1984. After having shelved the issue for several years, Crawford and his colleagues at CVM hoped they would now be able to proceed from a stronger position. However, Crawford acknowledged that they would have to handle the issue “gingerly” and “have the courage of [their] convictions” if they wanted to have any hope of pushing the proposals through, given the controversial nature of the topic and the negative feedback they had received from Congress and the industry during past attempts.¹⁷⁴ Al Gore, then a Democratic representative from Tennessee serving as the chair of the subcommittee, cited the new scientific evidence on antibiotic resistance as the reason for the hearing, which was meant to provide members of Congress with the opportunity to evaluate whether the evidence supporting FDA’s proposals was more conclusive now than it was when Congress had voted to block them.¹⁷⁵ Researchers from the CDC as well as Dr. Thomas O’Brien, author of the breakthrough research on plasmids, were called as witness to discuss the new studies, as was Lester Crawford representing FDA and Dr. Donald Houston, the Administrator of the Food Safety Inspection Service (FSIS) at USDA. During the hearing, Crawford expressed CVM’s view that Congress’s two major points of criticism regarding the agency’s 1977 proposals (that there was insufficient epidemiological evidence and there were no specific instances in which subtherapeutic antibiotic use in feed was linked with the subsequent development of human disease) were substantially addressed by the new studies. Crawford emphasized that now that the agency believed the

¹⁷⁴ Sun, “Use of Antibiotics in Animal Feed Challenged” (1984).

¹⁷⁵ U.S. Congress, House of Representatives, Committee, *Antibiotic Resistance*, 1984, 2 (Rep. Albert Gore).

scientific gaps Congress had identified had been filled, they planned to decide on the issue in the near future.¹⁷⁶

Crawford also discussed the petition that the Secretary of Health and Human Services had received from the Natural Resources Defense Council (NRDC) on November 20, 1984 to declare subtherapeutic use of penicillin and tetracycline in animal feed an imminent hazard to human health.¹⁷⁷ The “imminent hazard” power of section 512(e)(1) of the FD&C Act gives the Secretary the authority to immediately suspend the approval of any animal drug use if it poses an imminent hazard to the health of man or of the animals on which the drug is being used, though the agency is still required to undergo the formal procedure to permanently withdraw the product after the Secretary has declared it an imminent hazard.¹⁷⁸ Representatives from NRDC, called to testify in another panel during the hearing, said that the petition, signed by 300 leading scientists, represented not just NRDC’s position but “the concerns of the scientific community at large,” and was justified by NRDC’s morbidity estimates that subtherapeutic antibiotic use in animal agriculture was linked to between 100 and 300 human deaths each year.¹⁷⁹ Because formal withdrawal proceedings could take up to three years, the NRDC argued that the Secretary should immediately suspend approvals based on the evidence from recent scientific studies, since such action would pose no risk to human health and no significant risk to animal health.¹⁸⁰

Crawford said that the agency would hold a legislative-type hearing on the petition to gather and evaluate all available data and information, and then evaluate the petition based on the

¹⁷⁶ U.S. Congress, House of Representatives, Committee, *Antibiotic Resistance*, 1984, 81-83 (Lester Crawford, Director of Center for Veterinary Medicine).

¹⁷⁷ U.S. Congress, House of Representatives, Committee, *Antibiotic Resistance*, 1984, 82 (Lester Crawford, Director of Center for Veterinary Medicine).

¹⁷⁸ Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §512(e)(1) (1984).

¹⁷⁹ U.S. Congress, House of Representatives, Committee, *Antibiotic Resistance*, 1984, 142-143 (Dr. Karim Ahmed, National Resources Defense Council).

¹⁸⁰ U.S. Congress, House of Representatives, Committee, *Antibiotic Resistance*, 1984, 144 (Sarah Chasis, National Resources Defense Council).

criteria for designating an imminent hazard: (1) the likelihood that FDA would eventually withdraw approval; (2) the severity of harm pending withdrawal of approval; (3) the likelihood of harm pending withdrawal of approval; (4) the risk to treated animals from suspending marketing; and (5) other approaches to protect the public health.¹⁸¹ CVM would then provide a recommendation to the Secretary following this hearing, which was expected in the spring of 1985.¹⁸² Crawford emphasized that FDA intended to decide both whether to move forward with withdrawal proceedings and whether to call for an immediate ban on penicillin and tetracycline use in feed in the near future. This move indicated that the agency wished to reestablish its autonomy in dealing with this issue and perhaps discourage further intervention by Congress.¹⁸³

During the 1984 hearing, Congress also impaneled Dr. Houston of FSIS to testify on behalf of USDA on the question of antibiotics in animal feed. Though USDA had never taken an official position on the issue, their reports had stressed the benefits of subtherapeutic antibiotic use in feed for livestock producers and American consumers. USDA representatives in previous Congressional hearings had emphasized the uncertainty of the scientific evidence linking the practice to human illness, putting USDA at odds with FDA's position on its proposals. Interrupting Houston's prepared statement describing USDA's residue testing and meat inspection activities, the chairman of the subcommittee questioned Houston on USDA's position on the proposed restrictions on antibiotics in animal feed, requesting USDA's input on the questions they were discussing.¹⁸⁴ Houston said that USDA had no position on the issue and declined to comment further on it, and while Rep. Gore said he believed USDA should be

¹⁸¹ U.S. Congress, House of Representatives, Committee, *Antibiotic Resistance*, 1984, 82 (Lester Crawford, Director of Center for Veterinary Medicine).

¹⁸² *Ibid.*

¹⁸³ U.S. Congress, House of Representatives, Committee, *Antibiotic Resistance*, 1984, 83 (Lester Crawford, Director of Center for Veterinary Medicine).

¹⁸⁴ U.S. Congress, House of Representatives, Committee, *Antibiotic Resistance*, 1984, 99 (Dr. Donald Houston, Administrator, Food Safety Inspection Service of U.S. Department of Agriculture).

involved due to its expertise, he understood “the political pressures that are brought to bear” on the USDA regarding these issues that might make USDA “reluctant to get involved.”¹⁸⁵

This exchange is significant because it highlights several key aspects of the tension between USDA and FDA on the issue of antibiotics in animal feed that often lies below the surface of the debate. Though FDA and USDA are both charged with overseeing various aspects of food production that are often closely intertwined, their underlying mandates differ in ways that can cause conflict. Because FDA is charged with protecting human and animal health while USDA works on behalf of American agriculture, the issue of antibiotic use in animal feed is viewed through fundamentally different lenses by the two departments. Though tasked with working together on the regulation of animal agriculture and food production, FDA’s proposed regulations were largely opposed by farmers, placing USDA in a difficult position. While USDA did not actively involve itself in lobbying for or against FDA’s proposals, its veiled critique of FDA’s position during Congressional hearings and in its reports placed additional pressure on FDA that may have factored into FDA’s behavior on the issue.

Though USDA refrained from commenting on FDA’s proposals, representatives from the National Cattlemen’s Association, the National Pork Producers Council, and the National Feed Manufacturers Association called to testify during the hearing expressed concern about FDA’s proposals, criticizing the agency’s evaluation of the science and emphasizing the economic costs of restrictions on the subtherapeutic use of antibiotics.¹⁸⁶ Though they had declined to participate in the last Congressional hearing on the issue in 1980 because they felt the issue had already been adequately considered, the cattlemen and pork producers both sent the chairs of their

¹⁸⁵ U.S. Congress, House of Representatives, Committee, *Antibiotic Resistance*, 1984, 107 (Rep. Albert Gore).

¹⁸⁶ U.S. Congress, House of Representatives, Committee, *Antibiotic Resistance*, 1984, 189-229.

respective antibiotic task forces to urge Congress to block FDA. Their presence at the hearing suggests that they perceived the issue as a serious threat to their industry's practices.

During the following year, when FDA had planned to hold hearings on the 1977 proposals, the CVM came under increased Congressional scrutiny for its regulation of animal drugs. In July of 1985, a subcommittee of the House Committee on Government Operations held a hearing on FDA's regulation of animal drugs in which members called on CVM officials to explain why so many animal drugs currently on the market had not been adequately vetted or approved by the agency.¹⁸⁷ In December of that year, the subcommittee issued a report that provided the most in-depth evaluation of FDA's ability to oversee the animal drug industry in 15 years.¹⁸⁸ The report criticized FDA for failing to adequately regulate animal drugs, highlighting a number of cases in which the agency did not remove dangerous drugs from the market or prevent the illegal marketing or unapproved use of certain substances. However, the subcommittee focused mostly on carcinogenic substances and illegal sales of animal drugs, and did not mention the agency's regulation of subtherapeutic uses of antibiotics.

Perhaps this elevated level of scrutiny of CVM's regulatory behavior by Congress was one reason why the agency appeared to move the issue of subtherapeutic antibiotic use in animal feed to the back burner over the next several years. The report alarmed some already concerned about antibiotic use in animal agriculture, who believed that Congress and the agency should feel greater urgency now that FDA's ability to oversee the animal drug industry had been called into question.¹⁸⁹ However, with Congress forcing FDA's attention to the major cases identified in its

¹⁸⁷ U.S. Congress, House of Representatives, Committee on Government Operations, *Regulation of Animal Drugs by the Food and Drug Administration*, 99th Cong., 1st sess., July 24 and July 25, 1985.

¹⁸⁸ U.S. Congress, House of Representatives, Committee on Government Appropriations, *Human Food Safety and the Regulation of Animal Drugs*, H.R. Rep. No. 99-461 (1985); Keith Schneider, "FDA Faulted in Threat From Animal Drugs," *New York Times*, January 13, 1986.

¹⁸⁹ Keith Schneider, "Should Farmers Go Cold Turkey?" *New York Times*, January 19, 1986.

somewhat scathing report on CVM's performance, the agency may have determined that to focus on addressing the problems Congress identified was a better use of their resources than attempting to work against Congressional will to push through its 1977 proposals. Because both the budgetary and political costs of proceeding with the formal withdrawal process were high and unlikely to be outweighed by the political benefits, FDA's decision not to act on its proposals at this time was a rational response to the external signals it was receiving. After holding hearings on NRDC's petition for the agency to declare subtherapeutic use of penicillin and tetracyclines in animal feed to be an imminent hazard, the Secretary of Health and Human Services rejected the group's petition.¹⁹⁰ This marked the beginning of the period of several years in which the issue languished at FDA.

1985-1999: FDA Moves Towards an Informal Regulatory Strategy

During the decade following FDA's rejection of NRDC's imminent hazard petition, the agency was virtually silent on the issue of subtherapeutic antibiotics in feed. Nevertheless, other organizations continued to examine the link between the practice and the emergence of more antibiotic-resistant illnesses in humans, creating a growing body of evidence pointing to the need for regulatory action. In 1986, shortly after Congress had issued its report criticizing FDA for its inadequate regulation of animal drugs, the CDC published a report that made this link even clearer. The report found that food animals were a major source of antibiotic-resistant strains of salmonella, particularly those resistant to penicillin and tetracycline, and concluded that "these infections [were] associated with antimicrobial use on farms."¹⁹¹ The principal author of the new study said that it called into question the practice of using human antibiotics in animals; at the

¹⁹⁰ Karen Wright, "The Policy Response: in Limbo," *Science* 249.4964 (1990): 24.

¹⁹¹ M. Cohen and R. Tauxe, "Drug-Resistant Salmonella in the United States: an Epidemiologic Perspective," *Science* 234.4779 (1986): 964-69.

same time, both the cattlemen's and veterinarians' associations reportedly stated that "the routine use of antibiotics in animal feed is now discouraged."¹⁹² FDA did not comment extensively on the CDC report when it was released, but a representative said the agency was in the process of reviewing all new information and that they planned to decide by the end of the year whether to attempt a ban again or take a different position.¹⁹³

In 1987, Commissioner Frank Young of FDA requested that NAS's Institute of Medicine (IOM) carry out a study on the issue once again, this time focusing specifically on predictive risk evaluation.¹⁹⁴ In late 1988, IOM released its results, which prompted Gerald Guest, the Director of CVM at the time, to create a working group for evaluating the issues raised by the new study.¹⁹⁵ Headed by Gary Dykstra of CVM, the working group did not conclude its review until July of 1990, at which point the CVM said it hoped to decide on the issue by the end of that summer.¹⁹⁶ Expressing irritation at the slow pace of progress on the issue, Dykstra said, "It's very frustrating. Every time we try to do something definitive, Congress pokes its head in."¹⁹⁷

Congress had not directly interfered since 1984, when FDA had completed the Seattle-King study, but the agency had not made any moves to act on its proposals to withdraw approvals for feed antibiotics. Though CVM continued to evaluate new evidence on antibiotic resistance, they had ostensibly abandoned any plans to continue through the formal rulemaking process. Instead, the agency set out on a different course that would attract less resistance from industry and Congress.

