Impact of Antimicrobial Use in Animals and Regulatory Response

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Abstract

There is accumulating evidence that the use of antimicrobials in food-producing animals has adverse human health consequences. The use of these drugs in food animals selects for resistant pathogens and resistance genes that may be transferred to humans through the consumption or handling of foods of animal origin. Recent studies have demonstrated that antimicrobial resistance among foodborne bacteria may cause excess cases of illness, prolonged duration of illness, and increased rates of bacteremia, hospitalization and death.

The US Food and Drug Administration (FDA) is committed to resolving the public health impact arising from the use of antimicrobial drugs in food-producing animals. The FDA's goal is to ensure that significant human antimicrobial therapies are not compromised or lost while providing for the safe use of antimicrobials in food animals. The FDA published a guidance document titled "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern" that outlines a pathway drug sponsors can use to address concerns about antimicrobial resistance prior to approval of their drug.[30] The process uses a qualitative risk assessment approach to assess the potential of the intended use of a product to develop resistance in bacteria that may harm humans. The level of risk determines the level of risk management that is required for the drug to be approved.

Introduction

There is general agreement within the scientific community that the development of resistant human pathogenic bacteria results primarily from the direct use of antimicrobial agents in humans, but also from acquisition of resistant organisms or resistance factors from animal and environmental sources. Antimicrobial resistance includes resistance in both zoonotic pathogenic bacteria and animal origin commensal bacteria that may transfer resistance genetic material. Over the last several years, an increasing numbers of studies have been published that provide evidence of the development of resistant bacteria from the use of antimicrobial drugs in food-producing animals and their transfer to humans through contact with or consumption of contaminated food.[5,9,20,32]

The spread of resistant pathogens and resistance genes from food animals to humans has serious implications for the treatment of human infections. Many of the antimicrobials administered to food animals are either identical to or related to drugs used in human medicine, including penicillins, tetracyclines, cephalosporins and fluoroquinolones; many of these drugs are also used to treat foodborne disease in humans. This is problematic because resistance genes frequently encode resistance not just to a particular antibiotic, but to an entire class of antimicrobials[4,18] and some genes may cause cross-resistance to compounds that are structurally diverse.[4] In addition, mobile DNA elements often carry several resistance genes. Consequently, acquisition of a single mobile genetic element may confer resistance towards multiple antimicrobials[18] and resistance to several different antimicrobial drugs may emerge when only one antimicrobial drug is used.[4,15,16] Multidrug resistance among foodborne pathogens and other bacteria is becoming more and more common, threatening our ability to successfully treat certain infections.[10,36]

However, animals need antimicrobials for treatment of disease. Therefore, we need to safeguard the effectiveness of antimicrobials for both humans and animals while at the same time allowing for the safe use of some antimicrobials for animal treatment. FDA is concentrating on developing risk management tactics that will help to curb and control both the development of resistant bacteria in food animals and human exposure to them.

Evidence for the Transfer of Resistant Bacteria from Food Animals to Humans

Different types of evidence demonstrate that drug resistant bacteria in food animals, which result from antimicrobial use in food animals, are a source of infection and illness in humans. These include epidemio-

logical studies of outbreaks and sporadic cases of illness; microbiological and molecular studies of bacterial isolates from humans, food animals, and retail meats; temporal associations; and experimental studies.

Food animals were identified as the source of 69% of resistant salmonella outbreaks investigated by the Centers for Disease Control and Prevention (CDC) between 1971 and 1983.[5,11] A 1998 human outbreak of multidrug resistant *Salmonella* Typhimurium definitive type 104 (DT104) in Denmark was linked to a Danish swine herd. The outbreak strain, which had resistance to the quinolone nalidixic acid and reduced susceptibility to fluoroquinolones, resulted in infections that were difficult to treat.[20]

Case-control studies and case reports of sporadic infections have also provided evidence that resistant enteric pathogens are transmitted to humans from food animals and foods of animal origin. A multistate case-control study in the United States in 1998-1999 compared domestically-acquired fluoroquinolone campylobacter cases to age-matched well controls and found that cases were associated with eating chicken or turkey at a commercial establishment.[12] A retrospective case-control study of sporadic infections with *Salmonella* Newport MDR-AmpC in New England states demonstrated that infections were domestically acquired and associated with exposure to a dairy farm; isolates from humans and cattle had indistinguishable or closely related antibiograms and pulsed-field gel electrophoresis patterns.[9] *S.* Newport MDR-AmpC strains are resistant to at least nine antimicrobials, have either decreased susceptibility to or resistance to extended-spectrum cephalosporins, and are sometimes resistant to trimethroprim-sulfamethoxazole.[9]

