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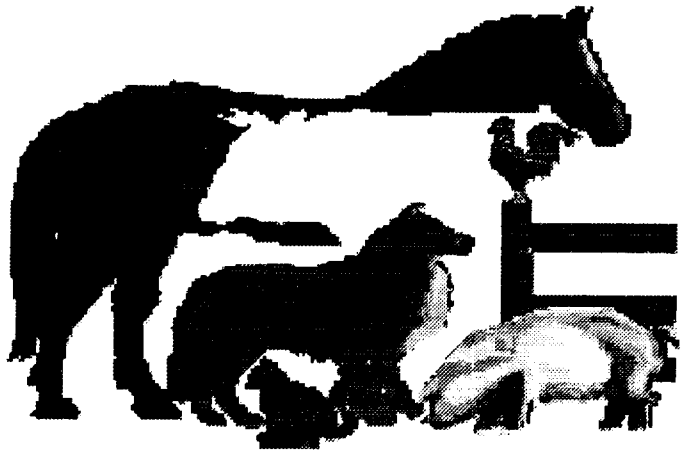
Veterinary Medicine Advisory Committee



January 25-26, 1999

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date 119 '99 APR 14 P2:07

From VMAC Executive Secretary

Subject Background Materials

To VMAC Members, Consultants, and Guest Speakers

We are enclosing background materials for the Veterinary Medicine Advisory Committee meeting to be held January 25-26, 1999.

As you prepare for the meeting, please give particular attention to the framework document and the questions for the committee.

Several of the enclosures, such as the agenda, are subject to change. Revised versions, if any, will be distributed at the meeting.

A reminder to guest speakers: Please provide a paper copy of your slides or overheads to me during the meeting.

We thank you for agreeing to participate in the meeting. If you have any questions about any of the enclosed materials, please contact Jon Scheid (301) 827-6514 or Jackie Pace (301) 827-6650.

Richard E. Geyer

Members, Consultants and Guest Speakers
Veterinary Medicine Advisory Committee Meeting
January 25 - 26, 1999

MEMBERS

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Food Animal Concerns Trust (FACT)

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Carl Norden, M.D.**
Cooper Hospital/University Medical Center

* *Chair*
**Division of Anti-Infective Drugs Advisory Committee

GUEST SPEAKERS

Sherwood Gorbach, M.D.
Tufts University

Scott McEwen, D.V.M., DVSc.
University of Guelph

David Bell, M.D.
Centers for Disease Control
and Prevention (CDC)

Patricia Lieberman, Ph.D.
Center for Science and the Public Interest
(CSPI)

J. M. Rutter, D.V.M.
Veterinary Medicines Directorate, U.K.

Abigail Salyers, Ph.D.
University of Illinois

Lyle Vogel, D.V.M., M.P.H.
American Veterinary Medical Association
(AVMA)

VETERINARY MEDICINE ADVISORY COMMITTEE
AGENDA

uary 25	
8:30	Introductions
8:45	Michael Friedman, M.D., Deputy Commissioner for Operations, Food and Drug Administration - Introductory Remarks
9:00	Nicole Lurie, M.D., M.S.P.H., Principal Deputy Assistant Secretary for Health, Office of the Secretary, Department of Health and Human Services - Introductory Remarks
9:15	Stephen F. Sundlof, D.V.M., Ph.D., Director, Center for Veterinary Medicine - A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals
10:00	*Break*
10:20	Mark Goldberger, M.D., M.P.H., Center for Drug Evaluation and Research - The Importance of Antimicrobial Drugs for Human Medicine
10:40	Margaret A. Miller, Ph.D., Center for Veterinary Medicine - The Animal Drug Approval Process for Antimicrobial Agents
11:00	Linda Tollefson, D.V.M., M.P.H., Center for Veterinary Medicine - Post Approval Surveillance Issues
	Guest Speakers
11:20	David Bell, M.D., Centers for Disease Control and Prevention - Need for Addressing Issue and Benefits of Establishing Threshold Levels
12:00	*Lunch*
	Guest Speakers (cont'd)
1:00	Scott McEwen, D.V.M., D.V.Sc., University of Guelph, Canada - Risk Assessment
1:30	Patricia Lieberman, Ph.D., Center for Science in the Public Interest (CSPI) - Overview of CSPI Report Recommendations Relevant to Use of Antimicrobials in Food Animals
2:00	Lyle Vogel, D.V.M., M.P.H., American Veterinary Medical Association (AVMA) - Need for Safe and Effective Antimicrobials for Food Animals, and AVMA Efforts on Prudent Use
2:30	J.M. Rutter, D.V.M., Veterinary Medicines Directorate, UK - The Authorization of Antimicrobial Products in the European Union
3:00	*Break*
3:15	Abigail Salyers, Ph.D., University of Illinois - Importance of Commensals in the Transfer of Resistance from Animals to Humans
3:45	Sherwood Gorbach, M.D., Tufts University - Importance of In Vitro Resistance Compromising Therapy for Diarrheal Disease
4:15	Animal Health Institute
5:00	Begin Public Speakers
January 26	
8:30	Public Speakers (as needed)
10:15	*Break*
10:30	Committee Deliberations; Dr. Sundlof - Presentation of Questions
12:00	*Lunch*
1:00	Committee Deliberations
4:00	Adjournment

QUESTIONS for the
VETERINARY MEDICINE ADVISORY COMMITTEE
JANUARY 25-26, 1999 MEETING

1. FDA's goal is to protect the public health by ensuring that the efficacy of human antimicrobial therapies is not compromised due to use of antimicrobials in food animals, while providing for the safe use of antimicrobials in food animals. Do the concepts laid out in the document entitled, "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals" provide a sound scientific basis for achieving this goal, if implemented?

2. Categorization of Antimicrobial Drugs for Human Medicine (see Pp. 8-11 and 14 of the Framework Document):

The agency is proposing that the categorization of antimicrobial drugs for human medicine take into account the usefulness of the drugs in both foodborne disease and non-foodborne infectious diseases, when evidence exists that use of the drug may result in induction of resistant pathogens or the transfer of resistant elements to human pathogens. This approach recognizes not only the well known risk of resistance transfer through classical food borne pathogens but also the threat of transfer of resistant bacteria or resistance genes from other intestinal bacteria of food animals resulting in resistant infections of humans with other types of pathogens (e.g., resistant *E. coli* or *Enterococcus*). Does the committee agree with this approach?

3. Monitoring Threshold Levels (see Pp. 15-16, 18 and 20 of the Framework Document):

A) Should multiple monitoring threshold levels be established and should they be based on animal data, human data or both? Should the levels be tied to specific actions, e.g., need for further investigation, need for mitigation strategies, need for withdrawal of product from the market?

B) What organism(s) should be the basis for the monitoring thresholds? In the interest of cost containment, should a sentinel organism(s) be designated or should a foodborne pathogen(s) be used?

4. Resistance Threshold Levels (see Pp. 14-16, 18, and 20 of the Framework Document):

The Agency has proposed the creation of different levels of resistance transfer to humans that would be acceptable based on the importance of the drug or drug class in human medicine. Category I antimicrobial drugs would require that use in food producing animals results in little or no resistance transfer to humans. Category II antimicrobial drugs would require that a pre-defined level of maximum resistance transfer be established prior to approval that would depend on several factors, such as the existence of alternatives to the drug, the human pathogen(s) of concern, etc. The level of resistance transfer must be low enough that there is a reasonable certainty of no harm to humans associated with the use of the product in food animals. What criteria should the Agency use to safely define the acceptable level of resistance transfer, if any, for antimicrobial drugs that fall into Categories I and II?

5. On-farm post-approval monitoring programs will be necessary for certain antimicrobials (Category I, Category II/H and some Category II/M products) (see Pp. 17, 19, and 20 of the Framework Document). Should on-farm monitoring be instituted immediately post approval or triggered by a change in data generated from other sources such as NARMS?