¹⁹² David H. Rhinelander, "Study Finds Danger in Routine Use of Antibiotics in Animal Feed," *The Hartford Courant*, March 5, 1987.

¹⁹³ *Ibid.*

¹⁹⁴ Institute of Medicine. Committee on Human Health Risk Assessment of Using Subtherapeutic Antibiotics in Animal Feeds. *Human Health Risks with the Subtherapeutic Use of Penicillin Or Tetracyclines in Animal Feed*. Washington, DC: National Academy Press; 1988.

¹⁹⁵ Wright (1990).

¹⁹⁶ *Ibid.*

¹⁹⁷ *Ibid.*

In August of 1995, FDA announced that it had approved a new antibiotic for chicken in order to prevent outbreaks of *E. coli* in poultry facilities.¹⁹⁸ Sarafloxacin, the new drug, was the first to fall under FDA's new monitoring program with the CDC and USDA, which required that the agencies test *Salmonella* and *E. coli* samples in humans and animals in search of evidence that resistance to the drug might be increasing.¹⁹⁹ The announcement of the National Antimicrobial Resistance Monitoring System (NARMS) was the first active step beyond requesting and reviewing new studies that FDA had taken since the 1977 proposals had been thwarted. This change of approach indicated that perhaps the agency was looking for a new path forward for regulating subtherapeutic antibiotic use in animal feed.

Shortly thereafter, FDA put its position on the practice into writing. In November of 1998, the agency published a draft of Guidance for Industry (GFI) 78, entitled, "Evaluation of Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals."²⁰⁰ The guidance document, which did not bind the agency or the regulated entities, reflected FDA's current thinking on the issue of subtherapeutic antibiotic use in animal agriculture, stating that FDA "now believe[d] it [was] necessary to evaluate the human health impact of the microbial effects" associated with all antimicrobial new animal drugs to be used in food-producing animals.²⁰¹ The draft stated that based on scientific evidence, the agency now believed sponsors of all antimicrobial new animal drugs that were intended for use in food-producing animals "should provide information relating to resistance and pathogen load

¹⁹⁸ "FDA Approves Antibiotic for Chickens; Drug Aimed at Preventing the Spread of Deadly E. Coli Bacteria," *Washington Post*, August 19, 1995.

¹⁹⁹ *Ibid.*

²⁰⁰ U.S. Food and Drug Administration, Notice, "Guidance for Industry: Evaluation of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals; Availability," *Federal Register* 63, no. 222 (November 18, 1998): 64094.

²⁰¹ U.S. Food and Drug Administration, *Draft Guidance for Industry 78: Evaluation of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals*, (November 1998): 2.

to allow FDA to determine if the products are safe” under the FD&C Act.²⁰² Although this would only apply to new animal drug applications, the draft guidance signaled that FDA had not abandoned its attempts to regulate antibiotic use in animal agriculture, but had decided on different tactics.

A few months later, FDA published a framework document in the Federal Register that represented the second step in the agency’s consideration of issues related to antimicrobial new animal drugs in food-producing animals.²⁰³ The document set out a conceptual risk-based framework that would serve as an official guide for FDA in evaluating the human safety of the use of new antibiotics in food-producing animals during the new drug approval process. Though it is unclear what motivated FDA to take these two steps after several years of inaction, they followed the publication of a widely-read study in the *New England Journal of Medicine* in 1998 that identified the emergence of a “superstrain” of *Salmonella* bacteria found in food that was resistant to most drugs.²⁰⁴

In June of 1999, FDA created the Interagency Task Force on Antimicrobial Resistance with CDC and NIH in order to coordinate efforts to manage antibiotic resistance across the federal government.²⁰⁵ The task force, which was later joined by several other agencies, created a “Public Health Action Plan to Combat Antibiotic Resistance” that was published two years later and specified a variety of steps to be taken by the three agencies.²⁰⁶ Though the task force created extensive recommendations related to preventing overuse and misuse of antibiotics in

²⁰² *Ibid.*

²⁰³ U.S. Food and Drug Administration, Notice, “Discussion Paper: A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals; Availability,” *Federal Register* 64, no. 3 (January 6, 1999): 887.

²⁰⁴ Kathleen M. Glynn, et al., “Emergence of Multidrug-Resistant *Salmonella enterica* Serotype Typhimurium DT104 Infections in the United States.” *N Engl J Med* 338.19 (1998): 1333–39; James Ciment, “FDA Proposes Measuring Antibiotics in Feed.” *British Medical Journal* 318.7187 (1999): 829.

²⁰⁵ U.S. Congress, Senate, Committee on Appropriations, *Antibiotic Resistance*, 106th Cong., 2nd sess., September 20, 2000, 9 (Dr. Jeffrey Koplan, Director, Centers for Disease Control and Prevention).

²⁰⁶ *Ibid.*

human medicine, it included few recommendations for new efforts in the realm of animal agriculture.

These actions represent a marked departure from the agency's original attempts to regulate subtherapeutic use of antibiotics in feed, which had indicated that FDA felt it held a strong position from which to initiate formal withdrawal proceedings that tend to be both politically and financially costly for the agency. The new actions were comparatively weak, as they bound neither the agency nor the drug sponsors and only applied to new animal drug applications. The framework document essentially created a suggested path forward for those applying for new drug applications without evaluating those already on the market. This move on the part of FDA to substitute a weaker, informal regulatory action for formal rulemaking reveals FDA's assessment that its political position had been compromised, and that the substantial expenditure of budgetary and political resources needed to move forward with rulemaking would be better used in other areas.

Though FDA appeared to have given up on taking tougher action on subtherapeutic antibiotic use in animals, proponents of the ban had not. In March of 1999, only a few months after FDA had published its draft guidance and framework document, the Environmental Defense Fund and the Center for Science in the Public Interest, along with 39 other groups, petitioned FDA for the second time to ban the use of antibiotics in animal feed if the same class of drugs were used in human medicine.²⁰⁷ The petition named seven antibiotics that were used in both humans and animals at the time, including penicillin and tetracyclines, and was similar to a ban that the European Union had put in place in 1998 after the occurrence of mad cow disease in

²⁰⁷ Peter Fairley, "FDA Weighs Animal-Feed Policy," *Chemical Week* 161.10 (1999): 10.

the UK.²⁰⁸ The petition also mirrored the recommendations of the WHO, which had met consider the issue in 1997 and 1998, and had advised that no antibiotics used in human medicine be used for growth promotion in animals.²⁰⁹ FDA was required to respond to the petition within 180 days, but at the time FDA received it, Stephen Sundlof, the director of CVM, said he “doubt[ed] that the agency ha[d] the authority to impose a broad ban on the use of antibiotics in animal feed.”²¹⁰ Even proponents of the petition seemed to agree with Sundlof that Congress was highly unlikely to approve the type of widespread ban that petitioners were pushing, citing the strong influence of pharmaceutical companies, which already objected to FDA’s milder plans to monitor and evaluate the influence of new antimicrobial drugs on resistance set forth earlier that year.²¹¹

Though Sundlof did not believe FDA had the authority to enact a ban, he did move forward with the agency’s guidance document, publishing the final version of GFI 78 on December 17, 1999.²¹² The guidance maintained most of its original content, but FDA noted that in response to public comments on the draft guidance and the framework document, the agency had altered some language to “indicate that additional testing would not always be needed to determine the potential human health impact of the microbial effects associated with antimicrobial new animal drugs” for use in food-producing animals.²¹³ FDA’s use of softer language in the final draft was likely aimed at appeasing pharmaceutical companies by assuring them that the guidance would not place a heavy burden on animal drug sponsors. Though GFI 78

²⁰⁸ “Push to Ban Use of Antibiotics in Animal Feed Gains Momentum,” *Chemical Market Reporter* 255.12 (1999): 10; Ciment (1999).

²⁰⁹ Charles Marwick, “Animal Feed Antibiotic Use Raises Drug Resistance Fear,” *JAMA* 282.2 (1999): 120–22.

²¹⁰ “Push to ban use of antibiotics in feed gains momentum” *Chemical Market Reporter* (1999).

²¹¹ Ciment (1999).

²¹² U.S. Food and Drug Administration, Notice, “Guidance for Industry: Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals (GFI #78); Availability,” *Federal Register* 64, no. 242 (December 17, 1999): 70715.

²¹³ *Ibid.*

did formally establish for the first time that FDA believed it was necessary to consider the human health impact of the microbial effects of all uses of all antimicrobial new animal drugs during the approval process, its status as a nonbinding guidance document and its applicability only to new animal drug applications made it a relatively weak regulatory step. This guidance document was also the first major indication that FDA was shifting strategies, increasing their focus on finding common ground with industry, rather than attempting formal rulemaking against a tide of opposition from pharmaceutical companies and livestock producers, both aimed directly at the agency and channeled through Congress.

The Early 2000s: Fluoroquinolone Use in Animals Raises Concerns

At the turn of the 21st century, FDA appeared to be reorienting its approach on subtherapeutic antibiotics in animal feed by aiming to build industry support for new regulatory steps, which had generally meant substituting weaker, informal actions for formal rulemaking. At the same time, the animal pharmaceutical industry was undergoing changes in the feed antibiotics market, as Europe began moving towards a full ban of most in-feed uses of antibiotics in animal agriculture.²¹⁴ By early 2000, industry leaders were predicting that Europe would ban all antibiotics used in animal feed by the end of 2001, and Denmark, Sweden, and Finland had already abolished the use of antibiotics for growth promotion.²¹⁵ In the previous two years, both the WHO and CDC had called for an end to growth promotion uses for several antibiotics in livestock. Even an undersecretary at USDA, which tended to side with agricultural interests over FDA, said in 2000 that the use of antibiotics in food-producing animals contributed to the

²¹⁴ Feliza Mirasol, "Ban on Animal Feed Antibiotics Opens Door to New Alternatives," *Chemical Market Reporter* 257.11 (2000): 14.

²¹⁵ *Ibid.*; Stanley Falkow and Donald Kennedy, "Antibiotics, Animals, and People: Again," *Science* 291.5503 (2001): 397–97.

problem of antibiotic resistance, and that “the agricultural community must accept part of the responsibility.”²¹⁶ The animal pharmaceutical industry was taking notice of these changes, and began to face the possibility that severe restrictions might be placed on these drugs not only in Europe, but perhaps eventually in the U.S., as well. In March of 2000, two major pharmaceutical companies were reportedly working to bring the first alternative feed supplements for growth promotion to market, chiefly due to the imminent closing of the in-feed antibiotic market in Europe.²¹⁷

Later that year, the pharmaceutical industry saw what the impact of such a ban would look like up close. In October of 2000, the financial fallout from a 1998 EU ban on Stafac, the company’s in-feed virginiamycin drug, forced pharmaceutical giant Pfizer to sell its animal feed drug business after total sales declined by approximately 60 percent from 1997 to 1999.²¹⁸ In 2000, Stephen Sundlof, Director of CVM, said that there were few companies coming to FDA with new low-dose antibiotic uses anymore, which he attributed to the industry’s realization that “the regulatory hurdles [were] going to be higher.”²¹⁹ Though the animal pharmaceutical industry seemed to be preparing for the worst, these changes did not necessarily indicate they would be any less vehement in their opposition to FDA regulation.

By 2000, a new concern had come to FDA’s attention that prompted the agency to reconsider the use of formal rulemaking. In 1986, FDA had approved the first drug for humans in a new class of antibiotics called fluoroquinolones, which were able to replace some of the older antibiotics that were no longer as effective due to widespread resistance.²²⁰ In 1995, FDA also

²¹⁶ American Public Health Association, “Antibiotics in Livestock Feed May Endanger Human Health,” *The Nation's Health* 29.3 (1999) 4.; Brownlee (2000).

²¹⁷ Mirasol (2000).

²¹⁸ Lisa Jarvis, “Antibiotic Feed Additives Under Review by FDA,” *Chemical Market Reporter* 259.4 (2001): 9.

²¹⁹ Brownlee (2000).

²²⁰ *Ibid.*

gave approval for the use of one fluoroquinolone, sarafloxacin, in the drinking water of chickens to prevent *E. coli* outbreaks because other antibiotics were not working. Sarafloxacin was the first drug to fall under NARMS, FDA's new resistance monitoring program with USDA and CDC.²²¹ FDA approval for animal use of a fluoroquinolone was intensely opposed by CDC, which cited concern about resistance due to the importance of fluoroquinolones in human medicine.²²² In the end, CDC's concerns were realized, when a 1999 study by CDC and Minnesota public health researchers published in the *New England Journal of Medicine* found a significant increase in fluoroquinolone-resistant *Campylobacter jejuni* infections in humans from 1992 to 1998, rising from 1.2 percent of the observed cases to 10.2 percent over the course of six years.²²³ By analyzing resistant *C. jejuni* from retail chicken products and comparing them with domestically acquired *C. jejuni* infections in Minnesota residents, researchers were able to determine that the increase in the fluoroquinolone-resistant infections in humans was almost certainly attributable to the use of the drug at subtherapeutic levels in chickens.²²⁴

At the time that this new evidence of fluoroquinolone resistance was becoming available, the GAO released a report requested by the Senate Committee on Agriculture, Nutrition, and Forestry regarding the human health implications of agricultural uses of antibiotics.²²⁵ The report noted that FDA and USDA held different views on whether the available scientific evidence warranted additional regulation or restriction of antibiotic use in animal agriculture, but recommended that FDA and USDA work together to create and implement a plan with specific goals, resources and timeframes to ensure the safe use of antibiotics in agriculture. Together with

²²¹ *Washington Post*. "FDA Approves Antibiotic for Chickens; Drug Aimed at Preventing the Spread of Deadly E. Coli Bacteria." August 19, 1995.

