ANTIBIOTICS IN FOOD ANIMALS: THE CONVERGENCE OF ANIMAL AND PUBLIC HEALTH, SCIENCE, POLICY, POLITICS AND THE LAW

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ANTIBIOTICS IN FOOD ANIMALS: THE CONVERGENCE OF ANIMAL AND PUBLIC HEALTH, SCIENCE, POLICY, POLITICS AND THE LAW

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ABSTRACT

The use of antibiotics in food animals, to prevent and/or control disease in these animals, has been a subject of discussion between the medical and veterinary and animal agricultural sectors and related national and international government entities for decades, because of concerns about the resulting increase in antibiotic resistance such practices facilitate. The underlying premise is that use of antibiotics in food animals leads to resistance of the bacteria consumed by humans, and reducing the effectiveness of antibiotics used to treat the resultant disease, usually diarrhea since it had created the resistant bug to which the human was exposed.

There are many significant variables to consider when analyzing the emergence of antibiotic resistance. First, an understanding of the science of microbiology is required, including the types of bacteria that exist, some harmful and some considered beneficial. The discovery and subsequent development and use of antibiotics, including the scope and limitations of such use must be considered. Then the evolution of bacterial resistance must be understood-how it develops, how it is spread, what parameters exist in the bacterial environment to promote or inhibit the development, mechanisms and success of resistance, and what measures can be employed to minimize or eliminate these actions.

Classes or types of antibiotics have been developed to kill or prevent the growth of specific types of bacteria. Both pathogenic, or disease-causing bacteria, as well as non-pathogenic, or commensal, bacteria exist in the digestive tracts of animals, sometimes causing disease. Exposure to antibiotics has resulted in antibiotic resistance from the selection of inherent or acquired mechanisms of resistance. Naturally occurring antibiotics and antibiotic resistance predate human evolution, but as pharmacologically produced antibiotic use expanded, so did evolutionary selection of bacteria resistant to antibiotics. Whether inherently or genetically acquired, bacterial resistance can spread horizontally to other bacteria within the same environment, or vertically, upon bacterial reproduction. Although understanding the specific mechanisms of resistance is beyond the scope of this discussion, the fact that resistance has been identified amongst non-pathogenic and pathogenic bacteria that commonly inhabit animals’ intestinal tracts, to all known antibiotics. Since the discovery of antibiotics, this subsequent resistance has been a known sequellae to its use, but concerns about antibiotic resistance are growing, as the availability of newer antibiotics is diminishing.

The scope of antibiotic use in human and animal populations and horticultural applications has only begun to be quantified worldwide. Federal regulations vary amongst countries regarding the approval and authority to provide or prescribe different types and quantities of antibiotics in different settings, and as importantly, systems for the collection of data regarding antibiotic use and surveillance for bacterial species, including identification of resistant organisms is severely lacking in many countries, and lacks uniformity and completeness when information is collected. There is widespread agreement that information not yet available is fundamental to our understanding of potential risk and harm. Despite the lack of definitive evidence proving antibiotic use in animals causes harm to humans, some countries, and many public health proponents in the United States, have been sufficiently convinced that antibiotics used for humans should not be allowed for use in food animals, in subtherapeutic and or even for therapeutic purposes.
In the United States, the FDA has recently withdrawn prior approval for Enrofloxacin therapeutic treatment for infectious disease in poultry, stating that the Food and Drug Cosmetic Act prohibits consideration of benefits when determining if antibiotics in animal treatment are safe for humans, including any identified in risk analyses typically employed by scientists and often federal agencies. At issue was the effect of the use of enrofloxacin in poultry, a fluoroquinilone antibiotic also relied upon in human medicine to treat diarrhea commonly caused by Campylobacter bacteria, would have on human health. The FDA Commissioner withdrew approval for the use of enrofloxacin in poultry, using case law to bolster his reasoning. The tension between the animal health and pharmacologic scientific community and the laws governing use of antibiotics in animals, especially food animals, is exemplified in this FDA decision.

While disagreements persist between many animal and public health advocates on the issue of harm to humans resulting from antibiotic use in food animals, most parties and agencies I acknowledge the importance of risk assessment tools to determine the safety of this use for animals and humans. When including all relevant parameters using a robust risk assessment tool, it is apparent that the abolishment of antibiotic use in animals, beginning with food animals, creates more potential hazards than have been proven to exist from their continued use.

A prohibition on the use of antibiotics in food animals has proven detrimental to both animals and humans in other countries. The benefits of antibiotics used judiciously in animals reduces bacterial contamination of food, minimizes subsequent human exposure, enhances the safety of food and decreases manure production. Antibiotics that minimize disease and mortality in animal populations allow producers in the U.S. to continue to survive providing the country and 35% of the rest of the world, safe wholesome food. Should antibiotics be prohibited in these populations, bacterial infections, animal disease and mortality will increase, and the welfare of these animals will suffer. Many in the farming community will be unable to withstand the increased economic burdens resulting from increased disease and animal loss, increased resources needed to feed fewer animals for longer periods of time, and the increased scrutiny from animal rights organizations accusing them of animal cruelty. This will not result in less protein eaten in the U.S., but more animal protein imported from other countries where safety and welfare requirements fall short of national standards, leading to diminished human health.

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The development of antibiotic resistance in human medicine has led to a global concern about our continued ability to control bacterial infections that result in human disease and death.\(^1\) While there are many causes of antibiotic resistance, the antibiotic treatment of food animals has been increasingly blamed as an unnecessary risk to human health. With the universal decreasing effectiveness of many antibiotics, greater emphasis is placed on judicious antibiotic use to preserve efficacious use in both veterinary and human medicine.\(^2\) Calls to prohibit use in food animals in deference to human health concerns have persisted for at least a quarter century, with increasing success. However, the evidence to support such bans is circumstantial and heavily contested by evidence demonstrating that the benefits to humans and animals far outweigh the minimal risk associated with continued use. The core of the debate involves a fundamental disagreement about the breadth and balance of risks and benefits that can be considered when analyzing the effects of antibiotic treatment of food animals.

Some public health advocates insist that a partial or total ban of antibiotic use in food animals is warranted to preserve antibiotic effectiveness for human illness, disregarding any benefits from continued use, or harm caused by denying access for animal treatment. There is particular concern about the use of antibiotics for growth promotion and feed efficiency which is considered by some to provide merely an economic benefit that therefore cannot justify the potential harm to human health. Additionally, ready access to these over the counter feed supplements creates concerns about their potential misuse. Alternatively, many animal health proponents maintain that the use of antibiotics in food animals, including those labeled for growth promotion, enhances food safety by providing for animal health and welfare which


results in safer food and greater consumer protection. They insist that decisions to alter or prohibit antibiotic use in food animals will negatively impact animal production and “can result in increased animal illness and eventually increased human illness from food.”

Regulators and policy makers disagree about the extent to which benefits may be considered when evaluating the use of antibiotics in animals raised for food. In the United States (U.S.), the governing statute requires proof of safety for humans and animals prior to approval of antibiotics by the Food and Drug Administration (FDA), but does not expressly limit or allow benefit analysis. In the past, FDA considered benefits to animal health, the environment and the economy as well as harm resulting from prohibitions, when reviewing approval or withdrawal of approval for antibiotic use in food animals. However, the FDA Commissioner, when issuing a final report withdrawing approval of an antibiotic used to treat a disease of poultry, stated that benefits were not allowed to be considered when the agency reviews a new animal drug application (NADA) for food animals that potentially exposes humans to safety risks though food consumption. While prior FDA decisions had allowed for consideration of risk and benefit, increasingly, the agency has rejected scientific findings that seriously question the risk to humans from continued use of antibiotics in animals, and found such use benefits both animals and humans. Public health advocates are equally upset by FDA’s failure to prohibit additional food animal antibiotics. A review of the statute, case law and agency actions may help clarify the legal

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boundaries affecting FDA’s authority, and the relevance of risk benefit analysis in legal considerations of food animal antibiotic use.

An understanding of this complex issue begins with a basic review of the pharmacological interactions of antibiotics and bacteria, the etiology and epidemiology of antibiotic resistance in animal and human populations, the risks and benefits of antibiotic use, and national and global aspects of food production. The issue cannot be adequately understood without also understanding the basic infrastructure of animal agriculture in the United States, including relevant animal welfare, environmental, economic and political components. We must then consider how to effectively balance all the variables-scientific, political and legal-to resolve the question of whether treatment of food animals with antibiotics creates a sufficient risk of harm to humans that such use should be restricted or prohibited.