A PROPOSED FRAMEWORK FOR EVALUATING AND ASSURING THE HUMAN SAFETY OF THE MICROBIAL EFFECTS OF ANTIMICROBIAL NEW ANIMAL DRUGS INTENDED FOR USE IN FOOD-PRODUCING ANIMALS

I. Statement of Purpose

Evidence of increasing resistance to antimicrobial drug treatment in bacteria that infect humans has raised questions about the role that antimicrobial drug use in food-producing animals plays in the emergence of antimicrobial drug resistant bacteria. Scientists generally agree that the development of resistant bacteria that cause human infections that are not foodborne primarily results from the use of antimicrobial drugs in humans. (7). FDA, along with other agencies and groups, is actively working to find ways to encourage the prudent use of antimicrobials in human medicine to help address the significant contribution of human use to antimicrobial resistance. The framework set out in this document, however, focuses only on the issue of use of antimicrobial drugs in food-producing animals, which is of key importance in the development of resistance in foodborne pathogens and may be important in some non-foodborne infections.

FDA is charged with the regulatory responsibility of ensuring that the use of antimicrobial drugs in food-producing animals does not result in adverse health consequences to humans. FDA also recognizes that the use of antimicrobial drugs in food-producing animals is important in helping to promote animal health and helping to provide an abundant and affordable supply of meat, milk, and eggs. However, FDA's primary public health goal must be to protect the public health by preserving the long-term effectiveness of antimicrobial drugs for treating diseases of humans.

FDA is undertaking an extensive process to evaluate issues related to the use of antimicrobial drugs in both humans and animals and develop policies that protect the public health. With regard to antimicrobial uses in animals, as a first step, on November 18, 1998, FDA made available to the public a draft guidance document, "Evaluation of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals." (3). That draft guidance announced that FDA believes that evaluating the human health impact of the microbial effects associated with all uses of all antimicrobial new animal drugs in food-producing animals is necessary. The draft guidance provides that in assessing the human health impact of such uses, two separate but related factors should be evaluated: 1) the quantity of antimicrobial drug resistant enteric bacteria formed in the animal's intestinal tract

following exposure to the antimicrobial new animal drug (resistance); and 2) changes in the number of enteric bacteria in the animal's intestinal tract that cause human illness (pathogen load).[1]

This document is the second step in the agency's consideration of issues related to use of antimicrobial drugs in food-producing animals. The document sets out a conceptual risk-based framework for evaluating the microbial safety of antimicrobials drugs intended for use in food-producing animals. FDA is making this document available to the public as a vehicle to initiate discussions with the scientific community and other interested parties on the agency's thinking about appropriate underlying concepts to be used to develop policies protective of the public health. Thus, FDA is seeking comments on whether the concepts set out in this document, if implemented, will accomplish the agency's goal of protecting the public health by ensuring that significant human antimicrobial therapies are not lost due to use of antimicrobials in food-producing animals, while providing for the safe use of antimicrobials in food-producing animals. The agency is also seeking input on important areas of scientific complexity identified in this document.[2]

II. Introduction

Antimicrobial drugs are products that affect bacteria by inhibiting their growth or by killing them outright. Antimicrobial drugs are used to treat bacterial diseases in humans, and since their discovery have prevented countless deaths worldwide. In animals, these drugs are used to control, prevent, and treat infection, and to enhance animal growth and feed efficiency. Since the 1950's, when use in animal production became widespread, the use of antimicrobials has enhanced production efficiencies that have contributed to the availability of a reasonably-priced and plentiful food supply.

That bacteria could select for and develop resistance to antimicrobial drugs became apparent

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[1]Enteric bacteria in animals represent a special risk for causing human illness and for inducing resistance in bacteria in humans because they are the bacteria most likely to contaminate a food product and then be ingested.

[2]After evaluating input on the framework, the agency will take appropriate procedural steps to develop and implement any resulting policies.

soon after the first antimicrobial drug, penicillin, was widely used.[3] Antimicrobial use promotes antimicrobial resistance mainly by selecting for resistant bacteria(5). When an antimicrobial drug is used to treat an infection, the bacteria most sensitive to the drug die or are inhibited. Those bacteria that have, or acquire, the ability to resist the antimicrobial persist and replace the sensitive bacteria. If these bacteria are disease-causing (pathogenic) in humans, they may directly cause disease resistant to treatment (2, 5, 8).

In addition, bacteria can become resistant indirectly when resistance traits are passed on from other bacteria by mechanisms which allow the exchange of their genetic material. In this way, resistance can be transferred between nonpathogenic and pathogenic bacteria and from bacteria that usually inhabit the gastrointestinal tract of animals to those that infect humans (16).

When antimicrobial drugs are administered to food-producing animals, they can thus promote the emergence of resistance in bacteria that may not be pathogenic to the animal, but are pathogenic to humans (6, 7, 9, 20). For example, *Salmonella, Campylobacter,* and *E. coli* O157 are common and can exist in the intestinal flora of various food-producing animals without causing disease. However, all three bacteria can cause severe foodborne illness in humans. If, when using an antimicrobial in a food-producing animal, resistance occurs in such bacteria, and the resistant bacteria are then ingested by and cause an illness in a consumer who needs treatment, that treatment may be compromised if the pathogenic bacteria are resistant to the drug used for treatment (8). The link between antimicrobial resistance in such foodborne pathogenic bacteria and use of antimicrobials in food-producing animals has been demonstrated in a number of studies (10, 11, 12, 13). For foodborne pathogens, especially for those such as *Salmonella* that are rarely transferred from person to person in the United States and, therefore, for which human use of antimicrobials is unlikely to be a significant contributor to development of antimicrobial resistance, the most likely source of most antimicrobial resistance is use of antimicrobials in food-producing animals.

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[3] Soon after the feeding of antimicrobials to animals became popular, scientists expressed concern about the effect of this practice on bacterial resistance (1, 18). In 1969, a report (1) that some bacteria were capable of transferring their antimicrobial resistance to other bacteria via the transfer of extra-chromosomal material called R-plasmids increased the concern that the use of subtherapeutic levels of antimicrobials in animal feed (e.g., for growth promotion) would promote the spread of drug resistance from bacteria in animals to bacteria in humans and thereby compromise human drug therapy.

The use of antimicrobial drugs in food-producing animals can also promote antimicrobial resistance in bacteria that ordinarily are not human pathogens. In some circumstances (e.g., in hospitalized or immunocompromised individuals), some of these bacteria may directly cause infections in humans (4, 15). Alternatively, the bacterial resistance gene(s) can be transferred to pathogenic bacteria in the human gastrointestinal tract or in the environment and these newly-resistant bacteria may then cause human infections in the immunocompromised host. One example of resistance in ordinarily nonpathogenic bacteria is the case of vancomycin resistant enterococci (VRE). Patients with bloodstream infections due to VRE may have higher rates of persistent bloodstream infections resistant to treatment and a higher frequency of adverse outcomes, including death, when compared to patients whose enterococcal infections are sensitive to vancomycin (17). Epidemiological evidence has raised concern that the development of vancomycin resistant enterococci in humans in Europe may have been related in part to the induction of cross resistance to vancomycin due to food animal use of the related glycopeptide antibiotic, avoparcin (9, 14, 22, 25).

As stated in the November 18, 1998, draft guidance, in addition to the issue of antimicrobial resistance, the agency believes that it needs to evaluate the effect of the use of antimicrobials in food-producing animals on pathogen load. Generally, antimicrobial drug therapy in animals cures clinical infections by reducing the level of specific pathogens. However, this therapy may also disturb the normal intestinal microbial ecosystem in the animal, resulting in an increase in the bacteria that can cause human infections or prolonging the duration of the carrier state of such bacteria (pathogen load). Animals carrying increased amounts of pathogens at the time of slaughter present an increased risk for contamination of food and resulting human illness.