²²² Falkow and Kennedy (2001).

²²³ Smith et al. "Quinolone-Resistant *Campylobacter jejuni* Infections in Minnesota, 1992–1998." *N Engl J Med* 340.20 (1999): 1525–32.

²²⁴ *Ibid.*

²²⁵ U.S. General Accounting Office, *Food Safety: The Agricultural Use of Antibiotics and its Implications for Human Health*, GAO-99-74 (Washington, DC, 1999).

the emerging concern about fluoroquinolone resistance, the GAO report provided advocates of greater restrictions on agricultural antibiotic use with hope that FDA would have renewed momentum.

Meanwhile, FDA was continuing its effort to gradually build consensus between the pharmaceutical industry and the public health community around less controversial measures. In January of 1999, FDA held a public meeting to receive comments on the framework document it had published the previous year. Less than a year before the *New England Journal of Medicine* study was published raising the alarm about fluoroquinolones (and just one month after FDA officials had told GAO researchers that they were concerned about fluoroquinolone resistance), FDA approved fluoroquinolones for use in beef cattle.²²⁶ Though FDA's actions in 1998 and 1999 suggested that the agency did not believe it had sufficient external support for strong action on antibiotics in feed, its position had changed by late 2000.

On October 31, 2000, FDA published its proposed rule withdrawing approval for fluoroquinolone use in poultry.²²⁷ If the FDA succeeded, the ban would be a major landmark in the agency's regulation of subtherapeutic antibiotics in animal feed, as it would be the first drug approval ever withdrawn due to concerns about the emergence of resistance and its impact on human health. Abbott Laboratories, one of the two companies that manufactured the drug, agreed to stop making the drug and voluntarily withdraw its product from the market, but Bayer, the drug's major manufacturer, decided to challenge the ban.²²⁸ Though FDA devoted considerable legal resources to the challenge, the procedural difficulties of withdrawing an existing approval

²²⁶ *Ibid.*

²²⁷ U.S. Food and Drug Administration, Notice, "Enrofloxacin for Poultry; Opportunity For Hearing," *Federal Register* 65, no. 211 (October 31, 2000): 64954.

²²⁸ *Biotech Week*. "Abbott Laboratories; FDA Plans to Ban Two Poultry Drugs That Result in Human Exposure to Resistant Bacteria." November 15, 2000, 15.

and Bayer's commitment to contesting FDA's proposal meant that to enact a ban on the drug use was not a forgone conclusion.²²⁹

FDA's decision to pursue formal action withdrawing fluoroquinolones from the animal pharmaceutical market marked a departure from its strategy of the previous several years. Though it was able to persuade one of the drug's two manufacturers to voluntarily comply with its proposal, the agency knew Bayer would challenge the withdrawal before it decided to take action. However, deviating from its pursuit of informal actions that were supported by industry, FDA chose to move forward with a formal withdrawal despite opposition from a major pharmaceutical corporation. FDA's decision to break from its previous strategy and undertake a procedurally and financially intensive regulatory action despite Bayer's opposition indicates that the agency believed its position on fluoroquinolones was strong, backed by external signals from those who favored the ban that outweighed Bayer's opposition.

In examining the factors FDA was weighing when it decided to propose withdrawal in late 2000, it is clear that the scientific context likely played a significant role in enabling FDA's regulation. CDC made a critical contribution by carrying out a key study on fluoroquinolone resistance, which made it difficult for those opposed to FDA restrictions on animal antibiotic use to deny the connection between the drug's use in poultry and the increased incidence of resistant infections in humans. The 1999 GAO report that urged FDA to work with other agencies to develop and implement a concrete plan for protecting human health against the hazard of growing antibiotic resistance likely signaled to the agency that they might have political support for action if they had a legitimate case based on human health concerns. In addition to the CDC study and the GAO report, FDA's success in persuading one of the two manufacturers to agree to

²²⁹ "Antibiotics Used in Farm Animals Causing Hard-to-Treat Infections in Humans." *Tufts University Health & Nutrition Letter* 19.9 (2001): 4.

voluntarily comply allowed them to avoid some of the backlash from industry, which might have otherwise changed FDA's calculus. According to a 2004 GAO report, FDA also decided to proceed with withdrawal efforts because the agency knew there were effective alternatives for treatment of this illness in poultry, which may explain why poultry producers did not provide more opposition.²³⁰

Though it is unclear to what extent each of these factors played a role in shaping FDA's decision to take action despite Bayer's opposition, revisiting the circumstances of the agency's last decision to engage in formal rulemaking on the issue in 1977 provides useful context. In a 1977 Congressional hearing on the FDA's proposed withdrawal of penicillin and tetracycline, Donald Kennedy, former Commissioner of FDA, said that when considering a resource-intensive action, one of the most important questions FDA officials consider is whether the evidence is strong enough for the proposed action to stand up to challenges.²³¹ Otherwise, to pursue such an action would be a waste of the agency's limited resources, Kennedy said. Even though FDA's 1977 attempts indicate that strong scientific evidence alone is not always enough to ensure an action will be successful, CDC's role in providing the scientific context combined with external signals likely persuaded FDA that to attempt to withdraw approval for fluoroquinolones at that time would be a fruitful use of agency resources.

Ultimately, FDA's decision to pursue a formal withdrawal proved successful. FDA held an evidentiary hearing at the request of Bayer and the Animal Health Institute, and in March of 2004, an FDA Administrative Law Judge issued its initial decision approving the withdrawal on the grounds that fluoroquinolone use in poultry had not been shown to be safe. Bayer then filed

²³⁰ U.S. 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 (Washington, DC, 2004), 34-35.

²³¹ U.S. Congress, House of Representatives, Committee, *Antibiotics in Animal Feed*, 1977, 77 (Donald Kennedy, Commissioner of Food and Drug Administration).

an exception to the initial decision, delaying the final ruling an additional year. Despite Bayer's sustained efforts to block the action and the lengthy procedure required of the agency, FDA issued its final decision to withdraw approval for fluoroquinolone use in poultry in August of 2005.²³² FDA's first successful attempt to ban an approved antibiotic drug use in animals due to concerns about resistance took five years of sustained effort, indicating that formal withdrawal proceedings might not be a feasible option for FDA's regulation of broad classes of antibiotic uses going forward.

FDA Pushes for a More Proactive Strategy

While FDA was working to advance its fluoroquinolone withdrawal, the agency was also continuing its efforts to strengthen scrutiny of antibiotics during the new animal drug approval process. In late December of 2000, FDA published a document proposing two thresholds that would be used in the regulation of antibiotics in food-producing animals in order to limit the emergence and spread of resistance.²³³ The draft document was intended to build on the framework document that FDA had published in 1999, which discussed approaches to monitoring antibiotic use in animals and the development of resistance, both before and after approval. The new draft also built on the framework document's recommendation for integrating consideration of the human health impact of resistance into the approval and evaluation processes for animal antibiotic drug uses. The new document proposed two monitoring thresholds that were centered on the standard of "reasonable certainty of no harm" to humans for

²³² U.S. Food and Drug Administration, Rule, "Animal Drugs, Feeds, and Related Products; Enrofloxacin for Poultry; Withdrawal of Approval of New Animal Drug Application," *Federal Register* 70, no. 146 (August 1, 2005): 44048.

²³³ U.S. Food and Drug Administration, Notice, "Discussion Paper: An Approach for Establishing Thresholds in Association With the Use of Antimicrobial Drugs in Food-Producing Animals; Availability," *Federal Register* 65, no. 251 (December 29, 2000): 83070.

any use of antibiotics in food-producing animals, and which would trigger both voluntary and mandatory regulatory steps. A human health threshold would be based on the prevalence of resistant infections in humans when the resistance was attributable the use of the antibiotic in animals. The threshold represented “the level at which there is no longer a reasonable certainty of no harm to human health associated with antimicrobial resistance development as a consequence of antimicrobial drug use in food-producing animals.”²³⁴ There would also be a resistance-in-animals threshold that represented the maximum acceptable level of resistance in food-producing animals, based on a risk-assessment model that linked resistance in animals to the human health risk. While certain voluntary steps would be triggered if FDA monitoring revealed decreased drug efficacy or increased resistance, if either threshold was exceeded, the agency would be required to initiate a withdrawal of the drug.

The threshold document was a discussion paper meant to reflect FDA’s current thinking on one way to develop resistance thresholds, and thus was an informal and relatively weak regulatory action because it did not bind the agency. However, FDA used the document to test the waters on two significant concepts that, if implemented, would result in a substantially stronger regulatory approach to antibiotic use in food-producing animals. FDA’s choice of the “reasonable certainty of no harm” standard for regulating animal antibiotic use represented a much stronger protection for human health than an approach that balanced risks and benefits, which had characterized discussion of the issue since FDA’s first attempted regulations in the late 1970s. Health and consumer groups applauded FDA for selecting this standard, as they considered the decision not to allow the weighing of economic risks and benefits to be a significant positive development in protecting human health.²³⁵ The pharmaceutical industry,

²³⁴ *Ibid.*

²³⁵ Bette Hileman, “Furor Over Animal Antibiotic Use.” *Chemical & Engineering News* 79.8 (2001): 47.

however, intensely opposed the proposed standard in a public meeting in late January of 2001, threatening to sue FDA if it decided to use a “reasonable certainty of no harm” standard in its regulation of the drugs.²³⁶ The draft document also took a significant step by putting forward a proactive plan that triggered formal regulatory steps, signaling that FDA would pursue more aggressive regulation going forward.

Continuing with this strategy, FDA published a draft guidance in September of 2002 that was intended to assist in the implementation of the framework and threshold documents that the agency had published in the previous three years.²³⁷ The draft guidance (GFI 152) provided drug sponsors with a recommended approach for conducting a qualitative risk assessment to evaluate antibiotic resistance concerns. This risk assessment was to be submitted to FDA as part of the preapproval safety appraisal. For months after the draft guidance was published, agricultural and pharmaceutical companies vigorously debated FDA and public health officials on the nature of the risk and the parameters of the risk assessment that should be conducted during FDA’s public hearings on the guidance.²³⁸ While concern about FDA’s mismanagement of the fluoroquinolones issue spurred many advocates of tougher action on antibiotics in animals to support the creation of an established framework for risk assessment, the pharmaceutical industry was lobbying for language that would make it difficult for FDA to deny approval for a new drug.²³⁹ One year later, FDA published the final version of GFI 152, which provided steps for characterizing the hazard to human health presented by the drug use as high, medium, or low risk based on the drug’s importance in human medicine and an assessment of the release,

²³⁶ *Ibid.*

²³⁷ U.S Food and Drug Administration, Notice, “Draft Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern; Availability,” *Federal Register* 67, no. 178 (September 13, 2002): 58058.

²³⁸ Wesley R. Dean and H. Morgan Scott, “Antagonistic Synergy: Process and Paradox in the Development of New Agricultural Antimicrobial Regulations,” *Agriculture and Human Values* 22.4 (2005): 79–89.

²³⁹ Rick Weiss, “FDA Rules Override Warnings about Drug,” *Washington Post*, March 4, 2007.

exposure, and consequences of the drug use.²⁴⁰ Though nonbinding, the guidance laid out another concrete step for implementing the ideas proposed in FDA's framework document and formalizing the consideration of resistance concerns in the human health evaluation of antibiotic new animal drugs.

Though both were informal actions, the threshold document and GFI 152 gave the impression that FDA was looking to move towards a more aggressive strategy for regulating antibiotic use in animals. Nevertheless, many advocates for a tougher regulatory stance were skeptical that these steps would lead to real action. A GAO report published in 2004 that had been jointly commissioned by three Senate committees echoed many of these concerns.²⁴¹ Though the report noted that FDA had begun using the framework from its guidance to evaluate new animal drug applications and to review existing approvals for animal antibiotics, it found that FDA had not prioritized for review the antibiotics that the agency itself had identified as "critically important to human health." As of April of 2004, over two years after FDA had finalized its threshold document, not one of the drugs FDA had identified as critically important to human health in its 2002 guidance had been reviewed using the framework, and the reviews the agency had conducted had taken at least two years to complete.²⁴² This meant that it would likely take many years, and perhaps several decades, for FDA to complete its review of medically important antibiotics. If the agency decided regulatory action on a drug was required, administrative proceedings could extend for several additional years before regulation could take effect.