**BACTERIA, ANTIBIOTICS AND THE MECHANICS OF ANTIMICROBIAL RESISTANCE.**

Bacteria are single-celled microorganisms that existed on the planet before human evolution began. Two types of bacteria exist in mammals: pathogenic or disease-causing bacteria, and non-pathogenic or commensal bacteria. Enteropathogens are pathogens that inhabit mammalian digestive tracts and cause diarrhea or occasionally more serious systemic, multi-organ infections. Typical enteropathogens include Campylobacter, Salmonella, Shiga toxin–producing E. coli, and Listeria, which are considered the common etiologic agents of human foodborne illness. The

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7 Stedman’s Online Medical Dictionary, supra note 6 (epidemiology is “[t]he study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems”).


9 Dorland’s Illustrated Medical Dictionary 344 (25th ed. 1974) (‘commensal’ is “an organism living on or within another, but not causing injury to the host”).

commensal bacteria that normally do not cause disease greatly outnumber these pathogens, yet the importance of antibiotic resistance in this bacterial population in humans or animals has not been adequately investigated.\textsuperscript{11}

[H]uman oral antibiotic use might predispose some parts of the population to increased susceptibility to enteric clinical infection with food-animal enteric pathogens; there are few data for assessing how genes that code for resistance in bacteria move among and between bacterial species, and there is no concrete information on whether or how nonpathogenic bacteria exposed to antibiotics participate in the resistance emergence phenomenon.\textsuperscript{12}

The scarcity of scientific research into the population dynamics of human enteropathogens and commensal bacteria, leads to important gaps in our understanding of the role and impact these commensals play in the transmission of antibiotic resistance.

Antibiotics can be naturally occurring or synthetic, with bacteriocidal or bacteriostatic mechanisms of action. Bactericidal antibiotics kill bacteria, while bacteriostatic action inhibits bacterial growth. These actions can vary with the concentration or dosage of the drug used. Depending on the desired outcome, the same drug may be used at dosages to either kill or inhibit bacterial growth.\textsuperscript{13} Bacteria can develop resistance in the face of minimal or maximum antibiotic concentrations assuming as least some organisms survive treatment, but theoretically more resistant bacteria survive when exposed to bacteriostatic dosages.

\begin{footnotesize}
\textsuperscript{12}National Research Council, \textit{The use of drugs in food animals: benefits and risks}, 8 (National Academy Press 1999).
\end{footnotesize}
Antibiotic resistant bacteria date back thousands of years, long before the discovery of penicillin by Alexander Fleming in 1927:  

Antimicrobial resistant bacteria estimated at being over 2000 years old have been recovered from glacial samples obtained from the Canadian Arctic Archipelago, while a more recent study detected TEM-type β-lactamases from a metagenomic library of cold-seep sediments of deep-sea Edison seamount (near Papua New Guinea) estimated to be about 10,000 years old.

While bacterial resistance initially developed naturally, the explosion of antibiotic resistance is believed to have resulted from selective pressure following exposure to man-made drugs.

Regardless of the method of resistance, bacteria exposed to antibiotics have evolved numerous mechanisms to survive such assaults.

Consistent with other evolutionary selection mechanisms, resistant bacteria that survived exposure passed those traits to other bacteria. Resistance may be inherited and passed to future generations, similar to hair and eye color in humans; or resistant traits may be shared between co-resident bacteria.

All antibiotic use creates antibiotic resistance to some degree. Sometimes one of the bacteria survives because it has the ability to neutralize or evade the effect of the antibiotic; that one bacteria can then multiply and replace all the bacteria that were killed off. Exposure to antibiotics therefore provides selective pressure, which makes the surviving bacteria more likely to be resistant. In addition, bacteria that were at one time susceptible to an antibiotic can acquire resistance through mutation of their genetic material or by acquiring pieces of DNA that code for the resistance properties from other bacteria. The DNA that codes for resistance can be grouped in a single easily transferable package. This means that bacteria can become resistant to many antimicrobial agents because of the transfer of one piece of DNA.

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15 Harbottle et al., supra note 2, at 112.
17 NARMS, supra note 14.
18 Id.
While the pathophysiologic mechanisms of bacterial resistance are beyond the scope of this discussion, we must recognize that resistant bacteria have now outpaced the discovery and development of new antibiotics,\(^{19}\) creating a risk of return to the pre-antibiotic era. Before the advent of antibiotics, bacterial infections caused significant illness and death amongst human and animal populations. There is significant fear that unless new pharmaceutical mechanisms are developed, bacteria will lose all susceptibility to antibiotics, medical treatments will fail and the expanding global human population will suffer from antibiotic-resistant infections with increased resultant mortalities. This concern is not new: it began almost as soon as the pharmacologic production of these drugs began.

**ETIOLOGY OF ANTIMICROBIAL RESISTANCE**

Antibiotics are used in human and veterinary medicine, aquaculture, horticulture and exist in the environment both naturally and as contaminants. Sorting out how these uses creates a quantifiable and unacceptable risk to human health is a task scientists have been painstakingly analyzing for the past 40-60 years. While scientific knowledge has expanded, significant gaps remain in our understanding of the physiologic and epidemiologic nature of antibiotic resistance and specifically how it is influenced by interactions amongst species, space and time. These uncertainties present a serious challenge to policy-makers attempting to base important decisions on sound science. The uses and effects of antibiotic therapy are briefly described below, including observations of the effects of antibiotic bans in European countries.

Humans and animals have both benefited from antibiotics used to forestall or eliminate bacterial infections that might otherwise have resulted in serious illness or death. However, these benefits were accompanied by the development of bacterial resistance. National and international

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public and animal health organizations, recognizing the impending expansion of pathogen resistance, have developed and encouraged the use of judicious-use guidelines, in an attempt to preserve antibiotic effectiveness. The World Health Organization (WHO) has issued continuous warnings beginning in 1978 about the impending global resistance of pathogens, blaming the problem on ‘the widespread and the indiscriminate use of antimicrobial drugs in man and animals.’

Guidelines promoting judicious use of antibiotics in human medicine recommend elimination of wasteful practices including: under-dosing; prescribing antibiotics without pathogen culture and sensitivity-testing; prescribing antibiotics to appease the patient or family members pressuring the doctor for antibiotic prescriptions; and patient non-compliance in following prescribed dosages.

In some cases, doctors prescribe antimicrobials too frequently or inappropriately. Sometimes patients do not complete the prescribed course of an antimicrobial, making it more likely that surviving microbes will develop resistance.

Antibacterial resistance can develop even when prescriptions are medically indicated. However, eliminating irresponsible use theoretically prolongs antibiotic effectiveness by decreasing exposure to pathogens that developed resistance in the face of unnecessary treatment.

Antibiotic resistance resulting from non-judicious medical practice pails in comparison to hospital-transmitted infections (nosocomial infections). Intensive care units, where antibiotics are used extensively, provide the ideal setting for the establishment and transmission of resistant

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22 Dunham, supra note 19, at 2.
pathogens to patients already compromised by their immuno-suppressed condition. One of the most prevalent nosocomial infections, Methicillin-resistant *Staphylococcus aureus* (MRSA), has now spread beyond the hospital environment, establishing community-based infections.

While antibiotic use in humans is considered the greatest risk factor in the development of pathogen resistance, humans are also susceptible to resistant pathogen transmission from companion animals, antibiotic-treated or pathogen-contaminated produce, the environment, and food animals. The risk from exposure to treated companion animals (pets) is a potentially significant yet commonly overlooked factor in the prevalence of antibiotic resistance. Human interaction with companion animals has been evolving throughout history, beginning with the domestication of the dog in the late pre-agricultural period of man’s evolution over 10,000 years ago, and as currently reflected by our ever-growing infatuation with pet ownership. Zoonotic infections, including bacteria that can be spread between humans and animals, have been the focus of public health concern for some time. Increased animal-human contact has been identified as one of the greatest risk factors for emerging zoonotic diseases.

Current reports estimate that nearly 60% of households in the U.S. include pets. Of the 68.7 million households with pets, “about half considered their pets to be family members.”

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28 *Zoonoses and veterinary public health (VPH)*, WHO (2009), available at http://www.who.int/zoonoses/en/, (any disease and/or infection which is naturally "transmissible from vertebrate animals to man" is classified as a ‘zoonosis’). See also Lonnie King, DVM, *Director, National Center for Zoonotic, Vector-Borne, and Enteric Diseases*, available at http://www.cdc.gov/about/leadership/leaders/king.htm (last visited March 16, 2009).
One of the measurements of ‘family status’ was the provision of veterinary care which includes antibiotic treatment of bacterial infections. Humans and animals share susceptibility to many bacteria and are treated with similar classes of antibiotics. Therefore treating pets for bacterial infections presents a risk of transmission of any surviving, resistant pathogens between pets and their ‘families.’ The risk of exposure increases proportionally with increased human-animal interaction. Sharing homes, beds and food, and failing to wash hands after handling pets facilitates sharing of disease organisms, including Campylobacter and Salmonella, also considered foodborne pathogens.\textsuperscript{32} Exposure to asymptotically-infected (carrier) dogs and cats has resulted in an estimated 200,000 cases of human gastroenteritis. Multi-drug resistant Salmonella in contaminated pet food has been identified as a high risk factor particularly for children.\textsuperscript{33}

Even when diseases result primarily from human exposure, animals are often erroneously implicated as the etiologic source, as recent news coverage of MRSA infections in animals demonstrates. MRSA, as described before, represents the greatest overall prevalence of antibiotic resistance in humans.\textsuperscript{34} There is widespread acknowledgment that hospitals created and spread MRSA in human populations, but, with the identification of MRSA in pets\textsuperscript{35} and food animal species, blame has shifted to animals, particularly food animals. While cases of MRSA infection in pets are rising, the American Veterinary Medical Association notes that humans are the likely

\textsuperscript{31} Id.  
\textsuperscript{32} Rabinowitz et al., supra note 26, at 1318.  
\textsuperscript{33} Id.  
cause of these animal infections. However, once infected, the pets may transmit the bacteria to others in the home, requiring antibiotic treatment of all human and animal household residents.