III. Current Regulatory Approach

Currently, the agency requires that applicants for over-the-counter uses of antimicrobials intended to be administered to food-producing animals in feed for more than 14 days (generally, for growth promotion rather than as therapies to prevent or treat disease) submit, as part of their safety data, results of preapproval studies intended to detect the development of antimicrobial resistance in enteric bacteria from treated animals. This approach for assuring the microbial safety for humans of food-producing animal uses of antimicrobial drugs was closely scrutinized as recently as 1995, when FDA approved two fluoroquinolone products for therapeutic use in poultry in the United States. Significant attention was focused on FDA's approval of these

products (even though they were intended for therapeutic use in animals), because fluoroquinolones, which have been used in human medicine since 1980, are very important for human therapy.[4] FDA approved these products for poultry use after having taken the issue of approvability of fluoroquinolones for use in food-producing animals to a panel of experts comprising FDA's Center for Veterinary Medicine Advisory Committee and the Center for Drug Evaluation and Research's Anti-Infective Drugs Advisory Committee. The panel supported several restrictions on the use of this class of drugs in food-producing animals to minimize the risks related to the development of resistant bacteria in animals. In accordance with the advisory committee recommendations, two fluoroquinolone poultry products were approved in 1995 under prescription status and for therapeutic purposes only. In addition, as a result of the advisory committee recommendations, FDA established in 1996 the National Antimicrobial Resistance Monitoring System (NARMS) to prospectively monitor changes in antimicrobial susceptibilities of selected enteric bacteria of animals that can cause disease in humans. Finally, FDA also issued an order to prohibit all extra-label use of fluoroquinolones in animals, which became effective in August 1997. These restrictions and conditions were put in place to assure that resistance to fluoroquinolones did not develop in bacteria that are transferred from poultry to humans, and that if a trend towards resistance were to develop, the agency would be able to detect such a trend at an early stage.

Recent reports from the scientific and public health communities, however, have rekindled concerns, both domestically and internationally, about the relationship between the approval of fluoroquinolones for therapeutic use in food-producing animals and the development of fluoroquinolone resistance in *Campylobacter*, a food borne human pathogen, and the increase in humans of fluoroquinolone resistant *Campylobacter* infections. The approval of these drugs in food-producing animals in the Netherlands (10), the United Kingdom (24) and Spain (19) temporally preceded increases in resistance in *Campylobacter* or *Salmonella* isolates. Moreover, despite the conditions and restrictions placed on the use of the two approved poultry products in the United States, there have been recent reports of an increase in fluoroquinolone resistance in *Campylobacter* spp. in poultry in the United States (23). In addition, an association has been

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[4]Fluoroquinolones are considered to be one of the most valuable antimicrobial drug classes available to treat human infections because of their spectrum of activity, pharmacodynamics, safety and ease of administration. This class of drugs is effective against a wide range of human diseases and is used in both treatment and prophylaxis of bacterial infections. Fluoroquinolones have been particularly important in the treatment of foodborne infections often resistant to other antimicrobials.

noted between fluoroquinolone resistance in *Salmonella Typhimurium* DT-104 and the approval and use of a fluoroquinolone for veterinary therapeutic use in the U.K. (21, 20, 24). Because of such information concerning the development of resistant bacteria following therapeutic use of drugs in food-producing animals, the agency believes that it needs to better address the development of bacterial resistance as part of the safety determination for antimicrobial new animal drugs used for therapeutic purposes.

FDA believes that the recent data concerning the transfer of fluoroquinolone resistant foodborne pathogens through the food supply and the *in vitro* and epidemiologic data supporting the possibility of resistance transfer in or mediated by other pathogens (e.g. vancomycin resistant enterococci) establish that, in order to protect the public health, previously accepted assumptions concerning the impact of therapeutic animal uses of antimicrobial drugs on human health must be reexamined. As previously stated, the agency took the first step by issuing the November 18, 1998 draft guidance. If the draft guidance is implemented, the agency recognizes that its current approach does not include all the elements necessary for evaluation of such complex issues. The agency has developed the concepts set out in the framework discussed below as a possible approach for evaluation of the complex public health issues related to the use of antimicrobial drugs in food-producing animals.

IV. A Framework for Evaluating and Assuring the Microbial Safety of Proposed Uses of Antimicrobials In Food-Producing Animals

This framework represents FDA's preliminary informed consideration of how to evaluate and minimize the potential human health effects of uses of antimicrobial drugs in food-producing animals. As set out in the November 18 draft guidance (Appendix A), FDA believes that microbial safety includes both pathogen load and resistance concerns. To address these concerns, this framework includes five components:

1) assessing the effect of proposed uses on human pathogen load;

2) assessing the safety of proposed animal uses of drugs according to their (or related drugs) importance in human medicine and the potential human exposure to resistant bacteria acquired from food-producing animals that are human pathogens or that can transfer their resistance to human pathogens;

3) assessing pre-approval data showing that the level of resistance transfer from proposed uses of drugs, if any, will be safe;

4) establishing "resistance" and "monitoring" thresholds to ensure that approved uses do not result in resistance development in animals or transfer to humans above the established levels; and

5) establishing post-approval studies and monitoring.

FDA believes that a system with these five components would allow the agency to best accomplish its goals of preserving antimicrobial drugs for use in both humans and animals.[5]

Pathogen Load

As discussed earlier in this document, the agency has explained the importance of evaluating pathogen load at the time of slaughter in its November 18, 1998 draft guidance. The manner in which the pathogen load evaluation would relate to other parts of the framework is discussed later in the document.

Resistance

With respect to resistance, the agency believes that the evaluation of the human health impact of the development of resistant bacteria from antimicrobial drugs used in food-producing animals depends primarily on the following two factors:

1) The importance of the drug or drug class in human medicine; and

2) The potential human exposure to resistant bacteria acquired from food-producing animals that are human pathogens or that can transfer their resistance to human pathogens.

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[5] FDA anticipates that the framework, if finalized and implemented, will be part of the approval of new animal drug applications, and as resources permit, will also be used for reviews of existing approved uses of antimicrobials for food-producing animals.

Based on an evaluation of these two factors, FDA believes that proposed uses of antimicrobials in food-producing animals can be placed into one of three main categories based on the importance of the drug or drug class in human medicine and then into one of three sub-categories determined by the potential human exposure, directly or indirectly, to resistant human pathogenic bacteria. FDA believes that these categories would aid the agency in evaluating the potential microbial human health impact of the use of the antimicrobial drug in food-producing animals, that is, the likely impact of the animal use of the antimicrobial drug on the long term availability of safe and effective antimicrobial drugs to treat human disease.[6]

A. Importance of Antimicrobial Drugs for Human Medicine

While recognizing that the importance of antimicrobial drugs for human medicine represents a continuum, in order to develop a rational and workable regulatory scheme, the agency is considering dividing antimicrobial drugs into three categories based on their unique or relative importance to human medicine. The agency realizes that the categorization will have to be flexible because new antimicrobials will be developed and the importance of existing therapies may change over time due to new medical needs and shifting patterns of antimicrobial resistance.[7] Despite these issues, FDA believes that it is crucial to determine the importance of an antimicrobial in human medicine before it can determine what effect the development of resistance to that drug from food-producing animal use will have on human health. The agency recognizes that obtaining public input will be important in developing the criteria for categorizing drugs as to their importance in human medicine.

Category I Drugs

Antimicrobial drugs would be considered to be in Category I if they or drugs in the same class

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[6]The agency discusses below, under C. Microbial Safety, an approach for dealing with antimicrobials whose categorization of importance in human medicine is based upon treatment of human non-enteric pathogens to which transfer of resistance from animal enteric bacteria would appear not to be biologically plausible.

[7]For example, if *Campylobacter* becomes increasingly resistant to quinolones, and erythromycin becomes the only effective drug to treat *Campylobacter*, the importance of erythromycin for human medicine may increase such that it would move to a higher category. Similarly, future development of human uses of an antimicrobial that currently is used only in animals would result in a reevaluation of that drug's importance in human medicine.

meet any of the following criteria:

1) Essential for treatment of a serious or life threatening disease in humans (conditions of high morbidity or mortality) for which there is no satisfactory alternative therapy.