²⁴⁰ U.S. Food and Drug Administration, Notice, "Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern; Availability," *Federal Register* 68, no. 207 (October 27, 2003): 61221.

²⁴¹ U.S. General Accounting Office, *Antibiotic Resistance* (2004).

²⁴² U.S. General Accounting Office, *Antibiotic Resistance* (2004), 7.

Furthermore, the GAO report expressed concern that the framework set out in GFI 152 might not be effective in preventing the spread of resistance, given that FDA had reviewed seven new animal drug applications under the new framework by spring of 2004 and had never denied a new or supplemental animal drug application due to evidence that the drug caused antibiotic resistance in humans.²⁴³ Under the guidance, even those drugs categorized as high risk could still be approved with certain restrictions if there was “reasonable certainty of no harm.” Though such a standard was thought to be more protective than a balancing of risks and benefits, it was unclear how much proof of harm would be needed in practice to justify denying a new drug application.

The first risk assessments the agency carried out under the new guidance were for subtherapeutic uses of penicillin and tetracyclines. These drugs had been the subject of FDA’s 1977 proposals and included in the 1984 and 1999 withdrawal petitions to the Secretary of Health and Human Services from NRDC and several other health and public interest groups. According to documents released under the Freedom of Information Act, after completing a two-year-long review, FDA sent letters to four producers of approved animal feed additives containing penicillin and tetracyclines stating that the administrative record did not contain sufficient information to alleviate safety concerns, and invited them to meet with CVM to discuss the findings of their review.²⁴⁴ A year later, FDA had still taken no action on these antibiotics. The Environmental Defense Fund, the American Academy of Pediatrics, the American Public Health Association, Food Animal Concerns Trust, and Union of Concerned Scientists then filed a petition requesting that FDA withdraw approvals for herdwide/flockwide

²⁴³ U.S. General Accounting Office, *Antibiotic Resistance* (2004), 36.

²⁴⁴ Environmental Defense et al. Appendix 3, “Letters from FDA to Manufacturers of Certain Antibiotic Feed Additives,” in *Citizen Petition Seeking Withdrawal of Approvals of Certain Herdwide/Flockwide Uses of Critically and Highly Important Antibiotics Pursuant to Guidance #152*. April 7, 2015.

uses of seven antibiotics, including penicillin and tetracyclines, for growth promotion and disease prevention and control uses. In doing so, health and public interest groups put pressure on FDA to take formal regulatory action to curtail subtherapeutic antibiotic use in animals.

By the end of 2005, FDA was under fire from members of Congress, scientists, public health officials, and health and public interest groups for its new strategy, which was criticized as weak, ineffective, and without a reasonable timeline. In August of 2005, the Preservation of Antibiotics for Medical Treatment Act (PAMTA) was introduced into the House and the Senate for the third time, which would order FDA to review the safety of approved growth-promotion antibiotics that were important to human medicine and collect data on their use, going further than FDA's risk assessment plans at the time.²⁴⁵ More than 380 organizations endorsed PAMTA, and the WHO, IOM, and NAS had recommended severe restriction or a full ban of growth promotion uses of antibiotics, advocating for action that was more aggressive than FDA's strategy at this time.²⁴⁶ In addition to the 2004 GAO report urging FDA to expedite its risk assessments and the 2005 petition from environmental, health, and consumer groups, support for more decisive action by Congress and the scientific community indicated that many important FDA influencers did not support a weak, informal strategy on this issue.

Weighed against this negative feedback was the positive feedback from industry, which tended to be more receptive of FDA's informal regulatory approach than its attempts to address the issue through formal rulemaking. The need for industry support proved more important to FDA than the negative political feedback it received for not taking a more hardline approach to the issue, likely due to the agency's constrained resources. As FDA was implementing this

²⁴⁵ Preservation of Antibiotics for Medical Treatment Act of 2005, H.R. 2562, 109th Congress (2005); Preservation of Antibiotics for Medical Treatment Act of 2005, S. 742, 109th Congress (2005).

²⁴⁶ Rebecca Clouse, "Nursing Organizations Call for Phase-Out of Agricultural Practices That Promote Antibiotic Resistance," *Policy, Politics, & Nursing Practice* 7.1 (2006): 17–22.

strategy, it was also going through the withdrawal process for fluoroquinolones. This experience was teaching FDA that engaging in formal regulatory procedures to withdraw approval for a drug without the cooperation of the drug's sponsor could be time-consuming and costly, even when Congress, the scientific community, and the public largely supported the action. Perhaps based on this experience, FDA determined it would not be feasible for them to work against industry in most cases. In explaining the agency's current strategy to GAO, FDA officials emphasized that by obtaining voluntary cooperation from a drug sponsor in implementing risk management strategies, FDA might be able to avoid "lengthy administrative proceedings" that are costly for the agency.²⁴⁷

Cephalosporins Put FDA's New Guidance to the Test

The efficacy of FDA's new guidance in protecting the public health was soon put to the test, as the agency considered a drug application that would allow a new class of medically important antibiotics to be used in animal agriculture. In the fall of 2006, FDA convened its Veterinary Medicine Advisory Committee (VMAC) to assess the safety of a new antibiotic drug application for cefquinome, a fourth-generation cephalosporin that was the first in its class to be developed for agriculture, intended for use in cattle to treat bovine respiratory disease.²⁴⁸

Because of the importance of cephalosporins in human medicine, the potential for cross-resistance, and the availability of more than a dozen other medicines already available and effective for treating bovine respiratory disease, VMAC voted to reject the application.²⁴⁹

However, FDA was not bound to follow the committee's recommendation, and Steven Sundlof,

²⁴⁷ U.S. General Accounting Office, *Antibiotic Resistance* (2004), 39.

²⁴⁸ U.S. Food and Drug Administration, 2006, *Transcript of the Official Meeting of the Veterinary Medicine Advisory Committee, New Drug Microbial Safety Review Under Guidance #152*, September 25, 2006.

²⁴⁹ Weiss (2007).

the director of CVM at the time, emphasized that the application would ultimately be judged under the parameters set out in GFI 152.²⁵⁰ Both Intervet, the drug's sponsor, and FDA found that under GFI 152, cefquinome could be classified as a medium risk. While some of those who voted against approval disputed that classification, most felt that the guidance simply did not adequately assess the real risk to human health posed by the drug.²⁵¹

By spring of 2007, FDA was reported to be on track to approve cefquinome, drawing significant backlash from health and public interest groups.²⁵² In January of 2007, Rep. Louise Slaughter, who sponsored PAMTA, wrote a letter to FDA urging it not to approve the drug. Several other organizations, including the American Medical Association, the Keep Antibiotics Working coalition, and the American Academy of Pediatrics, had communicated their opposition to FDA, as well.²⁵³ The criticism of FDA's handling of the cephalosporin case shed light on several failings of GFI 152, most notably its narrow consideration of applicable human health risks. The major reason cefquinome could be approved under GFI 152 despite its importance in human medicine was that although fourth-generation cephalosporins were the only drugs able to treat serious infection in cancer patients, and were ranked by WHO as critically important to human health, they were not used as frontline treatments for foodborne illnesses.²⁵⁴ In classifying drugs according to their use in human medicine, GFI 152 heavily prioritized those drugs used in treating foodborne illnesses, while "other bacteria [could] be considered when necessary."²⁵⁵ Many pointed out that this bias made it exceedingly difficult to deny a new drug application on

²⁵⁰ U.S. Food and Drug Administration, 2006, *Transcript of the Official Meeting of the Veterinary Medicine Advisory Committee*, Comments of Dr. Steven Sundlof.

²⁵¹ *Ibid.*

²⁵² Weiss (2007).

²⁵³ "FDA set to approve controversial cow drug: report," *Reuters*, March 5, 2007.

²⁵⁴ U.S. Food and Drug Administration, 2006, *Transcript of the Official Meeting of the Veterinary Medicine Advisory Committee*.

²⁵⁵ U.S. Congress, Senate, Committee on Appropriations, *Agriculture, Rural Development, Food and Drug Administration and Related Agencies Appropriations for Fiscal Year 2008*, 110th Cong., 1st sess., February 27, 2007, 704.

the grounds of its importance in human medicine if the drug was not used to treat foodborne illnesses, even if it was critical to therapy for other diseases.

Another key weakness of GFI 152 that was highlighted in the cefquinome case was what many considered an inadequate weighing of concerns about cross-resistance. Many scientists at the VMAC meeting noted the potential for fourth-generation cephalosporins to select for traits that would confer resistance not only to its own class, but also to third-generation cephalosporins, which were widely used to treat pneumonia, meningitis, and serious gastrointestinal infections. Because the classification of a cephalosporin into a given “generation” is unrelated to the drug’s chemical structure, and because cephalosporins are broad-spectrum antibiotics that use the same mechanism of action as other beta-lactam antibiotics, many felt that FDA’s assessment should have weighed more heavily the potential for cross-resistance, both to other cephalosporins and to beta-lactams like penicillin. The cefquinome case tested the efficacy of the agency’s new guidance on a drug that was known to be critical in human medicine and highly likely to confer cross-resistance. In doing so, this case revealed the weaknesses of the guidance’s qualitative assessment of the consequence of a lost treatment option in humans when evaluating new antimicrobial drugs.

Though FDA had still neither approved nor denied the cefquinome application by December of 2009, concern about off-label uses of cephalosporins arose during the public debate of the new drug. During the 2006 VMAC meeting, the CDC, along with the Infectious Diseases Society of America, the American Medical Association, the Keep Antibiotics Working coalition, and the Union of Concerned Scientists, advocated strongly for a prohibition on extra-label use of cefquinome, should it be approved for therapy. Third-generation cephalosporins were already being used off-label in livestock production under an amendment to the FD&C Act created by

the Animal Medicinal Drug User Clarification Act (AMDUCA) in 1994.²⁵⁶ AMDUCA allowed veterinarians to prescribe extra-label uses of any approved animal and human drugs unless specifically prohibited by FDA. In order to prohibit extra-label use, FDA must find that extra-label use presents a risk to the public health and go through a formal regulatory process that includes opportunity for public comment. Thus, in response to suggestions by VMAC members that if approved, cefquinome should be prohibited from extra-label use preemptively, the director of CVM stated that FDA could not prohibit extra-label use merely as a precaution. Rather, the agency would have to establish “a very strong, credible case” based on a scientific determination that it posed a risk before attempting such a prohibition.²⁵⁷ As a result, concerns about the impact of off-label use could not be incorporated into a new drug’s risk assessment under GFI 152, even though approval for any use would automatically allow off-label use until FDA specifically prohibited it through a separate, formal rulemaking process.

Despite the uphill battle it knew it would face, FDA attempted a formal prohibition of extra-label use of all cephalosporins in animals in July of 2008, citing NARMS data that showed increased resistance in animal and human isolates since cephalosporins were introduced into animal agriculture, as well as concerns about cross-resistance.²⁵⁸ However, after receiving extensive comments on the order of prohibition, FDA decided to withdraw the rule on November 26, 2008, until the agency was able to review and respond to all the comments.²⁵⁹ Animal drug manufacturers, trade associations representing food animal producers, and veterinarians

²⁵⁶ Animal Medicinal Drug Use Clarification Act of 1994, Public L. No. 103-396, 108 Stat. 4153 (1994); U.S. Food and Drug Administration, Rule, “New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition,” *Federal Register* 73, no. 129 (July 3, 2008): 38110.

²⁵⁷ U.S. Food and Drug Administration, 2006, *Transcript of the Official Meeting of the Veterinary Medicine Advisory Committee*, Comments by Dr. Steven Sundlof.

²⁵⁸ U.S. Food and Drug Administration, Rule, “New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition,” *Federal Register* 73, no. 129 (July 3, 2008): 38110.

²⁵⁹ U.S. Food and Drug Administration, Rule, “New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Revocation of Order of Prohibition; Withdrawal,” *Federal Register* 73, no. 229 (November 26, 2008): 71923.

submitted comments objecting to the original order because they argued it was too broad in its ban of all extra-label uses, and that FDA had not met the legal standard for enacting the prohibition because the order was based on the precautionary principle rather than sound science.²⁶⁰ Though FDA said that after considering the comments, they would reissue the prohibition if they felt it was appropriate, the agency was silent on the matter for several years. It was not until January of 2012 that FDA addressed extra-label use of cephalosporins, issuing a narrower prohibition that addressed the pharmaceutical and animal production industries' concerns about the breadth of the original ban, but rejecting arguments that the agency failed to meet the legal standard for prohibition.²⁶¹

The weaknesses of FDA's informal strategy for regulating animal antibiotics that were brought to light during the cephalosporins case underscored the influence of the animal pharmaceutical industry, and perhaps to a lesser extent the food animal production industry, on FDA's decision-making, as well as the constraints placed on the agency by the costs of formal rulemaking procedures. Both of these factors seemed to outweigh the pressure from members of Congress, the scientific community, and health and public interest groups for FDA to place more restrictive regulations on antibiotic use in animal agriculture through formal rulemaking. After the several-month-long battle over the language in GFI 152, industry interests appeared to triumph over the interests of public health and consumer advocates in narrowly tailoring the language to limit what could be considered under the human health consequences assessment. The cefquinome case demonstrated that even drugs critical to human medicine could be approved for animal use if they were not essential for treating foodborne illnesses due to the way in which the guidance prioritized certain health concerns over others. Though the VMAC voted

²⁶⁰ U.S. Food and Drug Administration, Rule, "New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition," *Federal Register* 77, no. 4 (January 6, 2012): 735.