Temporal data provide support for the association between antimicrobial use in food animals and the development of resistant infections in humans. In many countries, including the Netherlands, Spain, the United Kingdom and the United States, the licensure of fluoroquinolones for use in food animals, particularly poultry, has been followed by an increase in the isolation of fluoroquinolone-resistant campylobacter from humans that had not appeared when fluoroquinolones were licensed only for human use.[3,6,7,8,19,21-25,27] To further support this association, fluoroquinolone resistance has not emerged among campylobacter within Australia, where fluoroquinolones have never been licensed for food production animals but the drugs have been licensed and used in human medicine for many years.[29]

Commensal bacteria, which constitute a large reservoir of resistance genes, may also be transferred from food animals to humans.[1,13-15,32-33] Resistance genes from the commensal flora of food animals may be transferred to both human pathogens and commensal organisms.[1,17] The importance of this indirect transfer of resistance is less clear than for the direct transfer of resistant zoonotic pathogens and is the subject of several review articles.[13,26]

Adverse Human Health Impact

There is accumulating evidence that antimicrobial resistance originating from the use of antimicrobials in food animals adversely affects human health. Studies have shown that antimicrobial resistance in zoonotic foodborne pathogens increases the burden of disease in humans by causing excess cases of illness and increasing morbidity and mortality among cases.

In a review paper, Barza and Travers[2] estimated that between 13 and 26% of drug-resistant salmonella infections in humans could be attributed to the use of an antimicrobial to which the pathogen is resistant. Using a low estimate of 10%, they further estimated that in the United States, 29,379 infections, 342 hospitalizations and 12 deaths per year can be attributed to antimicrobial-resistance in salmonella acquired from food animals.[2]

Excess cases of infection may also occur among people who do not receive an antimicrobial. Exposure of food animals to antimicrobial agents may increase the amount of pathogens in animals through reduced colonization resistance, which could lead to more pathogens in the food supply.[1,31] In addition, resistant bacteria may be better able to colonize animals or persist in the environment than susceptible ones, thereby increasing the risk of foodborne infections in general.[35]

In addition to causing excess infections, antimicrobial resistance has been associated with prolonged illness and increased rates of hospitalization, bacteremia and mortality. The poorer outcomes associated with resistant infections may be due to greater virulence of resistant strains, ineffective treatment, or the need to use antimicrobials that are more toxic or less effective. The strongest evidence demonstrating that resistant foodborne bacteria result in adverse human health outcomes comes from studies specifically designed to address the issue. Studies that have utilized epidemiological and/or statistical methodologies to account for potentially confounding factors, including serotype and age, have demonstrated an association between resistance in salmonella and increased morbidity and mortality. Varma *et al* studied non-typhoidal salmonella cases diagnosed in the United States between 1996 and 2000 and found that antimicrobial resistance was associated with increased hospitalization and bloodstream infections.[34] Several campylobacter case-control studies in the United States and Denmark have demonstrated a relationship between quinolone resistance and prolonged duration of illness.[10,24] For more detailed

information on these and other studies, a recent article reviewed epidemiological studies that demonstrate the association between antimicrobial resistance and increased morbidity and mortality for salmonella and campylobacter infections in humans.[28]

Assessment of the Risk from Development of Resistance prior to Approval of the Drug

Given the increasing evidence that use of antimicrobials in food-producing animals is adversely affecting human health, the FDA needed a mechanism to assess the potential food safety risk from the use of antimicrobials prior to their approval. The goal of the FDA in addressing the issue of antibiotic resistance is to develop strategies to safeguard the effectiveness of antimicrobials for humans and animals while at the same time allowing for the safe use of some antimicrobials for animal treatment. The FDA held several stakeholder public meetings, two veterinary medical advisory committee meetings and several focus group meetings with key stakeholders such as the American Veterinary Medical Association, the Animal Health Institute, Coalition of Animal Health, Food Animal Concerns Trust and Environmental Defense Fund to gather input on developing a process for evaluating new animal antimicrobial drugs prior to approval with respect to antimicrobial resistance. In 2002, FDA published a draft guidance document and held an additional public meeting to gather input. After considering all comments, the final guidance published in 2003.[30]

The guidance sets out a three-part system for determining an antibiotic's risk to humans if used in food-producing animals. The Release Assessment estimates the probability that bacteria resistant to an antimicrobial would be present in an animal treated with the antibiotic. The Exposure Estimate is the probability of human exposure to resistant bacteria or resistance determinants through animal-derived food. It is calculated by considering both the species of animal from which the food is derived and the prevalence of contamination by the food-borne bacteria of interest on that food commodity (e.g., *Campylobacter* species on chicken.) The Consequence Assessment describes the human health consequence of exposure to resistant bacteria or determinants based on the importance of the drug or related drugs to humans. FDA then integrates the components of the risk assessment to provide a qualitative indication of the potential risk to human health from the proposed use of the antibiotic.