2) Important for the treatment of foodborne diseases in humans where resistance to alternative antimicrobial drugs (e.g., Category II drugs) may limit therapeutic options (recognizing the special risks of both resistance development in, and transmission to, humans of foodborne pathogens).

3) The drug is a member of a class of drugs for which the mechanism of action and/or the nature of resistance-induction is unique, resistance to the antimicrobial drug is rare among human pathogen(s), and the drug holds potential for long term therapy in human medicine.

In addition, any antimicrobial that can induce or select for cross-resistance to a Category I drug would be considered a Category I drug. Similarly, if an antimicrobial is not used in human medicine, and if it could be demonstrated to the agency's satisfaction that it does not induce cross-resistance to any antimicrobials in the same class used in human medicine that are Category I, then it would not be considered a Category I drug.

The following are examples of types of drugs that would be included in Category I:

1) Quinolones for serious infections caused by multi-drug resistant *Salmonella* spp. (resistant to Category II drugs). Quinolones are often the primary treatment for salmonellosis, which in the U.S. generally is food borne. Quinolones are also the drugs of choice and alternative therapies for many life-threatening resistant gram negative infections.

2) Vancomycin for serious infections (e.g., sepsis, pneumonia, endocarditis) caused by methicillin resistant *S. aureus*, and ampicillin resistant enterococci. Vancomycin is the only well proven treatment drug available to treat serious infections with these organisms.

3) Dalfopristin/quinupristin (Synercid) for vancomycin-resistant enterococcal infections. Additionally, Synercid has an unique mechanism of action. It was presented to an FDA Advisory Committee in February 1988.

4) Third generation cephalosporins used to treat foodborne infections (e.g., ceftriaxone for Salmonellosis in children).

Category II Drugs

Antimicrobial drugs would be considered to be in Category II if they do not meet any of the criteria for Category I and they or drugs in the same class meet the following criterion:

They are drugs of choice or important in the treatment of a potentially serious disease, whether food borne or otherwise, but satisfactory alternative therapy exists.

In addition, any antimicrobial that can induce or select for cross-resistance to a Category II drug would be considered a Category II drug. Similarly, if an antimicrobial is not used in human medicine, and if it could be demonstrated to the agency's satisfaction that it does not induce cross-resistance to any antimicrobials in the same class used in human medicine that are Category II, then it would not be considered a Category II drug.

The following are examples of types of drugs that would be included in Category II:

1) Ampicillin for treatment of infections due to *Listeria monocytogenes*. The disease is life threatening; however, alternative therapies are available (e.g., trimethoprim-sulfamethoxasole).

2) Cephalosporins not in Category I which do not induce cross resistance to those in Category I; beta lactams and beta lactamase inhibitor combinations because they represent both drugs of choice and alternative therapies for many life threatening gram negative infections.

3) Erythromycin for treatment of *Campylobacter* infections.

4) Trimethoprim-sulfamethosaxole for treatment of a wide range of serious enteric infections including susceptible *Salmonella* and *Shigella* infections.

Category III Drugs

Antimicrobial drugs would be considered to be in Category III if they do not meet the criteria

for Category I or Category II and they or drugs in the same class meet any of the following criteria:

1) They have little or no use in human medicine.

2) They are not the drug of first choice or a significant alternative for treating human infections including food borne infections.

The following are examples of type of drugs that would be included in Category III:

1) Ionophores (e.g., monensin) which currently have no usage in human medicine

2) The polymixins (e.g., Polymixin B and colistin) since they have significant toxicities and have been supplanted by other drugs for virtually all human use.

B. Evaluating the Potential Exposure of Humans

FDA believes that the effects of antimicrobial resistance transfer from animals to humans are determined by a complex chain of events which includes: the ability of the drug to induce resistance in bacteria; the likelihood that use in food-producing animals will promote such resistance; the likelihood that any resistant bacteria in or on the animal will then be transferred to humans; and the likelihood that such transfer will result in loss of availability of human antimicrobial therapies.

FDA believes that information concerning these events can be used to categorize the likelihood of human exposure to resistant human pathogens from a proposed use of an antimicrobial in a food-producing animal into High (H), Medium, (M) or Low (L) categories. FDA believes that the following are the kinds of factors that should be considered when classifying the potential exposure of humans to resistant human pathogens ultimately resulting from use of an antimicrobial in food-producing animals:

> **Drug attributes** (e.g., mechanism and rate of resistance induction, induction of cross-resistance to other related or unrelated drugs, activity spectrum);

Product use (e.g., dose, duration and route of treatment, number of animals treated, duration of time between last treatment and potential human impact, animal species [including general patterns of human consumption]); and

Potential human contact (e.g., microorganisms of concern, animal management practices, manure management practices, environmental contamination, food processing).

FDA anticipates that, with different uses, the relative contributions of factors to the likelihood of human exposure may vary. For example, under certain circumstances, treatment of only a low percentage of a species population with an antimicrobial may result in exposure of large numbers of humans to resistant human pathogens. Although treatment of a low number of animals might seem, at first, to be a medium or even a low potential human exposure, the proposed species to be treated, the frequency and extent with which that species is colonized by human pathogens, and the frequency of resistance induction associated with the antimicrobial could actually result in the proposed use being considered to pose a high human exposure. Thus, a low risk with respect to one of the factors listed above or even a low incidence of resistance in an animal population cannot, by itself, assure a low human exposure. Similarly, circumstances could occur where an antimicrobial is used widely in animals but the potential human exposure is low because the antimicrobial cannot induce resistance transferable to potential human pathogens treated by that antimicrobial. In short, if such a sub-categorization system is implemented, FDA believes that it will be complex and that the sub-categories will need to be determined on a product- use by product- use basis.

The examples and discussion that follow illustrate how these factors might be assessed to determine whether potential human exposure is High, Medium, or Low. FDA requests comment on the factors that the agency has set out with respect to evaluating potential human exposure.

1. High Potential Human Exposure

EXAMPLE: An antimicrobial drug which induces significant cross-resistance to an antimicrobial used in human medicine is used for improved growth or feed efficiency in cattle, swine, and poultry.

FDA believes that animal drug uses like this one are most likely to result in high potential human

exposure (H). Some antimicrobial drugs used for improved growth and feed efficiency are administered in feed throughout the life of the animal on a flock or herd wide basis. For such drugs, a significant percent of the animal population could be expected to be medicated since use of the drug would have a positive effect on growth or feed efficiency in all animals as opposed to antimicrobials intended for therapeutic purposes, when use of the drug would only have a positive effect on exposed or infected animals. Moreover, some of these species have significant baseline incidence of colonization with human foodborne pathogens, making resistance induction likely. However, FDA recognizes that it may be possible that antimicrobial drugs used for improved growth and feed efficiency may not pose a high human exposure risk, if the treated species has a low incidence of colonization with human foodborne pathogens and routine processing conditions reduce this incidence further.

2. Medium Potential Human Exposure

EXAMPLE: An antimicrobial drug administered in drinking water *ad libitum* is used for 7 days to treat *E. coli* infections in a herd of swine and the drug has been shown, *in vitro*, to induce resistance to an antimicrobial used in humans to treat foodborne pathogens such as *Salmonella* species. This drug is administered to all of the animals in the herd in the production class that is susceptible to the disease when a disease outbreak occurs. However, outbreaks occur in only a small fraction of the herds brought to market.

FDA believes that, typically, drugs intended for use for the control, prevention, mitigation, or treatment of disease conditions where use duration is between 6 and 21 days would tend to result in a medium potential human (M) exposure. However, if the proposed species to be treated has a significant baseline incidence of colonization with human foodborne pathogens, making resistance induction in a human pathogen more likely, the proposed use could be considered a high potential human (H) exposure.

3. Low Potential Human Exposure

EXAMPLE: An antimicrobial drug used for individual treatment of short duration, where the disease requires treatment of only a small percentage of the animals in a flock or herd.

FDA believes that treatments of individual animals for short duration (e.g., less than 6 days)

would tend to result in a low potential human (L) exposure. While a given drug might have attributes leading to a high potential to induce resistance, both the proposed short-term usage and the limited potential for human contact generally suggest a low potential human (L) exposure.