While MRSA has been identified in livestock, and humans associated with livestock, the strains are usually different that those isolated from hospitals and community-based outbreaks. The mere identification of a resistant pathogen in food animals is insufficient evidence of transmission to humans. As with pets, humans may be the source of infection. Despite de minimis evidence that swine are the root of the problem, a NY Times Op-Ed columnist recently implied that a definitive link exists between the 18,000 fatal MRSA human infections reported by the Centers for Disease Control and Prevention (CDC) and infected swine. Experts from the U.K. and the U.S. refute those claims. In the U.K., experts considered animal sources unlikely causes of resistance in human MRSA infections. A U.S. Congressional report, comparing risk of human exposure from hospital-based infections with potential exposure through food animals came to similar conclusions:

While the use of antibiotics in food animals can cause resistance emergence, not all instances of resistance are clinically significant, involve resistance in pathogens, or cause an actual illness. In contrast, because the occurrence of infection in hospitals is often considered life-threatening, the risk to human health of hospital-acquired infections might be thought of as a greater risk.

Even exotic animals have acquired human-transmitted MRSA infections. In 2008, an elephant calf requiring intensive neonatal care was infected with MRSA by a human handler at the San Diego Zoo. Transmission occurred when caretakers, later identified as subclinical

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36 Education is key to combating rise in MRSA, JAVMA News, 234(2) JAVMA (Jan 15, 2009), available at http://www.avma.org/onlnews/javma/jan09/090115g.asp.
38 Nicholas D. Kristof, Pathogens in Our Pork, N.Y. Times, March 15, 2009, at WK.
39 Bywater & Casewell, supra note 34, at 643-645.
carriers of MRSA, failed to adhere to universal sanitary precautions. Certain activities, including grooming, bottle feeding, medicating, and trunk blowing (to stimulate nursing) were identified as heightened risk factors. A total of 20 human cases (suspect or confirmed) were identified, but all the other elephants tested negative. The epidemiologic investigation clearly identified humans as the source of this outbreak.

Other sources of human exposure to resistant bacteria include the consumption of fruit treated with antibiotics to eliminate bacterial infections or from produce contaminated with human or animal based fertilizers. Antibiotics and other pharmaceutical compounds have also been identified in U.S. watersheds and drinking water in major cities. These potential sources of resistant pathogens have been inadequately considered when analyzing overall causation of antibiotic resistance in humans.

In the ANTIBIOTIC RESISTANCE report, GAO states that the full extent of the antibiotic resistance problem remains unknown [and] notes that the use of antibiotics in agriculture is only one of several factors that contributes to antibiotic resistance in humans… and that the debate extends to antibiotics used on plants… acknowledge[ing] the complexity of the antimicrobial resistance issue.  

ANTIBIOTICS IN FOOD ANIMALS

The greatest criticism of antibiotic use in animals, involves the treatment of food animals. Humans may be exposed from direct contact during animal production, slaughter or processing; or indirectly, through foodborne contamination.

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Farm workers and pharmaceutical technicians who work with antibiotic compounds, feeds, feed premixes, and concentrates, and people who work with sick and therapeutically treated animals also could be at greater risk for clinical resistance...[but] data suggest that most human disease scenarios associated with food-animal pathogens are related to enteric diseases contracted principally through consumption of pathogen-contaminated foods.\footnote{National Research Council, \textit{supra} note 12, at 8.}

Antibiotics have been used in food animals for more than 50 years and the transfer of resistant pathogens from cattle, swine and poultry to farmers and animal handlers has been documented without evidence of increased disease in this at-risk population.\footnote{Doyle et al., \textit{supra note} 2, at 93. \textit{See also} \textit{Antibiotic Use in Animals}, GAO-04-490 (2004) at 18.} No evidence of human disease was detected where transmission of resistant pathogens from chickens fed medicated feeds to people living on or near the farm was identified.\footnote{\textit{Id.} \textit{See also} \textit{Antibiotic Use in Animals}, \textit{supra} note 46, at 18.}

In the first reported case of ceftriaxone-resistant salmonella infection in the U.S., a 12-year-old boy, recovering from an appendectomy following a course of antibiotic treatment for a sinus infection, developed cephalosporin-resistant salmonellosis while hospitalized.\footnote{Doyle et al, \textit{supra note} 2, at 76. \textit{See also} Paul D. Fey et al., \textit{Ceftriaxone-Resistant Salmonella Infection Acquired by a Child from Cattle}, 342(17) New England Journal of Medicine, 1242 (2000).} Sick cattle from one herd owned by neighbors of were culture-positive for the same strain of Salmonella. Cattle from the child’s herd, were positive for a similar, but different strain of Salmonella. The report concluded that the cattle produced resistant pathogens after they were treated with cephalosporin antibiotics, but the farmers reported no history of antibiotic use in these herds. The conclusion that antibiotic treatment in cattle presented a human health risk in this case, is not supported by facts. Alternate sources of infection or explanations were not described.

The possibility that both cattle and humans could have been exposed to the same source of Salmonella was not discussed. Clustering of human and animal salmonellosis has been...
observed, but the nidus of infection, whether through domestic or wild animals, vegetation or water, must be determined on a case-by-case basis. The allegation that antibiotic treatment resulted in resistant bovine pathogens may also be erroneous. Isolation of tetracycline and penicillin-resistant E. coli pathogens have been cultured from herds and flocks with no prior antibiotic treatment. Finally, since prior antibiotic usage in humans has been identified with the increased risk of subsequent resistant pathogen infections, the child’s recent antibiotic treatment may have facilitated his salmonella infection.

While direct contact between humans and food animals may be a low risk for resistant pathogen transmission, foodborne illness caused by human exposure to pathogens in food, represents a greater potential risk for the transmission of resistant organisms and is a significant public health concern. To understand how antibiotics used in food animals may contribute to foodborne disease, the indications for treatment and the structure of animal agriculture in this country must be considered. Antibiotic usage in food animals falls into one of two broad categories: therapeutic and subtherapeutic use. Therapeutic use includes treatment of: clinically ill animals, those infected but without evidence of illness, healthy animals with known or anticipated exposure to sick animals, and animals expected to develop illness secondary to certain unavoidable physical stressors. While there is a universal acceptance of treatment of diseased animals with antibiotics not used in human medicine, treatment to prevent the incidence or spread of disease is increasingly criticized. These treatment regimes have been labeled,
'non-therapeutic' by critics, even though they were developed by animal scientists and veterinarians and are used in modern production settings, where animals are raised in large groups, to maintain animal health.\textsuperscript{54}

Given the close proximity of the animals to one another (commingling), physiological and environmental stressors, and immature immune systems, any underlying viral infections, or bacterial respiratory or enteric diseases that may occur in a few animals can spread to others including entire herds or flocks. Within the limits of the production system, and depending on the nature of the disease, the producer and/or veterinarian may intervene in such situations by medicating the entire group via the feed or water rather than treating each affected animal.\textsuperscript{55}

In addition to criticism over the practice of treating large groups of clinically normal animals to prevent illness, the method of delivery, by feed or water, is also criticized. Concerns involve the potential for imprecise dosages delivered to individual animals, which may increase the risk of pathogen resistance if inadequate antibiotic concentrations result. However, this method of treatment is the least stressful for the animals, and the only practical way of administering antibiotics to large numbers of animals to prevent and treat illness.