²⁶¹ *Ibid.*

that cefquinome should not be considered safe for animal use due to the risk to human health, under GFI 152, FDA and the drug sponsor found that cefquinome should be classified as a medium risk, which meant it could be approved with some post-approval risk management measures. GFI 152 also did not allow FDA to consider the availability of other treatment options or the risks of off-label use as a part of its risk assessment, both of which were major concerns of scientists and public health officials.²⁶²

The cefquinome case provided important insights into the effectiveness of FDA's new strategy. In evaluating the new animal drug application, FDA officials stressed that if drug sponsors followed the parameters of the guidance in their application, FDA would abide by the outcome recommended by the guidance's risk assessment despite the fact that the guidance was nonbinding. This led to a safety evaluation that many considered inadequate, raising questions about the ability of the new strategy to keep unsafe drugs off the market. Furthermore, FDA was unable to preemptively ban extra-label use of cefquinome as a stipulation of its approval for therapy due to procedural rules. FDA was also substantially delayed when it attempted a separate extra-label ban on all cephalosporins due to the ability for pharmaceutical companies and food animal producers to challenge the prohibition during the rulemaking process. These weaknesses indicated not only that FDA's informal regulatory strategy was inadequate in protecting human health, but also that the agency was hemmed in by the need for industry support in order to avoid delays and legal challenges FDA could not afford.

²⁶² U.S. Food and Drug Administration, 2006, *Transcript of the Official Meeting of the Veterinary Medicine Advisory Committee*.

The Obama Administration and Judicious Use

Over the past decade, the need for industry support had outweighed Congress' concerns that FDA's informal regulatory strategy was not sufficiently protective of human health in directing FDA's behavior. However, by 2007, Congress would no longer be ignored. After several years of expressing concerns in hearings and sending letters to FDA, Congress decided to take a more direct approach to ensure the agency would heed its directions. In 2007, the House Appropriations Committee wrote in its report on the 2008 FDA appropriations bill that it was "concerned that simply satisfying the requirements of the guidance document is not adequate to protect human health."²⁶³ Specifically, it noted that the committee felt the guidance did not assign enough weight to the impact of resistance to drugs that are highly important to human medicine but not used for treating foodborne illnesses.²⁶⁴ To address those concerns, the committee ordered FDA to "reevaluate the basis on which it makes such decisions" and provide a report to the committee by November of that year. The committee further stated that it was concerned that the agency had still not finished its review of the safety of the subtherapeutic use of penicillin in animal feeds, and ordered FDA to finish and publish its review by June 30, 2008.²⁶⁵

Congress had used the same tactic in the late 1970s and early 1980s in order to prevent FDA from moving forward with its 1977 proposals to restrict subtherapeutic uses of penicillin and tetracyclines, after FDA had decided to enact the rules despite the concerns voiced to agency officials by many members of Congress in hearings. By directly intervening through the appropriations process in order to ensure FDA was prioritizing its concerns, Congress indicated

²⁶³ U.S. Congress, House of Representatives, Committee on Appropriations, *Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2008*, H.R. Rep. No. 110-258, 98-99. (2007).

²⁶⁴ *Ibid.*

²⁶⁵ *Ibid.*

that it would no longer allow FDA to overlook congressional recommendations. This episode provides another example of a failure by FDA to adequately balance the feedback it receives, which often results in reduced autonomy for the agency, carried out here by Congressional intervention.

In August of 2008, Congress took another active step in directing FDA regulation of antibiotic use in animals by amending the Animal Drug User Fee Act to mandate that FDA collect and publish data on antibiotic use in food-producing animals each year.²⁶⁶ Though public health advocates had requested that the agency implement such a practice for many years, the animal pharmaceutical industry had opposed reporting requirements, citing concerns about revealing confidential business information. This victory for public health advocates showed their increasing influence after years of neglect by FDA.

With some members of Congress still dissatisfied with FDA's handling of animal antibiotic use, PAMTA was reintroduced into the 111th Congress in March of 2009 with unprecedented support in both the House and the Senate.²⁶⁷ On this iteration, Senate Majority Leader Harry Reid served as the primary sponsor of the Senate bill, along with 18 other cosponsors, two of whom were Republicans. The House bill also had more supporters than earlier versions of the bill had garnered. Though both bills died on the floor, the large number of sponsors supporting the House and Senate bills (127 and 19, respectively) indicated that Congress was paying attention to the issue once again, and that a growing number of members were dissatisfied with FDA's slow pace on the issue.

During a July 2009 hearing on PAMTA, FDA gave its support to the bill and signaled a shift in strategy. Joshua Sharfstein, Principal Deputy Commissioner at FDA, told the House

²⁶⁶ PL 110-316 (2008).

²⁶⁷ Preservation of Antibiotics for Medical Treatment Act of 2009, H.R. 1549, 111th Cong. (2009); Preservation of Antibiotics for Medical Treatment Act of 2009, S. 619, 111th Cong. (2009).

Rules Committee that growth promotion and feed efficiency uses of antibiotics in animals should not be considered judicious use, and that the agency supported ending the practice.²⁶⁸ This statement was the first public admission by FDA that it did not find production uses of antibiotics in animals to be safe, and indicated to Congress that the agency would take bold new steps to regulate the subtherapeutic use of antibiotics. While Sharfstein noted that the agency hoped to restrict production uses in a timely manner, he said that FDA hoped to accomplish its goals “without expending a tremendous amount of resources in the process.” These statements provided a clear signal to Congress that the agency recognized Congress’s concerns about FDA’s slow progress on the issue of subtherapeutic antibiotic use in animals. FDA indicated that it would respond by altering its approach from looking at drug approvals one at a time, to restricting all antibiotics used for purposes considered “non-judicious” by the agency. Sharfstein also commented that the current procedures needed to withdraw animal drug approvals were “very burdensome on the agency,”²⁶⁹ indicating that the agency was also conscious of its resource constraints, and that FDA might not be able to pursue formal withdrawals for broad categories of antibiotic use.

FDA finally appeared to be responding to Congress and public health advocates by taking more aggressive action on subtherapeutic antibiotic use in animals. Nevertheless, FDA would not heed Congress’ concerns entirely at the expense of other key stakeholders opposed to tighter control of animal antibiotic use, such as the pharmaceutical and animal production industries, as well as veterinarians and animal feed producers. With plans for more restrictive regulation looming, FDA published an advanced notice of proposed rulemaking in March of 2010,

²⁶⁸ U.S. Congress, House of Representatives, Committee on Rules, *H.R. 1549: Preservation of Antibiotics for Medical Treatment Act (PAMTA)*, 111th Cong., 1st sess., July 13, 2009, 9 (Joshua Sharfstein, Principal Deputy Commission of the Food and Drug Administration).

²⁶⁹ U.S. Congress, House of Representatives, Committee, *H.R. 1549*, 2009, 10 (Joshua Sharfstein, Principal Deputy Commission of the Food and Drug Administration).

soliciting comments on improvements to its Veterinary Feed Directive (VFD).²⁷⁰ The VFD was created in response to the passage of the Animal Drug Availability Act of 1996, which determined that certain new animal drugs should only be approved for use in feed under the order and supervision of a veterinarian.²⁷¹ Though there were few animal drugs approved under VFD at the time FDA published the notice, FDA stated that they intended to respond to concerns from stakeholders that the VFD process was too burdensome in order to prepare for an increase in VFD-approved drugs in the future. While the notice indicated that FDA intended to require more veterinary oversight for antibiotic use in animal feed, it also demonstrated that the agency was committed to ensuring that the concerns of industry stakeholders were addressed in the process.

In June of 2010, FDA took the first major steps in its new strategy by introducing a draft of a new guidance document designed to promote the judicious use of medically important antibiotics in food-producing animals.²⁷² The draft of GFI 209 recommended the introduction of measures to limit the use of medically important antibiotics in food-producing animals to those necessary to assure animal health and to uses that included veterinary oversight and consultation. FDA also noted in the draft that it intended to issue further guidance in the future to provide specific recommendations for implementing the document. The publication of this draft guidance revealed for the first time the key aspects of FDA's new strategy for addressing the human health hazards posed by animal antibiotic use, which would be implemented through several steps in the coming years.

²⁷⁰ U.S. Food and Drug Administration, Notice, "Veterinary Feed Directive," *Federal Register* 75, no. 59 (March 29, 2010): 15387.

²⁷¹ Animal Drug Availability Act, Public L. No. 104-250, 110 Stat. 3151 (1994).

²⁷² U.S. Food and Drug Administration, Notice, "Draft Guidance: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals; Availability," *Federal Register* 75, no. 124 (June 29, 2010): 37450.

The guidance reflected a careful balancing of the concerns of stakeholders by FDA. On one side, a substantial cohort in Congress was intent on forcing the agency to heed public health concerns and take concrete action after decades of delay. On the other side, industry stakeholders opposed restrictive regulation and could exploit procedural requirements in the rulemaking process to delay action. FDA's strategy was an attempt to appease both camps. The decision to look broadly at categories of subtherapeutic antibiotic use, instead of regulating drug by drug, indicated that FDA recognized the growing frustration among public health and consumer advocates, as well as members of Congress, with FDA's slow progress on the issue over the past several decades. FDA countered this with the choice of an informal, non-binding action, which revealed the power of industry stakeholders and the resource constraints facing the agency. Rather than initiating a formal ban on all production uses of antibiotics in food-producing animals, FDA substituted a weaker action that focused on working collaboratively with pharmaceutical and food animal production stakeholders to avoid a costly rulemaking process that would be held up by industry actors at every turn.

An unfortunate consequence of FDA's balanced strategy was that it failed to earn the full support of any key stakeholders. While health and public interest groups, and members of Congress advocating for their position, felt the voluntary approach was too weak, veterinarians, pharmaceutical companies, and food animal producers expressed concern about broad restrictions on antibiotic use like those proposed by GFI 209. In a July 2010 hearing of the House Energy and Commerce Committee, a representative from the AVMA stated that the veterinary community did not believe that restricting antibiotic drugs to prevent disease in animals was in the best interest of animal health and welfare, though they did support FDA's efforts to increase

veterinary oversight.²⁷³ Declining to address the draft guidance directly, a representative of the Animal Health Institute at the hearing said that the animal pharmaceutical industry appreciated FDA's cooperative approach and that it would work closely with the agency on this issue.²⁷⁴ The food animal production industry, however, was more outspoken. While a representative from USDA avoided opposing the guidance directly, he stated that USDA felt FDA's current risk-assessment process was "preferable to the approach that broadly eliminates antimicrobials for specific uses," which was essentially the purpose of GFI 209.²⁷⁵ The National Pork Producers Council was vocal in its opposition to the guidance, and even published an opinion piece in *USA Today* that argued that there was no scientific foundation for restricting antibiotic use in food animal production.²⁷⁶ Without full support on either side, FDA faced potential challenges from multiple stakeholders as it continued to carry out its new strategy.

The first major challenge to FDA's regulatory strategy for antibiotics in animals came a year later in May of 2011, when NRDC, Center for Science in the Public Interest, Food Animal Concerns Trust, Public Citizen, and the Union of Concerned Scientists jointly sued FDA for failing to respond to the petitions that the organizations had filed in March of 1999 and April of 2005. The groups asked a federal judge to order the agency to withdraw approvals for subtherapeutic uses of penicillin and tetracyclines, in accordance with their 1977 proposals.²⁷⁷

The plaintiffs claimed that FDA had not met its legal obligation to act on its own safety findings,

²⁷³ U.S. Congress, House of Representatives, Committee on Energy and Commerce, *Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture: Hearings before the Subcommittee on Health*, 111th Cong., 2nd sess., July 24, 2010, 336-337 (Christine Hoang, American Veterinary Medical Association).

²⁷⁴ U.S. Congress, House of Representatives, Committee, *Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture*, 2010, 205 (Richard Carnevale, Animal Health Institute).

²⁷⁵ U.S. Congress, House of Representatives, Committee, *Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture*, 2010, 42 (John Clifford, Deputy Administrator of the Animal and Plant Health Inspection Service, U.S. Department of Agriculture).