C. Microbial Safety

As described above, proposed antimicrobial drug usages in food-producing animals would be placed into two categories according to two factors (importance to human medicine and potential human exposure to resistant bacteria acquired from food-producing animals that are human pathogens or that can transfer their resistance to human pathogens). The two categorizations would then be combined to determine what actions would be considered necessary to assure the safe use of the drug.

The agency recognizes that there will be some antimicrobials whose categorization of their importance in human medicine would be based upon treatment of non-enteric pathogens. The agency recognizes that in this setting, certain uses of antimicrobials in food-producing animals would not be expected to lead to development of resistance that could be transferred from the animal's intestinal bacteria to those human non-enteric pathogens. For example, a drug's human importance category might be based primarily upon its use to treat a respiratory pathogen of humans which is not present in the gastrointestinal tract of animals. Given our current understanding of mechanisms of resistance, FDA believes that, generally, it would not appear biologically plausible for resistance to be transferred from animal enteric pathogens to the human respiratory pathogen. The agency believes that if the case can be made that such circumstances exist for a particular animal use, it would be appropriate to handle such a drug according to the criteria below for a Category III drug for purposes of pre- and post- market requirements pertaining to antimicrobial resistance. The agency seeks comment on this point, including input on the information that would be needed to support such an action.

1. Category I Drugs: (I/H, I/M, I/L)

Resistance Threshold: For Category I drugs, FDA believes that human exposure to resistant bacteria from animals must be avoided or extensively minimized to assure that these drugs remain effective for treating human disease.

The agency believes that it may be possible in certain cases to define a level of resistant bacteria in animals that would result in no or insignificant transfer of resistance to human pathogens. The agency believes that this level of resistant bacteria in animals would need to be determined for each antimicrobial prior to approval, and may vary depending on the human or animal pathogen of concern. The agency welcomes information and data that would support the establishment of safe resistance thresholds in animals for Category I drugs. However, in the absence of adequate data and other information to identify and support the safety to humans of any level of resistance increase in animals, the agency believes that any such increase would not be shown to be safe. The agency recognizes that, as part of this process, sufficiently sensitive tests would need to be available that have been shown to be able to detect whether any such increase occurs.

The agency is considering whether, in certain cases, defining resistance thresholds based on data from human isolates showing decreasing *in vitro* susceptibility or increasing resistance may provide the most sensitive methodology to detect an emerging resistance problem. The agency requests comments on whether and when it would be appropriate to set resistance thresholds on human data, animal data, or both.

Monitoring Threshold: For all Category I drugs, if a resistance threshold can be established, the agency would establish monitoring thresholds for resistance development in animals to guide the post approval monitoring programs for these products. The monitoring thresholds would be established so that they would serve as an early warning system signaling when loss of susceptibility or resistance prevalence is approaching a level of concern.

FDA believes that the monitoring threshold would serve to signal that further epidemiological investigation by the drug sponsor would be warranted to assess why a loss of susceptibility or an increase in resistance was occurring at an unexpected rate and whether there were ways to mitigate the loss of susceptibility or increasing resistance trend. If mitigation was not successful, and resistance or loss of susceptibility continued to increase such that it reached the resistance threshold, withdrawal of the drug for the use(s) of concern from the marketplace would be warranted.

The agency notes that the ability to set scientifically- based resistance and monitoring thresholds depends on at least two factors: 1) the ability to demonstrate that a particular resistance threshold

is adequately protective of the public health, and 2) the ability to detect when the resistance and monitoring thresholds are reached. In the absence of either factor, the agency presumably would not be able to approve new uses of antimicrobials in food-producing animals when such approval is dependent upon setting and monitoring such thresholds.

Pre-approval studies: For all Category I drugs, pre-approval studies to address antimicrobial resistance would be necessary to characterize the nature of resistance development. FDA believes that studies in the target animal would need to assess the rate and extent of resistance development in enteric bacteria of concern. FDA also believes that it would be appropriate to evaluate mitigation measures, including withdrawal periods, to determine their effect on decreasing the rate and extent of resistance development. If a drug sponsor intends to market a product for multiple indications and demonstrates that the highest exposure scenario is safe, FDA may reconsider the need for additional studies to demonstrate the safety of the lower exposure uses.

For all Category I/H and some Category I/M drugs, pre-approval studies to address pathogen load would also be necessary. For other Category I/M and all Category I/L drugs, pathogen load studies would not be necessary. Changes in pathogen load are generally related to the pathogen, the antimicrobial involved, the duration of antimicrobial therapy and the time between cessation of therapy and slaughter of the animal. Antimicrobial products used for a short duration generally do not disturb the normal intestinal microflora and thus generally do not cause an overgrowth of bacterial pathogens. Therefore, pathogen load studies for Category I/L drugs would not be necessary.

Antimicrobial products in the medium exposure category, i.e., those used for longer duration, may disturb the intestinal microflora and cause an overgrowth of bacterial pathogens. If there is a long inherent withdrawal time between treatment and slaughter of the animal, the normal intestinal microflora generally recover, and pathogen load is reduced prior to slaughter. Therefore, whether pathogen load studies would be needed for a Category I/M drug would need to be determined on a case by case basis.

Antimicrobial products in the high exposure group, i.e., long duration of use, would probably disturb the intestinal microflora and favor the increase in bacterial pathogens. Since products in this category generally would be used in a large number of animals, the amount of time required

for the pathogen load to decrease would need to be determined in order to ensure that human exposure to foodborne pathogens is minimized. Therefore, for all Category I/H drugs, pathogen load studies would be necessary.

Post-approval Studies and Monitoring: FDA believes that on-farm studies to monitor antimicrobial resistance prevalence by the sponsor would be necessary to ensure that resistance thresholds are not exceeded after approval. FDA believes that on-farm collection of information on resistance prevalence and associated risk factors would be necessary so that the agency and drug sponsor could monitor for established monitoring and resistance thresholds, and so that intervention and mitigation strategies could be investigated and initiated in a timely fashion. Data generated through these studies, in addition to other scientific data, would provide a critical early warning system for detecting and evaluating the emergence of resistance to antimicrobials under field conditions. FDA believes that the collection of this on-farm information could be addressed from a drug-specific approach or from a broad national on-farm program.

In addition, FDA would monitor resistance through the National Antimicrobial Resistance Monitoring System (NARMS). As noted earlier, NARMS, established in January 1996 and funded by the FDA, is a joint surveillance effort by the CVM, the Centers for Disease Control and Prevention, and the U.S. Department of Agriculture to prospectively monitor changes in antimicrobial susceptibilities of zoonotic enteric pathogens from human and animal clinical specimens from healthy farm animals, and from carcasses of food-producing animals at slaughter.

Reporting: FDA believes that more detailed drug sales information (e.g., submitted by state, species, dosage form, season when applicable, calendar year, and containing an estimate of active units sold) would be necessary to be submitted as part of the drug experience report. This information would allow more direct correlation between loss of susceptibility or increasing resistance trends observed in NARMS or on-farm monitoring programs with the actual use of both individual drugs and drug classes. FDA notes that this information would also allow more effective implementation and assessment of any intervention or mitigation strategies to be initiated in response to findings of decreased susceptibility or increasing resistance trends over time.

FDA requests comment on whether these concepts are appropriate for assessing and assuring the

safety of the use of Category I drugs in food-producing animals.

2. Category II Drugs (II/H, II/M, II/L)

Resistance Threshold: For Category II drugs, the agency believes that a defined level of increased resistance in humans due to use of the drug in food-producing animals could safely occur because there will be other safe and effective drugs available to treat human infections. However, FDA believes that the resistance thresholds would vary depending on many factors, including how many satisfactory alternatives to the drug exist, how much resistance exists to each alternative, and the human pathogen of concern. Moreover, due to the wide range of drugs that fall into Category II and due to the wide range of infections that these drugs treat, FDA notes that, for some Category II drugs (e.g., drugs of choice for life-threatening infections and drugs used for serious infections where pre-existing levels of resistance are low), the allowable increase of resistance in humans would likely be extremely low.