Subtherapeutic treatment occurs when food animals are fed low dosages of antibiotics in medicated feeds for the labeled purpose to enhance growth while improving feed efficiency. Subtherapeutic dosages are generally, but not always, lower than concentrations used for disease treatment, and are often fed for at least 2 weeks.\textsuperscript{56} Medicated feeds may be used intermittently to coincide with stressful situations such as weaning or transportation, or for longer durations without specific indications. The approval process and oversight of antibiotics administered through animal feed is stringently regulated by FDA, but critics object to the ease of access to medicated feeds by producers, without a veterinary prescription, which they believe may lead to

\textsuperscript{54} National Research Council, supra note 12, at 4.
\textsuperscript{55} Doyle et al., supra note 2, at 78.
\textsuperscript{56}Human-Use Antibiotics in Livestock Production, supra note 44 (1980 NAS report on [t]he effects on human health of subtherapeutic use of antimicrobials in animal feeds).
unnecessary use. As importantly, some critics believe that the sole benefit from subtherapeutic use is economic and insist that human health should take precedence over financial gain.

While not as important as human health, the economic benefits derived from antibiotic use in food animals are significant for producers and consumers. Subtherapeutic treatment increases animal growth by 1-15% which reduces feed costs and time to market, produces higher yields and decreases animal illness and death.57 Veterinary costs of dairy, beef, pork and broiler production are estimated at $1.6 billion per year.58 Food animal antibiotic bans are predicted to increase consumer costs by more than $700 million per year for pork alone.59 Increased costs to producers, passed onto consumers, must be weighed against the medical expenses resulting from antibiotic use in food animals if proven to cause human harm. Human antimicrobial resistance costs in the 1990’s were estimated at $100-200 million.60 Assuming the worst case scenario, that food animal antibiotics contribute to human disease, only 10% of those costs are estimated to be food animal related.61 Actual costs must be determined from data documenting the extent of antibiotic use in both human and animal populations and the actual human health harm from antibiotic resistance that results. The controversy over the use of subtherapeutic antibiotic use is confounded by conflicting data about the prevalence of and risks of antibiotic use in human and veterinary medicine and conflicting evidence over its animal health benefits.

To adequately understand the risk factors associated with antibiotic use, accurate data capturing the type, amounts, and duration of antibiotics used in various settings must be obtained. Unfortunately exact quantities of antibiotics used in human and animal medicine are

57 Doyle et al., supra note 2, at 88. See also National Research Council, supra note 12, at 74.
58 Matthews, supra note 1, at 5.
59 Antibiotic Use in Animals, supra note 46, at 14.
60 Doyle et al., supra note 2, at 112.
61 Matthews, supra note 1, at 1.
not known and estimates vary significantly with the source of the data. The Union of Concerned Scientists (UCS), a public health advocacy group intent on banning antibiotic use in food animals, extrapolated from agricultural surveys to estimate that 70% of the antibiotics in the U.S. are used for non-therapeutic agricultural purposes. The Animal Health Institute (AHI), an animal health industry trade association, rejected this estimate and, relying on member-submitted reports, found that 94.5% of antibiotic use in food animals is therapeutic and 4.6% is for subtherapeutic use. Notably, the UCS and AHI use different definitions for non-therapeutic and subtherapeutic use, contributing to the discrepancy of their findings. Without accurate data, projections about the impact of future bans on antibiotic usage in food animals are unpredictable. National and international pressure to create reliable and robust databases tracking antibiotic use has been mounting. The FDA’s efforts to require reporting of antibiotic use in food animals has been bolstered by a recent amendment to the Food and Drug Cosmetic Act (FDCA), mandating expanded reporting.

The most debated questions about antibiotic resistance involve the mechanism and extent to which subtherapeutic use benefits or harms animals and humans, and the harm that might result if this use were prohibited. Some public health advocates and animal rights activists consider subtherapeutic use equivalent to non-therapeutic use, deny that any health benefits result, and insist such use unnecessarily risks human health. On the other hand, supporters of subtherapeutic treatment argue that the practice enhances both animal and human health by

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65 Doyle et al., supra note 2, at 88.
modifying or eliminating intestinal bacterial organisms. This primary action has significant animal health, welfare and food safety benefits including:

- Enhance[ed]…efficiency of nutrient utilization… allow[ing] increased lean muscle gain to be added per pound of feed consumed, resulting in an overall reduction in feed consumption… reduced fecal output, lessening the environmental burden from excess nutrients such as nitrogen and phosphorous…maintaining a stable fermentation process within the rumen, small intestine and hindgut of ruminants [that]…decrease[s] the likelihood of metabolic disorders, such as ketosis, [and]can reduce emissions of methane, an important greenhouse gas…reduced need for the animal’s immune system to respond, thus contributing to a healthier animal and improvement in animal welfare…suppression of potential pathogens that may be present in low numbers can prevent important enteric diseases, which in a group setting, can maintain overall flock or herd health and welfare…reduce[d] the variation in size of slaughter animals…thereby improve[ing] the ability to process the carcass and improve the quality of the meat product.\textsuperscript{67}

The primary food safety benefits result from the decreased overall bacterial load in the animal which decreases bacterial contamination of food ultimately handled and consumed by humans.\textsuperscript{68}

While health benefits are most significant, there are important secondary economic and environmental benefits that also occur. The feed efficiency created by medicated feeds decreases the amount of land required for crop production. Further environmental benefits result from decreased manure and methane gas production resulting from consumption of medicated feeds. These benefits, combined with improved animal health, create an economic cushion that sustains the viability of U.S. producers.

The prohibition of subtherapeutic antibiotics in Europe, beginning in 1986, provides evidence of the intended and unintended effects of these bans. Except for a slight decrease in vancomycin-resistant enterococci, the expected decrease in the incidence of resistant human pathogens did not occur.\textsuperscript{69} Instead, prevalence of many resistant human pathogens increased, in

\begin{flushleft}
\textsuperscript{67} T.R. Shryock & S.W. Page, \textit{Growth Promotion Uses of Antimicrobial Agents}, Antimicrobial Therapy in Veterinary Medicine, 389, 395 (Blackwell Publishing 4\textsuperscript{th} ed. 2006).
\textsuperscript{68}Singer et al., \textit{supra} note 4, at 188.
\textsuperscript{69} Mark Casewell et al., \textit{The European ban on growth-promoting antibiotics and emerging consequences for human and animal health}, 52 Journal of Antimicrobial Chemotherapy, 159, 159-160 (2003).
\end{flushleft}
some cases up to 49% of the pre-ban incidence. This may have resulted from the 143% increased use of veterinary-prescribed antibiotics required to treat food animals experiencing significantly increased disease and death following the removal of subtherapeutic antibiotics. Humans may have been exposed to more resistant pathogens from the sick animals treated with antibiotics also used in human medicine. The use of similar antibiotics in human and veterinary medicine is common and in this case, the shift from subtherapeutic to therapeutic antibiotics in animals resulted in increased use of these antibiotics in animals to treat disease. This shift was also observed in 1970, following a similar ban in the U.K. that was also intended to decrease the prevalence of antibiotic resistance:

[T]he Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (the Swann Report) warned that uncontrolled use of similar antibiotics in humans and food animals could promote the emergence of resistant strains of foodborne bacteria that could endanger human health.

While the overall use of food animal antibiotics decreased following the European ban, these bans appear to have unintended harmful effects in both human and animal populations. In other instances, a decrease was documented in the prevalence of certain resistant pathogens in animals, but an unexplained increased prevalence was concurrently observed in humans. Antibiotic-resistant enterocci increased in prevalence by 25% in humans, while decreasing by 8-20% in poultry and swine.

This demonstrates that the correlation between antibiotic usage in food animals and humans must be more extensively explored before definitive a cause and effect can be established. Additionally, these unexpected results should help inform policies about the future use of antibiotics in food animals. It appears that the risk to humans would increase, not

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70 Hoang, supra note 62, at 6-7.
71 Louis A. Cox Jr. & Paolo F. Ricci, Causal regulations vs. political will: Why human zoonotic infections increase despite precautionary bans on animal antibiotics, 34 Environment International 459, 467 (2008) (citations omitted). See also Casewell et al., supra note 69, at 160.
72 Cox & Ricci, supra note 71, at 459.
73 Id.
decrease, if administration of antibiotics were limited to therapeutic usage. Further harm would result if antibiotics considered important for human medicine were entirely prohibited from use in food animals, since few alternate efficacious treatments are available.