²⁷⁶ Howard Hill, "Opposing view on food safety: Don't bar animal antibiotics," *USA Today*, July 11, 2010.

²⁷⁷ *Natural Resources Defense Council, INC., et al. v. United States Food and Drug Administration*, 884 F. Supp. 2d 127, 2012 U.S. Dist. LEXIS 39457; 42 ELR 20073.

which would compel them to initiate withdrawal proceedings for subtherapeutic uses of these antibiotics. This lawsuit was the type of costly engagement FDA had been attempting to avoid from the pharmaceutical industry by sidestepping the formal rulemaking process. Ironically, it was this informal regulatory strategy that ultimately landed them in a legal battle with health and consumer groups.

A few months after the lawsuit was filed, FDA sent letters to petitioners formally denying their March 1999 and April 2005 petitions.²⁷⁸ Though the plaintiffs subsequently withdrew their claim regarding the petitions, they separately filed a supplemental complaint claiming that FDA's responses to the petitions were arbitrary and capricious, and thus in violation of the FD&C Act and the Administrative Procedure Act.²⁷⁹ A month later, FDA published a notice withdrawing its 1977 proposals for withdrawal of subtherapeutic uses of penicillin and tetracyclines in animal feed.²⁸⁰ After carrying out these actions, FDA argued that the plaintiffs' claims were moot. Nevertheless, on March 22, 2012, the judge ruled against FDA on both claims, finding that the agency unlawfully failed to fulfill its statutory obligation to complete withdrawal proceedings if it finds that an approved drug use is not safe. The court ordered FDA to carry out the withdrawal proceedings for the 1977 proposals.

Though FDA appealed this decision, the court's finding that an entirely voluntary approach to animal antibiotic regulation was unlawful played a role in shaping FDA's strategy going forward. Internal FDA memos released under a Freedom of Information Act request reveal that FDA's revisions of GFI 209 and its strategy for releasing its subsequent guidance, GFI 213,

²⁷⁸ Leslie Kux to Sarah Klein, "Re: Original Docket No. 99P-0485/CP," November 7, 2011; Leslie Kux to Andrew Maguire, "Re: Original Docket No. 05P-0139/CP," November 7, 2011.

²⁷⁹ Natural Resources Defense Council, INC., et al. v. United States Food and Drug Administration, 872 F. Supp. 2d 318; 2012 U.S. Dist. LEXIS 77384; 42 ELR 20117.

²⁸⁰ U.S. Food and Drug Administration, Notice, "Withdrawal of Notices of Opportunity for a Hearing; Penicillin and Tetracycline Used in Animal Feed," *Federal Register* 76, no. 246 (December 22, 2011): 79697.

were affected by NRDC's legal challenge.²⁸¹ In a memo from March 27, 2012, FDA suggested altering language in GFI 213 because the agency believed "it may be helpful in obtaining a favorable decision with respect to the second prong of the lawsuit."²⁸² FDA proposed changing a vague statement that the agency might consider further action if warranted by industry adoption rates by adding a 3-year timeline for reevaluation. This change was proposed in hopes of "assuaging the court's concern that FDA is failing to protect the public health in accordance with FDCA by forecasting a possibility of appropriate regulatory action if necessary."²⁸³

On April 13, 2012, FDA published the final version of GFI 209, which reviewed the scientific evidence on the link between antibiotic use in animals and antibiotic-resistant pathogens in humans, and set out two principles for the judicious use of antibiotics in food-producing animals.²⁸⁴ On the same day, FDA also issued a draft of GFI 213, which was meant to assist pharmaceutical companies in removing production uses from approved antibiotics, adding disease prevention, control, and treatment uses where appropriate, and changing the marketing status to require veterinary oversight.²⁸⁵ In conjunction with the two guidance documents, FDA published a draft of proposed regulation for improving the efficiency of its Veterinary Feed Directive Program in order to facilitate the transition of many over-the-counter drugs to VFD

²⁸¹ U.S. Food and Drug Administration, Internal Strategy Memos Released Under Freedom of Information Act (2012). http://www.peer.org/assets/docs/fda/10_17_12_FDA_strategy_memos.pdf.

²⁸² *Ibid.*

²⁸³ *Ibid.*

²⁸⁴ U.S. Food and Drug Administration, Notice, "Guidance for Industry on the Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals; Availability," *Federal Register* 77, no. 72 (April 13, 2012): 22328.

²⁸⁵ U.S. Food and Drug Administration, Notice, "Draft Guidance for Industry on New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions With GFI #209; Availability," *Federal Register* 77, no. 72 (April 13, 2012): 22327.

status.²⁸⁶ These three documents were the cornerstone of FDA's strategy of informal, voluntary regulation that the agency hoped would appease both industry and public health advocates.

FDA emphasized its cooperative strategy in its press releases on the three documents. Michael Taylor, Deputy Director of Food at FDA, said that the significant change that allowed them to move forward with the strategy was "the willingness of many drug companies, veterinarians and animal producers to work collaboratively with FDA" on the issue.²⁸⁷ FDA's claim that industry was cooperating was supported by a statement from the trade group representing the feed industry, which said it supported the guidance and FDA's "collaborative approach on the issue."²⁸⁸ The National Pork Producers Council, however, slammed the guidance for its restrictions on antibiotics that they claimed were extremely important to animal health and its heightened veterinary requirements, claiming that FDA did not provide compelling evidence for the new regulations.²⁸⁹ Among consumer and public health advocates, FDA's strategy was met with a tepid response. While these groups expressed general support for the guidance documents as a first step, they were not satisfied with the voluntary nature of FDA's approach.²⁹⁰ Once again, FDA's hopes of appeasing both sides of the issue resulted in a strategy to which no party gave their full support.

FDA's recent progress on the issue did not satisfy Congress either. In its report on fiscal year 2013 FDA appropriations, the Senate Appropriations Committee directed FDA to finalize GFI 213 and report to Congress on compliance with the final guidance, with "further details about how FDA intends to meet its public health responsibilities" within 120 days of its

²⁸⁶ U.S. Food and Drug Administration, Proposed Rule, "Veterinary Feed Directive; Draft Text for Proposed Regulation," *Federal Register* 77, no. 72 (April 13, 2012): 22247.

²⁸⁷ Michael R. Taylor, "A Strategy to Keep Antimicrobials Effective," *FDA Voice*, April 12, 2012.

²⁸⁸ "Feed Industry Supports FDA's Antibiotic Stance," *Western Farm Press*, April 13, 2012.

²⁸⁹ "FDA antibiotics guidance tough on pork producers," *Western Farm Press*, April 13, 2012.

²⁹⁰ "Trust for America's Health Statement on the Food and Drug Administration's Guidance Documents 209 and 213 and Veterinary Feed Directive Proposed Rule on Antibiotic Use in Food Animals," *PR Newswire*, April 11, 2012.

publication.²⁹¹ Two months later, the House report on FDA appropriations also directed the agency to seek public comment on collecting more data on antibiotic use in food-producing animals and to collaborate with USDA to implement an approach for data collection.²⁹² These reports indicated that Congress would continue to carefully monitor FDA's behavior on this matter, and would limit the agency's autonomy until Congress was satisfied with FDA's ability adequately protect public health.

FDA's strategy was also being challenged in court, where NRDC and its fellow plaintiffs were fighting for their third complaint, challenging FDA's recent dismissal of the 1999 and 2005 petitions. On June 1, 2012, a federal judge ruled that the agency's proffered grounds for dismissing the two petitions were arbitrary and capricious, rejecting the notion that FDA could substitute proposed voluntary measures for those mandated by statute.²⁹³ The judge also found that by failing to make findings as to the drugs' safety, FDA "avoided the Congressionally mandated scheme for addressing drugs not shown to be safe," and that the agency's "eleventh hour response" of issuing the guidance documents did not relieve it of its responsibility to make such findings. As a result, the court ordered FDA to determine whether the scientific evidence supported the two citizen petitions, and initiate withdrawal proceedings for any drug use not found to be safe. In the fall of 2012, FDA appealed the decision, further delaying any formal action on subtherapeutic antibiotic use in animals.²⁹⁴

²⁹¹ U.S. Congress, Senate, Committee on Appropriations, *Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2013*, 112th Cong., 2nd sess., April 26, 2012, S. Rep. 112-163, 77-78.

²⁹² U.S. Congress, House of Representatives, Committee on Appropriations, *Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2013*, 112th Cong., 2nd sess., June 20, 2012, H.R. Rep. 112-542, 47.

²⁹³ *Natural Resources Defense Council, INC., et al. v. United States Food and Drug Administration*, 872 F. Supp. 2d 318; 2012 U.S. Dist. LEXIS 77384; 42 ELR 20117.

²⁹⁴ Avinash Kar, "An update on NRDC court wins on antibiotic use in livestock: FDA appeals the decisions," *NRDC Expert Blog*, October 15, 2012.

Over the course of the next year, FDA made little progress on the issue, frustrating consumer and public health advocates, as well as members of Congress. Though FDA held meetings with veterinarians and the animal agriculture industry to discuss VFD improvements,²⁹⁵ the agency failed to finalize GFI 213 and the VFD despite pressure from Congress. In June of 2013, over a year after FDA had published its draft of GFI 213, the House report on 2014 FDA appropriations directed the agency to finalize the guidance before January 1, 2014, and to submit data to Congress that would allow them to track industry cooperation and FDA progress on the issue.²⁹⁶

On December 12, 2013, FDA published the final version of GFI 213, which provided recommendations for pharmaceutical companies on how to comply with GFI 209 by changing product labels, and requested that the companies complete this process within three years.²⁹⁷ The guidance asked pharmaceutical companies to work voluntarily with the agency to review existing drug approvals for antibiotics, update the evidence for their use in disease control, prevention, or therapy, or consider withdrawing the drug from the market. On the same day, FDA also solicited comment on proposed changes to the VFD rule that would allow greater flexibility in the veterinary-client-patient relationship, reduce recordkeeping requirements, and allow some VFD drugs to be sold by unlicensed feed mills.

The response to GFI 213 from the pharmaceutical industry was largely supportive, indicating that FDA had considered industry input in drafting the guidance and that the strategy

²⁹⁵ Alaina Busch, “FDA Presses Ahead on new Animal Antibiotic Policies with Series of Meetings.” *InsideHealthPolicy.Com's Inside Health Reform* 5.11 (March 13, 2013).

²⁹⁶ U.S. Congress, House of Representatives, Committee on Appropriations, *Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2014*, 113th Cong., 1st sess., June 18, 2013, H.R. Rep. 113-116, 53.

²⁹⁷ U.S. Food and Drug Administration, *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: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209* (December 2013).

was indeed being implemented in collaboration with the pharmaceutical industry, as FDA claimed. Zoetis and Elanco, the pharmaceutical companies that together sponsored most of the drugs subject to the guidance, immediately announced their willingness to work with FDA to comply,²⁹⁸ and by June of 2014, FDA had secured the voluntary engagement of all affected pharmaceutical companies.²⁹⁹ Livestock and poultry groups also expressed their commitment to working with the agency on the issue, voicing appreciation for the collaborative process FDA had undertaken in crafting the strategy.³⁰⁰

Consumer and public health advocates, however, were critical of the guidance, though they expressed some hope that the recent moves indicated that the agency was taking the issue more seriously. The Keep Antibiotics Working coalition voiced concerns that the guidance would not lead to any real reduction in antibiotics use, since pharmaceutical companies could ignore FDA's recommendations, and food animal producers could switch from using antibiotics for growth promotion to using them for routine disease prevention instead.³⁰¹ Many in the public health community, as well as some in Congress, echoed these concerns, and urged FDA to create an enforcement plan. Rep. Louise Slaughter, a microbiologist and longtime advocate for restricting animal antibiotic use, called the guidance "an inadequate response" that "[fell] woefully short of what is needed to address a public health crisis."³⁰² Concerned members of Congress supported several pieces of legislation designed to create mandatory restrictions that went further than FDA's policies, including PAMTA and the Preventing Antibiotic Resistance

²⁹⁸ Alaina Busch, "New FDA Policies on Animal Antibiotic Prevention Uses Spark Industry Action," *InsideHealthPolicy.com's Daily Brief*, December 12, 2013.

²⁹⁹ David G. White, "Keeping You Informed: An Update on FDA's Judicious Use Strategy for Antimicrobial Drugs in Food-Producing Animals," *FDA Voice*, June 30, 2014.

³⁰⁰ National Chicken Council, "NCC Statement on FDA Final Guidance #213 and Veterinary Feed Directive Proposal," December 11, 2013; North American Meat Institute, "AMI Statement on FDA Guidance 213 and Proposed VFD Rule," December 11, 2013.

³⁰¹ Alaina Busch, "New FDA Policies on Animal Antibiotic Prevention Uses Spark Industry Action" (2013).