Resistance thresholds in animals would need to be determined for all Category II drugs. While the agency believes that some level of resistance transfer from animals to humans due to use of a Category II drug in animals may be shown to be safe, it does not have data and information currently that would enable it to establish such levels.

As stated under Category I above, the agency is considering whether, in certain cases, defining resistance thresholds based on data from human isolates showing decreasing in vitro susceptibility or increasing resistance may provide the most sensitive methodology to detect an emerging resistance problem. The agency request comments on whether and when it would be appropriate for Category II drugs to set resistance thresholds on human data, animal data, or both.

Monitoring Threshold: Monitoring thresholds for resistance development in animals would need to be determined for all Category II/H and some Category II/M drugs to guide the post approval monitoring programs for these products. For other Category II/M and all Category II/L drugs, the agency believes that monitoring thresholds would not need to be determined because of lesser potential human exposure.

Monitoring thresholds would be established so that they would serve as an early warning system for when loss of susceptibility or resistance prevalence is approaching a level of concern. FDA

also believes that the monitoring threshold would serve to signal that further epidemiological investigation by the drug sponsor would be warranted to assess why a loss of susceptibility or an increase in resistance was occurring at an unexpected rate and whether there were ways to mitigate the loss of susceptibility or increasing resistance trend. If mitigation was not successful, and resistance or loss of susceptibility continued to increase such that it reached the resistance threshold, withdrawal of the drug for the use(s) of concern from the marketplace would be warranted.

Preapproval Studies: For all Category II drugs, the agency believes that pre-approval studies to address antimicrobial resistance would be necessary. For all Category II/H and some Category II/M drugs, pre-approval studies to address pathogen load would also be necessary. For other Category II/M and all Category II/L drugs, pathogen load studies would not be necessary, as explained for Category I drugs.

Post-approval Studies and Monitoring: FDA believes that, for those Category II drugs with resistance and monitoring thresholds (all Category II/H and some Category II/M drugs), on-farm studies to monitor antimicrobial resistance prevalence by the sponsor would be necessary to ensure that resistance thresholds were not exceeded after approval. For all Category II drugs, including those that would not require on-farm studies by sponsors, FDA would monitor resistance through NARMS. If NARMS data indicated that unexpected or unacceptable resistance was emerging, FDA could reevaluate on-going post approval studies, order other studies to be conducted, or institute other appropriate actions.

Reporting: For Category II drugs, FDA believes that more detailed drug sales information (e.g., submitted by state, species, dosage form, season when applicable, calendar year, and containing an estimate of active units sold) would be necessary to be submitted as part of the drug experience report. This information would allow more direct correlation between loss of susceptibility or increasing resistance trends observed in NARMS or on-farm monitoring programs with the actual use of both individual drugs and drug classes. FDA notes that this information would allow more effective implementation and assessment of any intervention or mitigation strategies to be initiated in response to findings of decreased susceptibility or changes in increases in resistance trends over time.

FDA requests comment on whether these concepts are appropriate for assessing and assuring the

safety of the use of Category II drugs in food-producing animals.

3. Category III Drugs (III/H, III/M, III/L)

Resistance Threshold: For all antimicrobial drugs in Category III (III/H, III/M, III/L), the agency believes that resistance transfer from animals to humans would have no effect on the availability of effective antimicrobial drugs to treat human diseases. Thus, FDA believes that establishing resistance thresholds in animals would not be necessary to assure human safety.

Monitoring Threshold: FDA believes that it would not be necessary to establish monitoring thresholds for Category III drugs.

Pre-Approval Studies: FDA anticipates that pre-approval studies to address antimicrobial resistance would not be necessary to assess safety for humans other than those that could be needed to demonstrate that the drugs do not induce cross resistance to any Category I or Category II antimicrobial drugs. However, with respect to pathogen load, FDA believes that pre-approval studies would be necessary for Category III/H drugs and some Category III/M drugs. For other Category III/M and Category III/L drugs, pathogen load studies would not be needed, as explained for Category I drugs.

Post-Approval Studies and Monitoring: FDA does not think that on-farm studies of antimicrobial resistance by the sponsor would be necessary for any Category III drugs. However, resistance would be monitored through NARMS. Specific on-farm investigations could become necessary if data from NARMS indicated an unexpected or unacceptable emerging trend of increasing resistance.

Reporting: As with the other classes of drugs, for Category III drugs, FDA believes that more detailed drug sales information (e.g., submitted by state, species, dosage form, season when applicable, calendar year, and containing an estimate of active units sold) would be necessary to be submitted as part of the drug experience report.

FDA requests comment on whether these concepts are appropriate for assessing and assuring the safety of the use of Category III drugs in food-producing animals.

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Draft
Guidance for Industry

Evaluation of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals

This draft guidance document is being distributed for comment purposes only.

This draft guidance document announces that FDA now believes it is necessary to evaluate the human health impact of the microbial effects associated with all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals when approving such drugs.

This guidance represents the agency's current thinking on this matter. It does not create or confer any rights for or on any person and does not operate to bind the FDA or public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations or both.

The comment period for this draft guidance will begin on the day the Notice of Availability of the guidance publishes in the Federal Register. The Federal Register notice will state the length of the comment period. Comments and suggestions regarding the document should be submitted to the Docket Number that will be provided in the Federal Register notice.

For questions regarding this draft document, contact Margaret Miller, Center for Veterinary Medicine (HFV-100), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
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Introduction

This draft guidance document announces that FDA now believes it is necessary to evaluate the human health impact of the microbial effects associated with all uses of all classes of antimicrobial new animal drugs[1] intended for use in food-producing animals.[2] To assess this impact, the following two separate, but related aspects, should be evaluated: 1) the quantity of antimicrobial drug resistant enteric bacteria formed in the animal's intestinal tract following exposure to the antimicrobial new animal drug (resistance); and 2) changes in the number of enteric bacteria in the animal's intestinal tract that cause human illness (pathogen load). In the past, the agency evaluated the human health impact of the microbial effects of only certain uses of antimicrobial new animal drugs in animal feeds (1). Based on the scientific evidence referenced below, the agency now believes that sponsors of all antimicrobial new animal drugs intended for use in food-producing animals should provide information relating to resistance and pathogen load to allow the agency to determine that such products are safe under the Federal Food, Drug, and Cosmetic Act.[3]

Resistance

The use of antimicrobial drugs in animals selects for resistant bacteria (2-7). These resistant bacteria, if transferred to people via food or the environment, can have an adverse effect on human health. This effect can be direct, if the resistant bacteria are themselves human pathogens, or indirect, if the resistant bacteria are not human pathogens but transfer their resistance genes to human pathogens. Antimicrobial resistance sometimes develops in enteric bacteria that contaminate food and cause human illness (2,5-7). When food borne infections are caused by a resistant pathogen, medical treatment may be compromised (6,7). For example, the use of fluoroquinolones to treat various respiratory diseases in poultry has led to the development of fluoroquinolone-resistant *Campylobacter* in the intestinal tract of birds treated in The Netherlands (3). In poultry, *Campylobacter* from the intestinal tract can contaminate the carcass at

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[1] The term "antimicrobial" is used in this document to refer to new animal drug products that have bacteriostatic or bactericidal activity.

[2] For guidance on how to assess the safety of an antimicrobial new animal drug residue in edible tissue, see Guidance 52 "Microbiological Testing of Antimicrobial Drug Residues in Food."

[3] Since the 1970's FDA has evaluated the effects of an antimicrobial drug product on enteric bacteria of food-producing animals in determining whether certain feed uses of an antimicrobial new animal drug are safe under section 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b).

slaughter and during processing. Improperly cooked poultry is a vehicle for *Campylobacter* infections in humans. Therefore, humans could become infected with fluoroquinolone-resistant *Campylobacter* by consuming poultry previously treated with a fluoroquinolone. Because a fluoroquinolone, Ciprofloxacin, may be used as an empiric treatment for diarrheal disease in humans (7), the emergence of fluoroquinolone-resistant *Campylobacter* in poultry could compromise the public health by reducing the effectiveness of a treatment.