The Preservation of Antibiotics for Medical Treatment Act of 2009 (PAMTA), recently introduced in Congress, would harm animal and human health by “prohibiting the use of medically important human antibiotics for nontherapeutic purposes in food-producing animals.”74 “Nontherapeutic use” as defined in the bill, prohibits the use of antibiotics unless the animal exhibits signs of illness:

The term nontherapeutic use, with respect to a critical antimicrobial animal drug, means any use of the drug as a feed or water additive for an animal in the absence of any clinical sign of disease in the animal for growth promotion, feed efficiency, weight gain, routine disease prevention, or other routine purpose.75

If enacted, PAMTA would likely eliminate the use of subtherapeutic and therapeutic use that normally prevents the entry or spread of disease to non-infected cohorts. Proponents believe that such treatment would be unnecessary with simple modifications to animal husbandry practices. A persisting misperception, cited in the bill, states that antibiotics are used in modern agricultural settings to compensate for “crowded, unsanitary, and stressful farming and transportation conditions.”76

Intensive livestock agriculture that uses subtherapeutic doses of antibiotics has led to the emergence of antibiotic-resistant strains of Salmonella, Campylobacter, and Escherichia coli bacteria. Overcrowded and mixed livestock practices…can facilitate interspecies host transfer of disease agents, leading to dangerous novel pathogens such as SARS and new strains of influenza.77

However, unless raised in germ-free environments, animals will always be susceptible to infectious diseases, with increased transmissibility in larger production units. The infrastructure of animal agriculture in the U.S. involves the comingling of large numbers of animals within

75 Id.
76 Id.
77 Rogers & Haines, supra note 42, at 188.
constructed environments. In 2004, agriculture constituted 13% of the U.S. Gross National Product, including $1 trillion dollars of economic activity, in excess of $50 billion dollars in exports and providing 15% of American jobs.\textsuperscript{78} From 2001 to 2005, 8.4 billion chickens (broilers), 264 million turkeys, 103 million hogs, more than 37 million head of cattle, and 9.12 million dairy cattle were produced each year.\textsuperscript{79} Since 1987, more animals are raised on a smaller number of farms, with increased productivity, resulting from fundamental improvements in technology, nutrition, and genetics.\textsuperscript{80}

Whether raised inside or outdoors, the co-location of large numbers of animals results in the increased likelihood of disease transmission. Those raised indoors are spared the effects of weather extremes, environmental hazards, predation, parasitic infestation and diseases spread through vectors (insects and wild animals). However, once a pathogen is introduced in an indoor environment, more animals may be infected.\textsuperscript{81} Comparisons of disease prevalence in animals raised in cages, buildings and outdoors have demonstrated the advantages and disadvantages of these management practices. In Sweden, morbidity and mortality of chickens raised in indoor cages, indoor litter-based systems and free-range conditions were compared. Free-range chickens had the highest rates of cannibalism, bacterial and parasitic infections, while the caged birds experienced the highest incidence of viral infections.\textsuperscript{82} Overall, non-caged birds were found to be more prone to disease. In another study, antibiotic-free hogs raised outdoors had 54% and 39% seroprevalence rates for Salmonella and Toxoplasma, respectively, compared with 7% and 1%

\textsuperscript{78}Hoang, supra note 62, at 5.
\textsuperscript{79}\textit{Id.}
\textsuperscript{81}Drugs in Livestock Feed, Office of Technology Assessment for S. Comm. on Ag., Nutrition, and Forestry, 96\textsuperscript{th} Cong., L.of Cong. 79-600094, 4 (1979) (described how cleaning large production units would still not prevent disease).
\textsuperscript{82}Tim Lundeen, \textit{Free-range chickens more prone to disease}, 81(4) Feedstuffs (2009).
rates in conventionally raised hogs. Only outdoor-raised swine were seropositive to Trichinella, a swine parasite that can infect humans through consumption of undercooked meat. However, the number of animals raised together creates the greatest risk of disease transmission, whether raised indoors or outside.

The number of animals raised for food is driven by consumer demand, here and abroad, and is expected to increase as the global population continues to expand to nine billion by 2050.

Since 1960, global meat production has tripled; milk production has doubled, and egg production has increased four-fold... A 2004 report indicated that between 2000 and 2030, global meat production was expected to increase by 1.9% per annum until 2015 and then by 1.5% per annum until 2030.

Claims that antibiotics are only used in animal agriculture because animals are raised in filthy settings that would be remedied by simply moving animals to pasture, are scientifically and medically unsupported.

To those who believe that the solution is a return to a pastoral, early-20th-century model with millions of small farms producing more “natural” food, I would point out that even if the millions of farm workers who would be required were available to produce food on a quasi-boutique scale, the costs would be enormous; it would be impossible to feed 300 million Americans, let alone the rest of the world. Efficient, industrialized production of huge quantities of food is an inescapable necessity to avoid food shortages and global famine.

Assuming the number of animals produced for food will not decrease; antibiotics should not be prohibited in food animal production without definitive evidence of harm to human health, so that animal health does not unnecessarily suffer. However, greater emphasis should be placed on

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83 Wondwossen A. Gebreyes et al., Seroprevalence of Trichinella, Toxoplasma, and Salmonella in antimicrobial-free and conventional swine production systems, 5(2) Foodborne Pathogens and Disease 199 (2008).
85 Salman et al., supra note 50, at 12-13.
86 Maki, supra note 10, at 3-4.
prudent antibiotic use in all species, and research into antibiotic alternatives should be encouraged and funded.

Antibiotic use should be targeted to maximize the effectiveness of treatment in food animals:

[T]he magnitude of the response to antibacterial agents varies with stage of life cycle, stage of production and the environmental conditions to which animals are exposed. The response is greater during critical stages of production such as waning, breeding, farrowing or immediately post hatching in chicks and turkeys.\(^{87}\)

Subtherapeutic antibiotics that provide medical advantages in addition to increased growth and feed efficiency can be relabeled for therapeutic treatment, requiring veterinary oversight, thereby limiting over-the-counter and possibly, unnecessary use. Vaccines developed to reduce the incidence of infections requiring antibiotic treatment have been successful; an E.coli vaccine produced for cattle has recently been conditionally approved by USDA.\(^{88}\) Further developments in this area should be pursued. Unfortunately other alternatives to antibiotics in food animal production have not been as successful. Neither probiotics, that may work to increase beneficial intestinal bacteria and interfere with pathogens, nor mannanoligosaccharides, sugars that theoretically interfere with bacterial attachment to the intestinal lining, have enhanced growth or feed efficiency in clinical trials in pigs.\(^{89}\)

However, proven methods in food production and distribution have significantly decreased bacterial contamination of meat and poultry, with concomitant decreases in the incidence of Salmonella and Campylobacter confirmed human foodborne infections.\(^{90}\) These successes have been partially attributed to the Hazard Analysis and Critical Control Points

\(^{87}\) Shryock & Page, *supra* note 67, at 390-391 (quotation omitted).


(HACCP) system, initiated by the U.S. Department of Agriculture (USDA) in 1996 and adopted by FDA.\textsuperscript{91} This comprehensive program identifies and attempts to eliminate hazards of food contamination throughout all critical points in food production. Expanding this system to on-farm production may help minimize contamination before processing and identify methods to reduce environmental contamination from pathogens in manure. Adequate manure management should minimize the infiltration of water supplies from unintended spillage, or crop contamination with resistant pathogens in animal-produced fertilizers. Finally, practices that increase exposure to contaminated foods, such as raw milk consumption, should be discouraged; while technologies that reduce bacterial contaminants like irradiation, pasteurization, freezing and refrigeration should be encouraged.\textsuperscript{92}

**THE LAW AND ANTIBIOTICS IN FOOD ANIMALS**

The legal debate surrounding the use of antibiotics in livestock in the U.S. spans decades. The FDA is squarely at center stage, interpreting the governing statute as informed by case law and scientific evidence from epidemiologic and surveillance data used in ever-evolving risk assessment models. The FDA has predominantly upheld existing uses of antibiotics and medicated feeds despite increasing pressure to ban such use. “As of 2007, the US FDA has withdrawn only one antibiotic, enrofloxacin, a fluoroquinilone used to cure fatal respiratory illnesses in chickens.”\textsuperscript{93} FDA’s failure to prohibit subtherapeutic antibiotic use has been criticized by some public health advocates, while the decision to withdraw approval of one poultry antibiotic has been denounced by animal health advocates joined by the pharmaceutical and animal agricultural industries. All interested parties agree that risk analysis must form the


\textsuperscript{92} Hurd et al., \textit{supra} note 53, at 984. \textit{See also} Justin Denny et al., \textit{Outbreak of Escherichia coli O157:H7 associated with raw milk consumption in the Pacific Northwest}, 5(3) Foodborne Pathogens and Disease 321 (2008).

\textsuperscript{93} Cox & Ricci, \textit{supra} note 71, at 465.
foundation on which food safety policy is based,\textsuperscript{94} but there is little agreement about the
particular assessment tool to use, and great disagreement about the extent to which both benefit
and risk may considered. There are additional conflicts over the validity and strength of data
relied upon in analyses, yet all agree that more robust, reliable data is required. All these factors
create a tension between scientists and legal scholars which gives rise to an infectious legal
environment, making it difficult for objectivity to prevail and the law to provide the appropriate
result.