³⁰² *Ibid.*

Act, introduced in March of 2015.³⁰³ Congress was also monitoring FDA's progress on finalizing its strategy, and directed the agency to publish the final VFD rule by December of 2014.³⁰⁴

Though FDA's voluntary strategy continued to be challenged by consumer and public health groups and their supporters in Congress, the agency won a major victory in July of 2014, when the US Court of Appeals ruled in favor of FDA in a two-to-one decision to overturn the two district court decisions.³⁰⁵ The court found that the statute did not require FDA to hold hearings until it made a final determination on the drugs, and that the decision was thus left to agency discretion. This ruling validated FDA's voluntary plan at a crucial time for the agency as it worked to implement the key steps in its strategy, and provided FDA with assurance that informal regulation could be substituted for formal rulemaking.

The court's decision coincided with a push by the Obama administration to make addressing the problem of antibiotic resistance a national priority. In early July, the President's Council of Advisors on Science and Technology (PCAST) met to discuss a policy document on antibiotic resistance.³⁰⁶ Consumer and public health groups hoped the report would push FDA to go further than its current voluntary strategy, and sent a letter to PCAST urging them to recommend more aggressive steps for curbing animal antibiotic use.³⁰⁷ Three months later, President Obama issued an executive order, entitled "Combating Antibiotic-Resistant Bacteria," which declared antibiotic resistance to be a "serious threat to public health and the economy" and

³⁰³ Preventing Antibiotic Resistance Act of 2015, S. 621, 114th Congress (2015).

³⁰⁴ U.S. Congress, House of Representatives, Committee on Appropriations, *Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2015*, 113th Cong., 2nd sess., H.R. Rep. 113-468 (2014).

³⁰⁵ *Natural Resources Defense Council, INC., et al. v. United States Food and Drug Administration*, 760 F.3d 151; 2014 U.S. App. LEXIS 14136; 44 ELR 20174.

³⁰⁶ Alaina Busch McBournie, "Groups Press Presidential Advisors to Nudge FDA on Animal Antibiotic Policy," *InsideHealthPolicy.com's Inside Health Reform* 6.29. July 16, 2014.

³⁰⁷ *Ibid.*

established an interagency task force to create a national action plan addressing the issue.³⁰⁸ Simultaneously, the White House released its National Strategy for Combating Antibiotic-Resistant Bacteria, based on the PCAST report developed earlier that year.³⁰⁹ The strategy laid out five goals for action by the federal government, which included slowing the emergence of resistant bacteria, strengthening surveillance, improved testing and diagnostics for resistant infections, accelerating the development of new antibiotics, and improving international collaboration on the issue.³¹⁰ By the end of 2014, the Obama administration had engaged in an unprecedented level of involvement on the issue of antibiotic resistance, providing the political capital needed for FDA to take strong action on animal antibiotic use.

In March of 2015, the interagency task force released its National Action Plan for Combating Antibiotic-Resistant Bacteria.³¹¹ Despite the hopes of consumer and public health advocates that the White House would pave the way for more aggressive steps by FDA, the action plan essentially restated the strategy FDA had already set out. With regard to animal antibiotic use, the plan outlined two major objectives: first, “to eliminate the use of medically important antibiotics for growth promotion in food-producing animals and bring under veterinary oversight other in-feed and in-water uses of antibiotics that are medically important for treatment, control, and prevention of disease;” and second, “to identify and implement measures to foster stewardship of antibiotics in animals.”³¹² In order to achieve the first goal, the plan directed FDA to complete the implementation of GFI 213 and finalize the VFD rule within one year. FDA was also instructed to complete all changes recommended by the two guidance

³⁰⁸ Exec. Order No. 13676, 79 FR 5693, “Combating Antibiotic-Resistant Bacteria.” September 23, 2014.

³⁰⁹ The White House, *National Strategy for Combating Antibiotic-Resistant Bacteria* (Washington, DC: September 2014).

³¹⁰ *Ibid.*

³¹¹ The White House, “National Action Plan for Combating Antibiotic-Resistant Bacteria,” (Washington, DC: March 2015).

³¹² The White House, “National Action Plan for Combating Antibiotic-Resistant Bacteria,” 19-23.

documents within three years, after which time growth promotion uses of medically important antibiotics would not be permitted, and all other water or feed uses of these drugs would require veterinary oversight. The plan also provided milestones for progress assessment, and goals for outreach, training, and transparency with regard to FDA's actions on the issue. To achieve the second objective, the action plan directed FDA, in partnership with USDA, to develop and implement outreach programs for veterinarians and animal producers to advance antibiotic stewardship, and to promote public-private partnerships with public health, pharmaceutical, and agricultural stakeholders in order to facilitate the implementation of best practices and effective interventions. The plan also set specific goals for monitoring, data collection, and reporting in order to gauge the effectiveness of FDA's strategies.

Though consumer and public health groups expressed support for the creation of a comprehensive plan to tackle antibiotic resistance, many criticized the plan for its inadequate provisions for addressing animal antibiotic use. Rep. Louise Slaughter said that “the administration has fallen woefully short of taking meaningful action to curb the overuse of antibiotics in healthy food animals,” and emphasized that pursuing FDA's voluntary policy was the wrong path forward.³¹³ NRDC's statement expressed similar concerns, and added that “the national plan perpetuates a massive loophole in FDA's existing approach to the use of antibiotics in animal agriculture” by allowing routine disease prevention uses of antibiotics to continue.³¹⁴ Despite unprecedented attention paid to the issue of antibiotic resistance by the White House, FDA appeared poised to continue with its voluntary strategy.

³¹³ Louise Slaughter, “Rep. Slaughter, Only Microbiologist in Congress, Responds to Administration's Antibiotics Plan,” March 27, 2015.

³¹⁴ Mae Wu, “More Action Needed in National Action Plan for Combatting Antibiotic Resistant Bacteria.” *NRDC Expert Blog*, March 27, 2015.

On June 2, 2015, FDA published the final VFD rule, completing the last step in the three-pronged approach it had initiated five years before.³¹⁵ In anticipation of the increased number of drug uses falling under requirements for veterinary oversight as part of FDA's judicious use strategy, the amended VFD allowed for greater flexibility with regard to several aspects of the rule in order to improve the efficiency of the VFD process. Based on feedback that FDA received during the formal comment period and in the public meetings that FDA held throughout the country in 2013, FDA altered the provisions relating to the veterinary-client-patient relationship in order to allow greater state-by-state flexibility, rather than mandating that all veterinarians issuing VFDs meet the federally defined standards. The final rule also clarified record-keeping requirements and removed VFD drugs from the definition of Category II drugs, which require a withdrawal period, so that VFD drugs would instead be categorized on case-by-case basis.³¹⁶

On the same day that FDA announced the final VFD rule, the White House held its "Forum on Antibiotic Stewardship," bringing together more than 150 stakeholders involved in human and animal health as part of President Obama's national strategy to combat antibiotic resistance.³¹⁷ The forum was a public display of industry cooperation with the White House's new plan that furnished FDA with the political support necessary to press forward with its judicious use strategy, despite criticism from consumer and public health advocates. At the forum, the AVMA lauded FDA's new VFD rule, crediting the AVMA's "early and ongoing collaboration with FDA" for an outcome that was "in the best interests of animal health, public

³¹⁵ U.S. Food and Drug Administration, Rule, "Veterinary Feed Directive," *Federal Register* 80, no. 106 (June 3, 2015): 31707.

³¹⁶ New Animal Drugs for Use in Animal Feeds: Definitions and General Considerations Applicable to this Part, 21 C.F.R. §558.3.

³¹⁷ Jenna Brayton, "The White House Hosts a Forum on Combating Antibiotic Resistance," White House Press Office, June 2, 2015.

health, and the veterinary profession.”³¹⁸ The National Chicken Council, along with other food animal producer organizations, participated in the forum and publicly expressed support for all three documents in FDA’s judicious use strategy.³¹⁹ Other stakeholders from animal agriculture, including several large animal pharmaceutical companies, the American Feed Industry Association, and major food producers, used the opportunity to announce their own antibiotic stewardship initiatives, including a commitment from Tyson Foods to eliminate the use of human antibiotics from its U.S. broiler chicken flocks by September of 2017.³²⁰

The public support from industry stakeholders for the White House’s strategy was not matched by consumer and public health groups, which gave the forum and FDA’s final VFD rule a lukewarm response. A senior analyst for the Keep Antibiotics Working coalition said that while the group appreciated that the White House was giving the issue the attention it needed, many were “troubled by the fact that most of the consumer advocacy organizations” that had been working for decades to address antibiotic use in animal agriculture were not invited to participate in the forum.³²¹ NRDC expressed a similar sentiment, and added that FDA’s VFD was a positive step, but did not go far enough by failing to include data collection on antibiotic use.³²²

During the Obama Administration, FDA’s regulation of antibiotic use in animal agriculture was swept into a broader national strategy to combat antibiotic resistance, giving the agency more political backing on the issue than ever before. As part of the administration’s focus

³¹⁸ American Veterinary Medical Association, “Antibiotic use & resistance: AVMA’s efforts seen in federal initiatives,” *AVMA@Work* (blog), June 3, 2015.

³¹⁹ National Chicken Council, “Chicken Council Supports Responsible Antibiotic Use, Veterinary Oversight,” June 2, 2015.

³²⁰ White House, *Private Sector Factsheet: More than 150 Animal and Health Stakeholders Join White House Effort to Combat Antibiotic Resistance*, June 2, 2015.

³²¹ Erin Durkin, “FDA Rule Outlining Veterinarians’ Oversight of Feed-Use Antibiotics Is Key Part of New White House Plan,” *InsideHealthPolicy.com’s Inside Health Reform* 7.22 (June 3, 2015).

³²² Mae Wu, “White House Misses Golden Opportunity to Push for Meat Raised Without Abusing Antibiotics,” *NRDC Expert Blog*, June 3, 2015.

on the judicious use of antibiotics, FDA's regulatory approach moved firmly away from product-by-product regulation, and towards broad guidelines regarding how and when antibiotics should be used in animal agriculture. In order to achieve this, FDA relied on voluntary guidance documents and the cooperation of key industry participants, including pharmaceutical companies, feed manufacturers, and food animal producers. Ultimately, FDA succeeded in getting the support of industry stakeholders by involving them in the development of GFI 209, GFI 213, and the revised VFD, the three key documents that formed its strategy. Despite sustained attempts to push the agency towards formal regulation of subtherapeutic animal antibiotic use by consumer and public health groups and their advocates in Congress, FDA solidified its voluntary strategy with the publication of the final VFD rule in 2015.

CHAPTER 4: DISCUSSION AND CONCLUSION

Since Thomas Jukes made his incredible discovery that antibiotics from pharmaceutical waste could speed the growth of animals in his laboratory and the Swann Committee revealed the dangers of this practice, FDA has been caught in an unwinnable battle among a host of stakeholders vying for influence over the agency. Despite FDA's early recognition in the mid-1970s that the subtherapeutic use of antibiotics in animal agriculture posed a significant health risk, FDA spent decades attempting to find a viable path towards regulation. Constrained by the demands of external stakeholders and the costs of regulation, FDA continued to display an inability to effectively curtail subtherapeutic antibiotic use in animal agriculture over the course of more than forty years.

FDA's long history of regulating subtherapeutic antibiotic use reveals a great deal about the factors that affect FDA's decision-making in the complex environment of the food supply.

Interpreting this case through the framework of external signals yields important insights into the way FDA balances the feedback of stakeholders with the costs of regulatory action, calibrating its behavior to maximize positive political feedback and minimize cost. Though certain interests may dominate FDA in the short term, taking a broader temporal view of FDA's behavior suggests that the agency responds to a diverse range of feedback. Thus, this case indicates that external signals theory provides a more appropriate frame through which to interpret FDA behavior over the long term, and rejects the idea that the agency's behavior is determined solely by Congress, industry, or the public interest. Nevertheless, an analysis of external signals does not fully explain FDA's behavior; the history of the agency's regulation of subtherapeutic antibiotic use in animal agriculture brings to light several other factors that influence FDA's decision-making. This chapter takes a broad view of the case and identifies key trends in FDA's behavior over the period between 1970 and 2015. Placing these trends in context, the discussion turns to an analysis of external signals in an effort to explain the observed trends in FDA's behavior. The chapter concludes by examining factors that impact FDA's decision-making in this case that are not explained by an external signals approach, and addressing the lessons that can be drawn from this case.

Trends in FDA's Behavior: An External Signals Approach

Throughout the course of this case, FDA employed a number of different regulatory strategies in its attempts to combat antibiotic resistance through restrictions on antibiotic use in animal feed. Early regulatory endeavors centered on careful study of the emerging scientific evidence regarding the development of resistance and observation of the United Kingdom's efforts to restrict antibiotic use in animal agriculture. FDA carried out this strategy throughout

the early 1970s by commissioning a task force to review the scientific evidence, and subsequently requiring sponsors of any antibiotic-containing feed compounds to submit data establishing the safety of these products. When the advisory committee impaneled to review this data recommended that FDA withdraw approval for certain growth promotion and feed efficiency uses of penicillin and two tetracycline drugs, FDA decided to move forward with formal withdrawal proceedings for the drugs in 1977.