A key component of the guidance document is a ranking of antimicrobial drugs based on their importance to human health. In developing criteria for the ranking, the FDA requested the Anti-Infective Drugs Advisory Committee to consider broad issues associated with the efficacy of drugs in human medicine and factors influencing the development of antimicrobial resistance. The criteria are ranked from most to least important, i.e., criterion 1 is the most important:

1. Antimicrobial drugs used to treat enteric pathogens that cause food-borne disease
2. Sole therapy or one of few alternatives to treat serious human disease or the drug is an essential component among many antimicrobials in the treatment of human disease
3. Antimicrobials used to treat enteric pathogens in non-food-borne disease
4. No cross-resistance within drug class and absence of linked resistance with other drug classes
5. Difficulty in transmitting resistance elements within or across genera and species of organisms.

Critically important drugs are defined as those that meet both criteria 1 and 2. The fluoroquinolones, macrolides, third-generation cephalosporins and trimethoprim/sulfamethazine are the only drugs classified as critically important. Highly important drugs are defined as those that meet either criteria 1 or 2. Examples of highly important antimicrobial drugs include the penicillins, aminoglycosides, tetracyclines, streptogramins and fourth-generation cephalosporins. Important drugs are defined as those that meet either criterion 3 and/or 4 and/or 5. Examples of important antimicrobials include first and second generation cephalosporins, quinolones and monobactams. The development of new antimicrobials for human therapy, the emergence of diseases in humans, or changes in prescribing practices, etc., are among the factors that may cause the rankings to change over time.

The overall risk estimation represents the probability that the use of an antimicrobial animal drug will adversely impact human health. Antimicrobial drugs in Category 1 are associated with a high risk ranking and would typically be subject to the most restrictive use conditions. Category 3 drugs have the lowest risk ranking and would typically be subject to the least limitations. Category 2 drugs, ranked intermediate for risk to human health, would typically be subject to limitations that are intermediate between those of Categories 1 and 3. Examples of risk management steps and how these steps might be applied to manage the estimated level of risk are shown in Table 1.

Since the final guidance published in 2003, FDA has successfully approved several antimicrobials using this process. The most recent example is the approval of tulathromycin for bovine and swine respiratory disease.

Table 1. Examples of risk management options based on the level of risk identified (High, Medium or Low).

Approval conditions	Category 1 (High)	Category 2 (Medium)	Category 3 (Low)
Marketing Status[1]	Rx	Rx/VFD	Rx/VFD/OTC
Extra-label use (ELU)	ELU restrictions	Restricted in some cases	ELU permitted
Extent of use	Low	Low, medium	Low, medium, high
Post-approval monitoring (e.g., NARMS[2])	Yes	Yes	In certain cases
Advisory committee review considered	Yes	In certain cases	No

[1] Prescription (Rx), Veterinary Feed Directive (VFD), Over-the-counter (OTC)
[2] National Antimicrobial Resistance Monitoring System

Conclusion

Antimicrobial resistance not only endangers the efficacy of products in the treatment of animal diseases but, can also cause problems in human health. Transfer of resistant zoonotic or commensal bacteria or transfer of resistance determinants, either directly from treated animals to humans or indirectly via food, is of growing concern.

Regulators in countries around the world have developed standards for assessing the risks associated with the use of veterinary medicinal products, appropriate market approval requirements, and post-marketing control and surveillance methodology in order to ensure that these products are used in a prudent manner. The goal of these efforts with respect to the issue of antimicrobial resistance is to balance the need to minimize the impact on human health while having appropriate veterinary medicinal products available to meet the health and welfare needs of animals. The continued availability of safe and effective antimicrobials for humans and animals depends upon the responsible use of these products.

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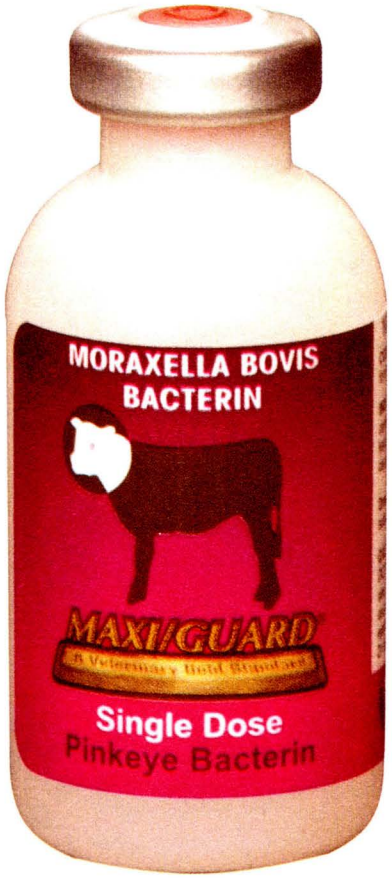

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