The federal authority governing antibiotic use in food animals falls largely upon the FDA
which approves applications of new animal drugs for sale and regulates the manufacture and
distribution of antibiotics used in animals, as prescribed by veterinarians or through access to
licensed feed mills that add specific antibiotics to animal feed, in subtherapeutic dosages for
growth promotion.\textsuperscript{95} Once medicated animal feeds are approved by the FDA, they are available
over the counter without veterinary oversight.\textsuperscript{96} Two other federal agencies, the CDC and
USDA, assist FDA with the collection of pathogen resistance data from human and animal
populations, and food processors and distributors.\textsuperscript{97}

Congress empowered the FDA with the authority to implement the approval of new
animal drugs\textsuperscript{98} and withdrawal of prior approvals pursuant to the FDCA.\textsuperscript{99} The statute is
administered by the FDA Commissioner with input from the Director, Center for Veterinary
Medicine (CVM), using decisional law to supplement statutory interpretation. While the safety
of drugs approved by FDA must be determined with regard to human health, that is not the only
parameter the agency must consider:

\begin{thebibliography}{99}
\bibitem{Hurd et al.} Hurd et al., \textit{supra} note 53, at 980.
\bibitem{Antibiotic Use in Animals} Antibiotic Use in Animals, \textit{supra} note 46, at 2.
\bibitem{Antibiotic Use in Animals} Antibiotic Use in Animals, \textit{supra} note 46.
animals other than man, including any drug intended for use in animal feed.”).
\end{thebibliography}
The Federal Food, Drug and Cosmetic Act and its regulations establish complicated procedures by which new drugs proposed to be used in treating animals both subtherapeutically as feed additives and therapeutically, are approved before they can be marketed. Human safety is specifically considered, because it is in animals raised for food that these drugs and feeds will be used.¹⁰⁰

Prior to approving a new animal drug application, FDA must determine that the drug is safe and effective for its intended use in the animal and that any residue that may exist in animal-based food is safe with regard to human health.¹⁰¹ “[S]afe” as used in the animal drug sections of the FDCA “has reference to the health of man or animal.”¹⁰² There are several ‘safety clauses’ in the statute which acknowledge the inherent risks of drug use, yet provide for their use under prescribed guidelines. The statute also references a number of considerations in addition to safety that must be considered.

Animal drugs with identified risks may be approved at dosages that do not result in residue levels pursuant to 21 U.S.C. §360 (a)(4)(B):

(B) If the Secretary finds that there is a reasonable probability that a use of an animal drug authorized under subparagraph (A) may present a risk to the public health, the Secretary may--
(i) establish a safe level for a residue of an animal drug when it is used for such different use authorized by subparagraph (A); ¹⁰³

In addition to human safety, other factors the Secretary “shall” consider, when reviewing new animal drug approvals include:

(A) the probable consumption of such drug and of any substance formed in or on food because of the use of such drug, (B) the cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance, (C) safety factors which in the opinion of experts, qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use of animal experimentation data…¹⁰⁴

Finally, when considering withdrawal of prior approval, based on new evidence of risks to human and animal safety, the Secretary must consider this information along with the facts included in the initial drug application, including those mentioned above:

\[
\text{(e)(1)} \quad \text{The Secretary shall...issue an order withdrawing approval of an application... if the Secretary finds—}
\]

(B) that new evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved or that subparagraph (I) of paragraph (1) of subsection (d) applies to such drug.\(^{105}\)

The statute appears to provide the flexibility needed to consider the benefits of use, negative impacts from prohibited use, and the myriad of other factors relevant to antibiotic use in food animal production, in addition to the overarching concerns about human safety.

The production and consumption of food is central to any society, and has economic, social and, in many cases, environmental consequences. Although health protection must always take priority, these issues must also be taken into account in the development of food policy.\(^{106}\)

Until recently, the FDA acknowledged the importance of the benefits of antibiotic use in response to comments of regulatory proposals.\(^{107}\) In 1977, when abandoning a proposal to withdraw approval of sulfonamide drugs in animal feeds,\(^{108}\) the agency remarked on the importance of continued access to these drugs to maintain animal health. At that time, antibiotics had been used safely and effectively in billions of animals for nearly 20 years and this use was considered pivotal in maintaining the health of these animals raised in concentrated and intensified production systems.\(^{109}\)


\(^{106}\) Commission White Paper on Food Safety, supra note 3, at 6.

\(^{107}\) The role of antibiotics in agriculture, supra note 11, at 6. See also Human-Use Antibiotics in Livestock Production, supra note 44.

\(^{108}\) 42 FR 43772 (1977).

\(^{109}\) 38 FR 9811(1973) Antibiotic and Sulfonamide Drugs in Animal Feeds.
The Commissioner acknowledges the benefit from such drugs, when properly used...[including] increased rate of gain, improved feed efficiency, and animal disease control... [and] [i]mmediate and total withdrawal of these drugs from animal feeds could seriously disrupt the quality and quantity of an important portion of our total human diet.\textsuperscript{110}

The Commissioner commented that:

\begin{quote}
the concept of ‘safety’ as used in the act does not require complete certainty of the absolute harmlessness of a drug but rather the reasonable certainty in the minds of competent scientists that it \textit{is} not harmful, \textit{when balanced against the benefits to be obtained from the drug}.\textsuperscript{111}
\end{quote}

The FDA required enhanced testing and reporting of antibiotic use, but declined to ban the use of sulfonamides in all animal feed without sufficient evidence of harm to humans to counterbalance the benefits.\textsuperscript{112}

Following a similar proposal in 1977 to withdraw approval of subtherapeutic use of penicillin and tetracycline, FDA again determined there was insufficient evidence of harm to human health, relying on equivocal data from the National Academy of Sciences.\textsuperscript{113} Since that time, FDA has continued to revisit the question of subtherapeutic use, but both former and current FDA-CVM directors continue to recognize the value of properly managed antibiotic use in food animals, despite some risks,\textsuperscript{114} noting that “[w]hile potential public health concerns must be addressed, it is critical that veterinarians continue to have access to effective antimicrobial drugs for the treatment, control, and prevention of disease in animals.”\textsuperscript{115}

The federal courts have confirmed this position. In 1974, the D.C. Circuit, reviewing an FDA decision to withdraw approval of a food animal hormone, concluded that since drugs were inherently unsafe to some degree, decisions allowing continued sales of drugs with demonstrated

\begin{footnotes}
\item[110] \textit{Id.}
\item[111] \textit{Id. (emphasis added).}
\item[112] \textit{Id.}
\item[114] \textit{Id. (citing Antibiotics in Animals, The International Food Information Council Webpage, available at http://ificinfo.health.org/insight/antibiotic.html).}
\item[115] \textit{Dunham, supra} note 19 at 10.
\end{footnotes}
risks required the agency to determine whether the benefits of use outweighed the risk of use.\textsuperscript{116}

In another case, the Supreme Court, reviewing the FDA’s decision on the approval of a cancer drug for terminal patients, acknowledged that:

\begin{quote}
[f]ew if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk. Thus, the Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use.\textsuperscript{117}
\end{quote}

Several years later, the Court, while rejecting FDA’s assumed authority over tobacco, nevertheless upheld FDA’s reasoning that allowed for considerations of risks of continued use and the effects of a withdrawal:

\begin{quote}
[I]n determining whether a device is safe under the Act, it must consider ‘not only the risks presented by a product but also any of the countervailing effects of use of that product, including the consequences of not permitting the product to be marketed.’\textsuperscript{118}
\end{quote}

Based on these court decisions, FDA’s 2005 decision to withdraw approval of the new animal drug application (NADA) for use of the fluoroquinolone enrofloxacin in poultry, without any consideration of benefits, seems inconsistent.

FDA, at least since this 2005 decision, rejects the consideration of benefits when reviewing the safety of drugs with regard to the safety of food produced for human consumption.

In its Final Decision, the FDA Commissioner remarked:

\begin{quote}
I find that the FDCA as a whole, as well as its legislative history, makes clear that Congress did not intend to allow FDA to weigh costs or benefits associated with the use of a new animal drug in deciding whether its use has been shown to be safe for humans when used in food-producing animals…FDA is not authorized, under the FDCA, to weigh economic, health or other benefits that the drug provides against a health risk to the ultimate human consumers of food from or contaminated by treated animals... no benefits of any kind are relevant when
\end{quote}

\begin{flushright}
\textsuperscript{116} Hess & Clark, Division of Rhodia, Inc. v. Food & Drug Administration, 495 F.2d 975, 993-994 (C.A.D.C. 1974).
\textsuperscript{117} U. S. v. Rutherford, 442 U.S. 544, 555-556 (U.S. Okl., 1979) (discussing the safety of a drug used to treat terminally ill patients).
\end{flushright}
assessing the human safety of a new animal drug used in a food-producing animal.\textsuperscript{119}

FDA follows a two-step analysis to determine first, that the drug is safe and effective in the animal, and then determines that any food produced from the animal presents a reasonable certainty of no harm to humans.\textsuperscript{120}

Based on this analysis, FDA concluded that enrofloxacin, a fluoroquinolone antibiotic used to treat a respiratory condition of poultry (air sacculitis), created resistant Campylobacter species in poultry resulting in reasonable certainty of harm to humans. While there is agreement that fluoroquinolone-resistant Campylobacter was isolated from poultry and poultry products following its approval, respondent Bayer and amicus Animal Health Institute insist that proof of harm to humans was not sufficiently proven.\textsuperscript{121} In addition to rejecting the bulk of the scientific evidence relied upon by FDA, there was disagreement about FDA’s ability to consider the benefits of antibiotic use for animals and humans.