An analysis of the external signals FDA was receiving at this time suggests that this early strategy was driven primarily by growing concern in the scientific community and by international regulatory efforts, which FDA was following closely. Though pharmaceutical companies were required to submit data establishing the safety of their products, they did not appear to be providing significant resistance to FDA's regulatory efforts. Other key industry stakeholders, including food animal producers and feed manufacturers, were also not providing public resistance to FDA's handling of the issue prior to the proposed withdrawals in 1977, which may have led FDA to believe it had the political support necessary to proceed with formal rulemaking. Because formal rulemaking is the statutorily mandated process for withdrawing approval for drugs that have not been shown to be safe, it is not surprising that FDA would select this method in its first attempt to address the issue, particularly in the absence of strong negative feedback from stakeholders.

After refusing to yield to Congress' concerns regarding its 1977 proposals, FDA experienced a sharp reduction in autonomy. In several hearings held on the issue after FDA's proposals were published, members of Congress representing agricultural districts and other sympathetic Republicans expressed doubt about the strength of the scientific evidence that the agency was using to justify regulation, and emphasized the economic importance of the use of

antibiotics in animal feed. Instead of surrendering to the concerns of a significant contingent in Congress, as well as the AVMA, USDA, and livestock and poultry interests, FDA decided to push ahead with its proposals. This decision demonstrates the consequences for FDA when it fails to properly adjust its approach in response to feedback from key stakeholders: here, FDA's miscalculation of the strength of its own position with relation to the negative feedback it was receiving from Congress and other important stakeholders led to a significant reduction in agency autonomy for several years, as Congress used the appropriations process to direct FDA to delay action on the issue.

FDA's activity related to the issue during the 1980s was therefore limited to reviewing new scientific evidence and carrying out additional studies to clarify the relationship between subtherapeutic antibiotic use in animal feed and drug-resistant disease in humans. Despite continued statements by FDA officials that the agency believed subtherapeutic antibiotic use in animals posed a hazard for human health and limits on antibiotic use in animal agriculture were necessary, FDA took no active steps to regulate the practice from 1980 to the mid-1990s. During this period, several breakthrough studies were published that should have provided FDA with firmer grounds for restricting antibiotic use in animal feed, as they got closer to establishing the "direct link" that those opposing FDA's attempts in the past had questioned. Why, then, did FDA remain silent on the issue for nearly fifteen years?

An analysis of the feedback FDA was receiving at the time helps answer this question. During the early 1980s, Congress used the appropriations process to intervene in FDA's regulation of this issue for several years, directing FDA to carry out studies on the link between subtherapeutic antibiotic use on farms and resistant pathogens in humans. Each time it requested a new study, Congress mandated that FDA hold in abeyance any action on the issue until the

study was completed. Thus, from 1980 until 1984, FDA had no choice but to postpone taking action on subtherapeutic antibiotic use on farms. During the mid-1980s, key industry stakeholders were also vocally opposing regulation, as exhibited in the comments of the cattlemen and pork producers during the 1984 Congressional hearing, and more subtly by officials from USDA. Meanwhile, FDA's CVM was under heightened scrutiny from Congress on a number of other issues, such as their failure to prevent the illegal marketing and sale of animal drugs and concerns about the use of carcinogenic substances. Furthermore, these events were all taking place during the Reagan administration, which was famously hostile towards regulation and thus unlikely to provide any political support (and perhaps likely to provide disincentives) for regulatory action on this issue. Collectively, these factors were able to move the regulation of subtherapeutic antibiotic use in animal agriculture down FDA's priority list, as the political and budgetary costs of taking action became increasingly prohibitive. Given these costs, the sustained attention paid to the issue by the scientific community and consumer and public health advocates during this period was unable to provide sufficient political motivation for FDA to take action.

FDA's trend of inaction slowly shifted during the early 1990s, eventually transitioning to a strategy of informal regulation that became the basis of FDA's actions on subtherapeutic antibiotic use in animal agriculture for the next twenty years. Between 1995 and 2003, FDA took a sequence of steps to create an informal regulatory framework for addressing this issue, beginning in 1996 with the creation of NARMS, an interagency effort to monitor the development and spread of antibiotic resistance. FDA followed this with a series of guidance documents that established that the agency would consider the potential emergence of resistance in safety evaluations for antibiotic drug uses, and defined the standards by which it would

evaluate this risk. During the late 1990s and early 2000s, FDA conducted safety assessments for new animal antibiotic drug applications and for approved antibiotic uses under these new guidelines.

This period saw not only renewed momentum at FDA for regulatory action on subtherapeutic antibiotic use in animals, but also a major substitution of informal guidance documents for formal rulemaking. During the mid-1980s to the mid-1990s, scientific evidence had amassed that pointed to a direct connection between subtherapeutic antibiotic use in animals and antibiotic-resistant infections in humans. As a result, several European countries enacted strict limits on antibiotic use in agriculture, and major health institutions such as WHO and CDC recommended that production uses of medically important antibiotics be banned. At the same time, consumer and public health organizations continued to push FDA to take action on the issue. These influences likely played a significant role in FDA's decision to take up the issue once again.

FDA's decision to substitute informal guidance for formal rulemaking allowed them to respond to the concerns of the scientific and public health communities in a way that attracted less opposition and used fewer agency resources than formal regulatory procedure. During this time, FDA was increasingly utilizing informal rulemaking to achieve its objectives across many sectors. After FDA rendered its guidance documents nonbinding in 1992, revoking a previous rule, the agency began to rely on guidance documents for more flexible and responsive regulation and engaged regulated industries and regulatory beneficiaries in the drafting process.³²³ As FDA was rolling out its guidance-based strategy, it was learning the price of attempting formal rulemaking against the opposition of industry during its five-year battle with Bayer over sarafloxacin withdrawal.

³²³ Lewis (2011).

The final trend in FDA's regulation of subtherapeutic antibiotic use in animal agriculture was a shift from product-by-product regulation to broad principles of judicious use that were implemented through informal actions. By 2005, FDA's strategy of assessing the safety of each drug use through qualitative risk assessment was frustrating consumer and public health groups, as well as their advocates in Congress, who felt the strategy was weak, ineffective, and slow. This dissatisfaction culminated in a second proposal from public interest groups to withdraw approval for routine growth promotion and disease prevention uses of seven antibiotics used in animal feed. Meanwhile, the controversy over approval for cephalosporin use in animal agriculture revealed the weaknesses in FDA's prior approach, drawing criticism and ultimately direct intervention by Congress in 2007.

These factors all contributed to a clear shift in strategy that began with a hearing in 2009, in which the Obama administration signaled that they would create a new plan for antibiotic regulation that focused on judicious use. As public health advocates had hoped, FDA determined that production uses of antibiotics were not considered judicious and set out to discontinue this practice. However, FDA planned to implement its new strategy through voluntary recommendations put forth in a series of guidance documents, which would achieve FDA's goals only with the cooperation of industry stakeholders. After years of courting pharmaceutical companies, animal producers, animal feed manufacturers, and veterinarians, FDA rolled out a voluntary strategy that had support from industry stakeholders and the White House. Though a legal challenge to FDA's reliance on voluntary guidance influenced several aspects of the final documents (most notably the inclusion of a timeline for reevaluation of FDA's plan), the political and budgetary benefits of a voluntary strategy backed by the White House and industry ultimately outweighed the negative feedback from other stakeholders.

Lessons for Future Strategies

An analysis of external signals provides distinct insight into how and why FDA makes regulatory decisions in complex environments. Nevertheless, several other key factors influenced FDA's regulatory behavior in this case and warrant consideration, though a full treatment of these topics is outside the scope of this paper. Understanding how these factors, in conjunction with feedback from external stakeholders and budgetary costs, impact FDA's behavior provides important lessons for the development of more effective strategies for influencing regulatory outcomes.

Throughout the FDA's regulation of subtherapeutic antibiotic use in animal agriculture, science plays a major role in determining the options available to FDA and the firmness of the agency's position. Before FDA can take regulatory action, it must have a strong scientific basis for its decision in order to avoid, or at least weaken, challenges from the regulated industry and Congress. Without a strong body of evidence indicating the need for regulation, formal regulatory efforts generally prove to be a waste of agency resources. Science is also used as a tool by those opposed to regulation in order to delay or prevent FDA action. In this case, stakeholders accomplished this both by requesting additional scientific studies to strengthen the grounds for any regulatory action, and by finding or generating scientific evidence that countered the agency's claims. Due to the uncertainty inherent in science, navigating a regulatory problem that involves challenging scientific questions, such as the emergence, spread, and risks of antibiotic resistance, can constrain FDA's ability to act. This challenge is particularly relevant in the complex environment of the food system, as demonstrated in Chapter 1.

Institutional constraints also influenced FDA's decision-making. From the late 1970s until 2015, consumer and public health advocates were consistently pushing for FDA to take

strong action to curtail the use of antibiotics in animal feed. On the whole, these groups were well organized, unremitting, and successful in courting an ardent cohort of advocates in Congress. Nevertheless, they were considerably less effective in influencing FDA's behavior than industry stakeholders that opposed action. While there are likely several reasons for this imbalance, the conservative nature of the regulatory process is one major factor. Due to the burdensome procedural requirements for rulemaking, FDA's regulatory process is biased against taking action, providing numerous opportunities for those opposed to regulation to step in and block FDA action or create additional resistance that makes the action more costly. The resource-intensive nature of rulemaking, particularly when the regulated industry in opposition is organized, powerful, and well-funded, makes it much more difficult for those seeking regulatory action to obtain their desired outcome than it is for those opposed to regulation. While informal regulation through guidance documents decreases the costs of regulation by reducing procedural requirements, its nonbinding status renders it ineffective without the support of the regulated industry, giving them the upper hand in this arena as well. As was evident in the case of antibiotic regulation in animal agriculture, consumer and public health advocates seeking regulation are fighting an uphill battle, even when science and public opinion are on their side.

At the intersection of science and institutional constraints are the standards for scientific evaluation and the burden of proof, which are crucial factors in shaping regulatory outcomes. The questions of who must provide evidence in order for an action to be taken and which bar they must meet were central to several key moments in the story of subtherapeutic antibiotic regulation. The shift to a standard of "reasonable certainty of no harm" in the early 2000s marked a significant change in momentum for FDA, establishing that drug sponsors were responsible for proving safety if FDA had a reason to question whether the drug could harm

humans. These factors also played a role throughout the agency's attempts to deal with new scientific evidence, as the burden for proving harm or safety shifted between FDA and the regulated industry. When the burden of proof was placed on sponsors to prove safety, FDA was in a significantly stronger position than when they were required to prove harm in order to take regulatory action.

A final element of this story that is not discussed extensively here is the role of presidential administrations in changing FDA's trajectory, both on a particular issue and in its overall regulatory strategy. The White House is able to exert influence over FDA both through its political appointees, which can drive the agenda set by the President, or by providing the agency with political capital and public support to carry out a particular action. Both mechanisms of influence likely shaped the observed trends in FDA's behavior in this case. This was particularly evident in the 1980s, given that FDA's decade of inaction on subtherapeutic antibiotics coincided with the Reagan administration, which is commonly considered the most anti-regulatory administration in recent decades. The active role of the Obama administration, beginning in 2009, in spurring national action to combat antibiotic resistance and pushing a judicious use strategy provides another clear example. Future research should look more closely at this interesting question.

FDA's efforts to regulate subtherapeutic antibiotic use in animal agriculture over four and a half decades paint a picture of an agency severely constrained by external forces. FDA's belief that the routine use of antibiotics in animal feed posed a hazard to human health that necessitated regulation never wavered after its original assessment of the issue in the mid-1970s. Nevertheless, FDA was not able to carry out the regulatory actions it believed were necessary due to the constraints placed on the agency by Congress, industry stakeholders, procedural

requirements, and its budget. Even with consumer and public health advocates pushing the agency to carry out its original objectives, FDA was unable to effectively uphold its mission to protect the public health by assuring the safety of the food supply.

Though FDA's recent informal regulatory strategy may prove to be effective in reducing the use of antibiotics in animal agriculture, the agency's need to rely on a voluntary plan that requires industry cooperation does not bode well for its ability to effectively protect the public health from risks in the food system. The lessons we can draw from FDA's behavior in the regulation of antibiotic use in animal feed over 45 years about the dynamic nature of its decision-making, its constant attempts to balance external feedback, and the power of procedural constraints can help us better understand future regulatory outcomes. Concern about the safety and sustainability of the American food system is growing rapidly, leading to greater scrutiny of FDA's ability to regulate health risks in the food supply by consumers and academics alike. This paper seeks to contribute to these ongoing efforts to identify and address challenges in the food system.

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