Antimicrobial resistance sometimes develops in enteric bacteria that contaminate food but do not typically cause human illness (2,8). When humans ingest resistant enteric bacteria of food animal origin, the resistance genes can be transferred to bacteria indigenous to the intestinal tract of humans. Bacteria indigenous to the human intestinal tract frequently cause human disease. If these indigenous human bacteria become resistant to drugs used in human therapy, human health may be compromised due to limited therapeutic options (2,8).

Pathogen Load

Bacteria present in the intestinal tract of the animal at slaughter including *Salmonella*, *Campylobacter*, and *Escherichia coli* can contaminate food and cause human illness (9). In the U.S., an estimated 1% of the beef carcasses, 8.7% of the swine carcasses and 20% of the poultry carcasses are contaminated with *Salmonella*. Also, 4% of the beef carcasses, 31.5% of the swine carcasses and 88% of the broiler chickens are contaminated with *Campylobacter* (10). Generally, antimicrobial drug therapy cures clinical infections by reducing the level of specific pathogens. However, this therapy may also disturb the normal intestinal microbial ecosystem in the animal causing an increase in the bacteria that cause human infections or duration of the carrier state of such bacteria (pathogen load), thereby increasing the potential for contamination of food and consequent human illness (2,4).

Conclusion

The consumption of animal products contaminated with bacteria may compromise human health. Changes in animal enteric bacteria, including increased pathogen load and antimicrobial resistance, may occur as a result of any antimicrobial use (not just feed use) in food-producing animals. Therefore, FDA believes that drug sponsors of all antimicrobial new animal drug products intended for use in food-producing animals should evaluate the human health impact of microbial effects of such drugs. Pre-approval study(s) may be needed. FDA recognizes that there is no standardized protocol established for determining the human health impact of the microbial effect(s) of an antimicrobial product, and that one standard protocol is likely to be inappropriate for all intended uses. FDA believes, however, that the principles are available to assess resistance, pathogen load, and the interaction of these microbial effects. Before

conducting a study, drug sponsors are encouraged to consult with the agency on study design.

Citations

The following references have been placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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BACKGROUNDER

Antibiotic Use In Farm Animals

Antibiotics have been used on the farm along with other animal drugs for almost half a century to treat and control disease in animals, and to improve animal productivity. Antibiotics are one reason why the U.S. food supply is one of the highest quality, most nutritious, safest, and most affordable in the world. The use of antibiotics assures an abundant food supply, and makes it more healthful and safer for human consumption.

Animal drugs enter the market only after extensive data has been presented to the U.S. Food and Drug Administration's Center for Veterinary Medicine to demonstrate their safety and efficacy. The Center for Veterinary Medicine is responsible for protecting society from harmful animal drugs and maintaining public confidence in the drugs that are in use. They do this by ensuring that, prior to their approval, all new drugs pass a rigorous approval process.

Almost from the first, however, concerns have been expressed that the very clear benefits of using antibiotics to make animals healthier might also present a human health risk. Since the discovery that bacteria often possess or can develop resistance to antibiotics, there has been watchful concern: What if resistant strains are transferred to humans through improper handling or the consumption of undercooked food? Might it compromise the ability of even the newest antibiotics to treat disease? Can this lead to a public health problem?

The animal health product industry shares the concern of public health officials that the injudicious use of antibiotics on the farm can contribute to the increase of antibiotic resistant bacteria being transferred to people via undercooked food. The industry takes the issue seriously, even though the data are only suggestive, and not definitive. Veterinarians, food producers, animal health product manufacturers, federal government agencies, and numerous other stakeholder groups are participating in the development of new prudent-use guidelines and education programs that further assure antibiotics are used wisely, safely, and responsibly. Also, the animal health industry is supporting a risk/benefit assessment and enhanced surveillance and monitoring efforts to further ensure the careful and safe use of antibiotics.

In two recent reports, scientific experts gathered by the World Health Organization and the National Research Council examined the extent to which the use of antibiotics in farm animals causes antibiotics to be less effective in fighting foodborne infections. Among the international experts who have reviewed current research, a consensus has emerged: There is a link between the use of antibiotics in food animals and the development of resistant bacteria in those animals. There is also concern that resistant bacteria in food animals can transfer to humans and lead to human illness that may be difficult to treat; however, "the incidence of such disease is very low," according to a 1998 National Research Council report. There is a great need to better understand both the magnitude of the risk and the options available to minimize the risk while maintaining the benefit that these drugs confer on agriculture. Following a June 1998 World Health Organization meeting in Geneva, Switzerland, experts concluded that "further research and data gathering are essential" to fill the gaps in our understanding of antibiotic resistance.

- 1970, the New York Academy of Sciences, after extensive study, was unable to establish a conclusive link between the subtherapeutic use of antibiotics and any human health problems.

- In 1972, an FDA task force split 8-7 in concluding there might be human health problems connected with using antibiotics in feeds.

- In 1977, in response to a proposal from a food safety advisory committee, the FDA proposed to ban entirely the use of penicillin and restrict the use of tetracyclines in feed. Congress directed FDA not to act without adequate scientific evidence to support the actions, and after the National Academy of Science (NAS) completed a study on the issue, the FDA took no action.

- In 1980, the FDA contracted with the NAS to perform an exhaustive review of all the literature and data on the subject of subtherapeutic use. The NAS study found that "the postulated hazards to human health ...were neither proven nor disproven." The report found "...no data linking human illness with the subtherapeutic use of antimicrobials in any aspect of animal husbandry."

- In 1987, the National Institutes of Health conducted a worldwide survey of the underlying issue – the prevalence of resistance to antibiotics. Once again, the results as they related to the issue of farm use were inconclusive, and sometimes confusing. For example, evidence turned up that antibiotic resistance was more prevalent in less developed countries, where antibiotic use in agriculture was uncommon. In all, the report found no evidence that farm use added to any human health problems connected with resistance.

- In 1988, the Institute of Medicine (IOM), an arm of NAS, returned to the issue at the FDA's request. Rather than just survey the data again, the FDA requested a risk assessment of antibiotic use in feed. The IOM found existing information "primarily circumstantial, often ambiguous and sometimes conflicting," and said it could not establish the existence of a human health hazard.

- A review by the Office of Technology Assessment in 1995 reached the same conclusion: As with the other studies, OTA was not "able to pinpoint data that show the extent of the problem."

- In 1997, the World Health Organization (WHO) gathered representatives of academia, industry and government to review the use of antibiotics as feed additives and therapeutic products in animals. The participants agreed that antibiotics are vital for use in animals to eliminate or control bacteria; however, they also recommended that the use of antibiotics in animals, particularly for enhancing growth, be reduced.

- In 1998, the National Research Council (NRC) initiated a project to examine the use of antibiotics in food animals. The NRC concluded that "the use of drugs in the food-animal

compromised. The term is misleading since a decrease in susceptibility does not indicate a reduced response to antibiotic therapy.

In the U.S., results from a 1997 government testing program show "Salmonella with increased resistance to new classes of antibiotics are rare or non-existent," according to scientists at U.S. Department of Agriculture/Agriculture Research Service. To date, no resistance has emerged to ciprofloxacin, a fluoroquinolone used in human medicine. Less than 1% of all isolates were resistant to nalidixic acid, an earlier generation quinolone antibiotic, and a less potent relative of the fluoroquinolones. Increased levels of resistance to other commonly used and older antibiotics were noted.

Antibiotic resistance also received new attention in connection with another, lesser-known bacteria, campylobacter. These bacteria can cause intestinal distress that is self-limiting and usually not treated with antibiotics. New information from the Minnesota Department of Health reportedly has shown signs of resistance to fluoroquinolones in some Campylobacter species in poultry. In 1998, testing of campylobacter and generic E. coli will be added to the federal government's monitoring program.