The Commissioner rejected consideration of all benefits in his analysis, including those permitted by the agency’s Administrative Law Judge:

\begin{quote}
\textit{to the extent it deals with human health effects, \textit{i.e.}, whether the human health benefits of using the drug outweigh the human health risks from use of the drug.}\textsuperscript{122}
\end{quote}

In addition to a lengthy review of the legislative evolution of the FDCA, the Commissioner referenced two Supreme Court decisions in support of his decision. However, reliance on both these cases may be flawed.

In \textit{American Textile Mfrs. Institute, Inc. v. Donovan}\textsuperscript{123} the issue was whether a cost/benefit analysis was permitted by OSHA when establishing a cotton dust standard. The

\begin{footnotesize}
\textsuperscript{119} Final Decision, supra note 5, at 94.
\textsuperscript{120} Id.
\textsuperscript{121} See generally Bayer’s Reply, supra note 5.
\textsuperscript{122} Final Decision, supra note 5, at 93.
\end{footnotesize}
Court held that a cost/benefit analysis was not required for consideration because it was not expressly included in statutory language, but a feasibility analysis was required. This case is distinguishable from FDA’s enrofloxacin decision. First, while safety is a consideration for both FDA and OSHA, respectively, the statutes in question have sufficiently different language to preclude a cross interpretation from the statute in *Donovan* to the FDCA. The critical language in the OSHA statute required consideration of human safety, ‘to the extent feasible.’ There is no similar language in the FDCA. Therefore, the Court’s conclusion in *Donovan* does not necessarily direct FDA action pursuant to the FDCA. Equally important, as Chief Justice Rehnquist noted in dissent, while the Court did not require a cost/benefit analysis, they also did not conclude that such consideration was prohibited:

> [A]t least as to the “Cotton Dust Standard,” the Act does not require the Secretary to engage in a cost-benefit analysis, which suggests of course that the Act *permits* the Secretary to undertake such an analysis if he so chooses.125

Therefore, the FDA Commissioner’s reliance on *Donovan* to prohibit his consideration of risk/benefit is not valid.

In the second case, *Whitman v. American Trucking Associations*,126 the Court reviewed the provisions required in the Clean Air Act (CAA) for the Environmental Protection Agency’s (EPA) establishment of national ambient air quality standards (NAAQSs), for ozone and particulate matter. The Court found that Congress had recognized, but did not permit, the consideration of economic factors when establishing NAAQSs:

> In particular, the economic cost of implementing a very stringent standard might produce health losses sufficient to offset the health gains achieved in cleaning the air—for example, by closing down whole industries and thereby impoverishing the workers and consumers dependent upon those industries. That is unquestionably true, and Congress was unquestionably aware of it.127

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124 Donavan, 452 U.S. at 508.
125 Id. at 544 (Rehnquist dissenting).
127 Id. at 466.
However, as in the FDCA where Congress recognizes the multiple variables involved even in matters affecting public health and safety, Congress allowed for the consideration of other factors in other CAA statutory sections:

Congress…not only anticipated that compliance costs could injure the public health, but provided for that precise exigency. Section 110(f)(1) of the CAA permitted the Administrator to waive the compliance deadline for stationary sources if, inter alia, sufficient control measures were simply unavailable and “the continued operation of such sources is essential ... to the public health or welfare.” (citation omitted). Other provisions explicitly permitted or required economic costs to be taken into account in implementing the air quality standards.  

Therefore, the Commissioner’s reliance on this case may also be faulty. Instead of supporting FDA’s new position, both cases may support FDA’s previous approach to subtherapeutic antibiotics that allowed for consideration of factors in addition to human safety. However, until FDA’s interpretation is reviewed by the Courts, or readdressed by Congress, they will likely continue their current line of reasoning.

APPLICATION OF RISK ASSESSMENT IN ANTIBIOTIC TREATMENT OF FOOD ANIMALS

Fortunately, FDA’s policies and regulations allow for and recommend the use of risk assessments in the application process for new animal drug approvals. Risk assessment is considered integral to the regulation of antibiotic use in the U.S.:

In contrast, in 1998, the European Union banned five antibiotics... including streptogramins, macrolides, and fluoroquinolones by appeal to the Precautionary Principle, where no [risk assessment] predicting human (or animal) health consequences [were] considered necessary.  

In the U.S., all parties agree that risk assessments are essential to provide objective, science-based information to help inform the decision-making process:

\[M\]any government regulatory authorities, industry associations, and other organizations are proposing that risk assessment (RA) methods be applied to the issue of antibiotic resistance associated with food-producing animals… An RA combines information on the consequence of an event with the probability of

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128 Id. at 466-467.

129 Cox & Ricci, supra note 71, at 466.
occurrence of that event, within the current state of technology and common practice.\textsuperscript{130}

However, there are many types of risk assessments, and both the type and process of choosing the risk assessment creates additional conflicts. The difficulties inherent with risk assessments have been recognized by other agencies also reliant upon their use. The EPA, concerned about the validity of its risk assessments to identify human risk, recently requested assistance from the National Research Council to assess and improve upon their risk analysis tools.\textsuperscript{131} The Council found that reliance on risk assessments was increasingly used as a primary tool to ensure public health, and specifically “to address broader environmental questions, such as life-cycle analysis and issues of costs, benefits, and risk-risk tradeoffs.”\textsuperscript{132} They identified the criticality of addressing uncertainty and variability within the risk-assessment process:

Uncertainty can be reduced by the use of more or better data. Variability is an inherent characteristic of a population, inasmuch as people vary substantially in their exposures and their susceptibility to potentially harmful effects of the exposures. Variability cannot be reduced, but it can be better characterized with improved information.\textsuperscript{133}

Variability is the heart of a valid risk assessment model for antibiotic resistance analysis. A risk assessment is only predictive if it can analyze the multiple factors that impact the prevalence of resistant pathogens. FDA’s selection of a simplistic risk assessment to evaluate the risk of enrofloxacin use in poultry was criticized since it excluded considerations of issues other than the risk to human health, despite the relevance of other complex factors.\textsuperscript{134} Notably, the FDA has abandoned this particular risk assessment tool and adopted others.

There are two basic types of risk assessments used to analyze antibiotic resistance: quantitative tools measuring the amount of resistant pathogens present or qualitative tools that

\textsuperscript{130} Hurd et al., supra note 53, at 980.
\textsuperscript{132} Id.
\textsuperscript{133} Id.
\textsuperscript{134} Human-Use Antibiotics in Livestock Production, supra note 44.
identify the presence of resistant bacteria. While quantitative assessments identify pathogens, qualitative tools do not measure pathogen concentrations. This deficiency has been heavily criticized since establishing the dose of resistant pathogens needed to result in human harm is considered a fundamental factor in disease pathogenesis. The WHO, reviewing human risk associated with Salmonella exposure from eggs and poultry, considered quantitative tools the only predictive measure of microbial loads. The National Research Council also recommended quantitative assessments and “encourage[d] EPA to move toward the long-term goal of quantifying population variability more explicitly in exposure assessment and dose-response relationships.” Further, the failure to use quantitative assessments may yield erroneous results leading policy makers to disallow practices that are not harmful to human health.

Even though FDA’s currently recommended assessment tool is a qualitative analytical model, a draft quantitative risk assessment was recently published by FDA evaluating whether virginiamycin, a streptogramin antibiotic used in food animals for over 20 years, presents a risk to human health following the 1999 approval of the human antibiotic equivalent, Synercid®. The report concluded that there was insufficient evidence that use in animals resulted in transmission of resistant organisms to people with resulting harm. Without the quantitative analysis applied, a different conclusion may have been reached. Fortunately, the tools used for risk assessment have begun to evolve, incorporating both quantitative and qualitative measurements that capture dose-response data required to determine the actual risk of infection, as described below.

137 Singer et al., supra note 4, at 199.
138 FDA Guidance #152, Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern.
139 69 FR 226 (2004), Risk Assessment of Streptogramin Resistance in Enterococcus faecium Attributable to the Use of Streptogramins in Animals.
Not only must the risk assessment be reliable; they require accurate, reliable data obtained from robust national surveillance systems to provide valid data points for sound analysis. The current surveillance systems in use to collect data from human and animal populations and in food production systems, remain suboptimal and yield inconsistent results, adding to discrepancies between scientists and officials studying the issue.\textsuperscript{140} Surveillance data is collected by FDA, CDC and USDA:

FDA, CDC, and USDA have six surveillance activities ongoing to identify and assess the prevalence of resistant bacteria in humans, animals, or retail meat….National Animal Resistance Monitoring System (NARMS) and Collaboration in Animal Health, Food Safety and Epidemiology (CAHFSE)—focus on antibiotic resistance from animals. The other four activities—Foodborne Diseases Active Surveillance Network (FoodNet),PulseNet, PulseVet, and National Animal Health Monitoring System (NAHMS)—focus on foodborne disease or animal health in general…\textsuperscript{141}

Surveillance includes bacterial isolation from human and animal samples, farm animals, carcasses, slaughter plants, meat, and other animal derived foods. The bacterial varieties monitored have varied over time, but currently includes: Salmonella, Campylobacter, E. coli, Enterococcus and Shigella.\textsuperscript{142} Laboratory testing methods and the concentrations of bacteria considered critical also vary, making comparisons of data obtained difficult, if not impossible.

These discrepancies were one source of contention between FDA and Bayer in the Enrofloxacin decision. Bayer identified flaws in laboratory methods used in scientific studies reviewed by FDA, and demonstrated how the variant critical concentrations of pathogens identified in epidemiological findings skewed results, invalidating conclusions.\textsuperscript{143} Scientists and policy makers must establish universally acceptable, science-based testing methods, critical pathogen concentration points and surveillance tools so that uniform data is available for analysis in appropriate risk assessment tools.

\textsuperscript{140} Antibiotic Use in Animals, supra note 46, at 7.
\textsuperscript{141} Id. at 27.
\textsuperscript{142} Doyle et al., supra note 2, at 94.
\textsuperscript{143} Bayer’s Reply, supra note 5, at 46, 74.
Once the risk assessment model is chosen and the data used for analysis is reliable and robust, there must be agreement about the quantity and quality of factors to be considered. As discussed before, a simplistic model that allows only for the consideration of human health risks cannot provide an understanding of the overall impact of antibiotic use in food animals. For an adequate understanding, variables affecting human and animal risk and benefits must be considered.

Of the 76 million annual CDC-estimated cases of foodborne illness in the U.S., only a fraction are laboratory-confirmed bacterial infections, and an undetermined portion of those cases involve bacteria transmitted from food animals. To result in human harm, food animals treated with antibiotics must produce resistant bacteria that contaminate the food products marketed to consumers. Following improper product handling and preparation exposure that allows the bacteria to survive, the person must become infected, instead of merely exposed to bacteria transiting through their intestinal tracts. Finally the resistant bacteria must either cause more serious disease than its non-resistant counterpart, or requires treatment which fails as a result of the antibiotic resistance created. Bayer described these required levels of causation of fluoroquinolone-resistant-Campylobacter gastroenteritis in humans:

Even if enrofloxacin use select for fluoroquinolone (“FQ”) resistant *Campylobacter* (“*CP*”) in poultry (which it does), and even if clinically relevant microbial loads of FQ-resistant *CP* are transferred from chickens or turkeys (which does not seem to occur detectably often under current conditions), such resistance does not harm human health unless FQ-resistant infections in humans are worse in some way than FQ-susceptible infections.

FDA found sufficient proof of reasonable harm to humans from continued use of this antibiotic to treat poultry disease, despite evidence that Campylobacter resistance in humans

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145 Bayer’s Reply, supra note 5, at 4.
decreased during the period of time this drug was used in poultry in the U.S.\textsuperscript{146} Risk factors that were insufficiently considered in FDA’s analysis, that may have yielded a different result include: human disease caused by international travel or prior antibiotic exposure; prevalence of resistant pathogens in humans eating poultry in commercial establishments compared with home consumption; increase in enteropathogens in poultry and poultry products following removal of access to enrofloxacin; and greater overall risk to human health resulting from enrofloxacin bans.

It seems reasonable to include all these relevant factors in a risk assessment attempting to analyze the interrelated parameters of this complex issue. If the use or lack of use of antibiotics in food animals can result in human harm, both alternatives should be considered. Fortunately, the statutory language provides for the inclusion of impacts to animal health in any analysis.

The health status of food animals destined to enter the human food supply chain is an important, although often overlooked factor in predicting the risk of human foodborne infections.\textsuperscript{147} Without antibiotics, a greater number of food animals processed will have higher levels of intestinal pathogens that will contaminate carcasses and processed food.\textsuperscript{148} Failure to treat certain bacterial diseases can result in diminished intestinal integrity leading to increased contamination at slaughter.\textsuperscript{149} Whether the risk of increased microbial carcass contamination is greater than the risk of exposure to a smaller number of potentially resistant pathogens is a question that must be captured in the analysis and considered by policy-makers.\textsuperscript{150} The benefit to animals and humans of antibiotic use compared with the risk of transmission of resistant pathogens can be incorporated in the robust risk assessment models recently developed:

[They] evaluate the relationship between on-farm animal health status, animal health interventions and human foodborne disease risks\textsuperscript{151} [by] “assessing pre-harvest animal health intervention strategies, such as the use of antibiotics in

\textsuperscript{146} Id. at 91.
\textsuperscript{147} Singer et al., supra note 4, at 186.
\textsuperscript{148} Id. at 187-8.
\textsuperscript{149} Id.
\textsuperscript{150} Id.
\textsuperscript{151} Id. at 188.
animals, and the potential human health risks and benefits from these interventions.”

When applied to scenarios in which important human antibiotics are used to treat animals, these tools have demonstrated minimal risk of antibiotic treatment failure in humans (less than 1 in 10 million Campylobacter and 1 in 3 billion E. faecium human infections). A study, analyzing the removal of a medicated feed for poultry, predicted “[an] increased rate of clinically and subclinically ill animals [that] could harm human health by increasing the level of Campylobacter-contaminated chicken.” Another study, examining the benefits and risks of continued access to virginiamycin, a food animal antibiotic, following the release of a similar human drug, predicted that 6,660 additional cases of human campylobacteriosis would result if this drug were no longer available for the treatment of food animals.

The effects of bans on animal health must be considered in terms of the welfare of the animals in addition to the increased costs resulting from animal illness and death. Animal welfare suffers with increased disease and death. While economic benefits of antibiotic use cannot outweigh harm to human health, detriments to animal health cannot be discounted merely as an economic loss. For those who may not consider animal health an important independent consideration, there is ample evidence that continued use of antibiotics in food animals should be continued, if only to protect human health.

Healthy animals make healthy food; for veterinarians to be effective in protecting our food supply, the appropriate tools for preventing, mitigating and treating disease, which includes antimicrobials, are paramount for veterinarians to be able to utilize.

CONCLUSION

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152 Id. at 189.
153 Hoang, supra note 62, at 17. See generally Hurd et al., supra note 53.
154 Singer et al., supra note 4, at 198.
155 Hoang, supra note 62, at 17 (citation omitted).
156 Id. at 3.
The preservation of the effectiveness of antibiotics is essential to protect the health of animals and humans. Insufficient evidence currently exists to support prohibitions on the use of antibiotics in food animals, even those currently labeled for subtherapeutic treatment. The advantages provided to both human and animal populations from continued use of antibiotics in food animals outweigh the minimal risk to humans currently documented. The unintended consequences resulting from prohibitions in Europe, negatively impacting both human and animal health, must inform future decisions. The FDA, implementing the FDCA with analyses obtained from robust risk assessment tools that measure critical quantitative and qualitative data points from farm to fork, should consider benefit and risk to humans and animals. While developing more uniform and robust surveillance programs to collect data about antibiotic usage and resistant-pathogen prevalence in human and animal specimens, the judicious use of antibiotics in all species should be encouraged.

At the same time, techniques successfully used in food production to minimize bacterial contamination of food can also be implemented on the farm. Since subtherapeutic or therapeutic antibiotics can contribute to the reduction of bacteria in manure, minimize carcass contamination, and decrease the microbial load of food consumed, such use should continue. Tools to eliminate pathogens from animal-produced fertilizer and advanced food preparation methods to eliminate surviving bacteria can be employed. Unexplained illness from food consumed at commercial establishments should be investigated and identified hazards should be targeted for elimination. Objective, science-based analyses are required to satisfactorily understand the complex factors contributing to the risk of antimicrobial resistance.

Preconceived notions of agricultural management techniques must be replaced by an understanding of the full range of medical, nutritional and technical tools that allow for the production of healthy animals and wholesome, safe food. Our tendency to create homocentric policies and laws must be tempered by an obligation to maintain the health and welfare of
animals raised for food production, which will allow us to provide food for the world’s ever-expanding population. In conclusion, the cost to animal health resulting from prohibitions on the use of antibiotics in food animals is unwarranted without definitive evidence that such use creates a public health risk. Until sufficient evidence proves that antibiotic treatment of animals results in disease or harm to humans, prohibitions should not be pursued.