At the June 1998 WHO meeting, experts reviewed data on the use of flouoroquinolones in animal agriculture and its implications for human health. The international participants concluded that "although no human cases have been documented, the experts expressed concern that there could be treatment failures in humans" if resistance were to increase and spread. Therefore, "further research and data gathering are essential" to fill the gaps in our understanding of antibiotic resistance.

The most recent review, conducted by the National Research Council in July 1998, concluded "the use of drugs in the food-animal production industry is not without some problems and concerns but does not appear to constitute an immediate public-health concern." The committee encouraged "constant vigilance in monitoring trends in antibiotic resistance in farm animals and humans."

CONCLUSION

The perceived risks of using antibiotics in farm animals are related to the remarkable ability of bacteria to develop resistance to antibiotics. Given that pathogenic bacteria are sometimes transferred from animal protein to its consumer, it is prudent to ask whether this creates any risk of compromising the ability of antibiotics to treat human illness. That question has been on the scientific and political agenda, and subject to repeated debate, since the 1950s. The "when in doubt, don't" logic of critics of present-day uses of antibiotics is tempting. Regulatory policy, however, should not be made on whim and hypothesis. Nevertheless, a hazard has been identified. But is there a public health risk associated with that hazard? Potentially; so why not be safe rather than sorry?

That logic excludes another primary consideration almost always absent from the debate. Why are antibiotics used on the farm? They are essential tools of a disease-management regimen in food animals. When we ask the question, "What if we don't restrict antibiotic use," we need also answer the question, "What if we do?" Would more restrictions prove to be prudent – or imprudent?

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Campylobacter and Resistance

Campylobacter are bacteria that can cause human illness and have recently captured media attention. Undercooked poultry is believed to be a source for intestinal campylobacter infections in people, but raw milk, untreated surface water and pets also play a role.

Because intestinal campylobacter infection is self-limiting, antibiotics are usually not used to treat it. If necessary, several antibiotics are effective for treating campylobacter infections in people. Fluoroquinolones, in particular, are not the preferred drug to treat human campylobacter infections because the bacteria quickly and naturally develop resistance to this drug. Nevertheless, sometimes physicians rely on fluoroquinolones, a broad-spectrum antibiotic, to treat intestinal infections in people before they have determined the cause of the infection.

New reports suggest signs of resistance to fluoroquinolones in campylobacter isolated from poultry, coupled with resistance to fluoroquinolones in people with campylobacter infections. Current published data leave it unclear whether the introduction and use of fluoroquinolones in veterinary medicine, in human medicine, or in both humans and animals are responsible for the high percentage of fluoroquinolone-resistant campylobacter in humans.

The exact and accurate extent to which fluoroquinolones in veterinary medicine contribute to the current resistance situation is far from clear and is complicated by a lack of standardized testing. In many instances, the current findings are problematic due to incomplete study parameters (e.g., number of investigated isolates, randomization scheme for collecting isolates, and duration of study) and thus do not allow for thorough statistical analysis. Some studies that have attempted to address the possible link between fluoroquinolone use in animals and resistance include the following:

The Netherlands --A study from The Netherlands showed fluoroquinolone resistance in campylobacter isolates of human and poultry origin collected in 1989 when compared to isolates from 1982. Details from the study reveal the following:

- ***Norfloxacin was the first fluoroquinolone approved for human use in 1985. Enrofloxacin was approved for use in animals in April 1987 and ciprofloxacin for use in humans in October 1988. Because fluoroquinolone resistance in human campylobacter was first observed in 1987 – before fluoroquinolones were marketed for use in animals -- it is possible that this resistance was caused by the use of norfloxacin in human medicine.***
- ***The Dutch study lacks treatment information for the human and animal subset of isolates and information on the travel history of study participants. (Travel histories are considered critical as other authors repeatedly cite the impact of travel, especially in less-developed countries, on the transfer of fluoroquinolone resistant campylobacter).***
- ***Results of the serotyping of strains are given only for the human isolates. In later studies, the Dutch scientists also serotyped the poultry strains. Only a few serotypes were observed to occur in both humans and poultry, which raises the question of how many of the human campylobacter isolates were of poultry origin.***

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Approving Antibiotics for Animals

It takes more than a decade and millions of dollars to complete the necessary federal testing and approval processes to gain permission to market a new veterinary antibiotic. But the result of all this time and effort is well worth the wait: using tools of modern food production are one reason why America enjoys the safest, most abundant food supply in the world.

Within the Food and Drug Administration, two centers are responsible for the safety and wholesomeness of the human food supply. The Center for Food Safety and Applied Nutrition (CFSAN) regulates foods intended for human consumption; the Center for Veterinary Medicine (CVM) ensures that animal drugs are safe and effective, and that food from treated animals is safe for human consumption.

Before being permitted for sale in the U.S., an animal drug must receive FDA approval. Those seeking FDA approval of the drug for manufacture and sale are known as drug sponsors, who must prove that their products are safe and effective for animals, safe for the environment, and safe for people who may eat meat, milk or eggs from the treated animal. A new animal drug developed by sponsors is not available for sale until the FDA has approved a new animal drug application.

If a product is intended for use in a food-producing animal, it must be tested for safety to human consumers, and the edible animal products must be free of unsafe drug residues. The drug sponsor must also develop analytical methods to detect and measure drug residues in edible animal products. It is the responsibility of the drug sponsor to conduct the necessary tests.

Once a sponsor feels adequate data have been gathered to support the safety and effectiveness requirements of a new animal drug, the data are organized and submitted to FDA as a New Animal Drug Application (NADA).

FDA's Office of New Animal Drug Evaluation (NADE) reviews the information submitted and determines whether or not an animal drug should be approved for marketing. Pre-marketing divisions within FDA are responsible for reviewing NADAs. The NADA review evaluates data regarding an animal drug's safety to the animal and to humans who might consume products from the treated animal; the review also evaluates effectiveness for the purposes claimed. The review process also assures that the product will consistently maintain its quality and effectiveness during manufacturing, and will not harm the environment.

If the pre-marketing divisions decide the information in the NADA shows the drug will be safe and effective for its intended use, a recommendation is provided to the Center Director that the NADA should be approved. If the Director agrees, the application is approved and a notice of approval is published in the Federal Register.

Following approval, the sponsor may propose changes. These changes may range from a simple

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Summary of Major Reviews and Studies on Antibiotic Resistance

- ***National Research Council (NRC)***, 1998, of the National Academy of Sciences (NAS), initiated a project to examine the use of antibiotics in food animals. NRC concluded that "the use of drugs in the food-animal production industry is not without some problems and concerns but does not appear to constitute an immediate public-health concern." The committee encouraged "constant vigilance in monitoring trends in antibiotic resistance in farm animals and humans."

- ***World Health Organization (WHO)***, June 1998, convened a three-day meeting to review data on the use of fluoroquinolones in animal agriculture and its implications for human health. The international experts concluded that "further research and data gathering are essential" to fill the gaps in our understanding of antibiotic resistance.

- ***World Health Organization (WHO)***, October 1997, gathered representatives of academia, industry and government to review the use of antibiotics as feed additives and therapeutic products in animals. The participants agreed that antibiotics are vital for use in animals to eliminate or control bacteria; however, they also recommended that the use of antibiotics in animals, particularly for enhancing growth, be reduced.

- ***Office of Technology Assessment***, 1995, was not "able to pinpoint data that show the extent of the problem."

- ***Food and Drug Administration Joint Advisory Committee***, 1994, at the request of the FDA to approve fluoroquinolones for use in animals, concluded that fluoroquinolones were needed to treat certain infections in animals. The agency's final approval to use fluoroquinolones was cautious in that fluoroquinolones could be used only for therapy and only under a veterinarian's prescription.

- ***Institute of Medicine (IOM)***, 1988, also of the NAS, returned to the issue at the FDA's request. Rather than just survey the data again, the FDA requested risk assessment of antibiotic use in feed. The IOM found existing information "primarily circumstantial, often ambiguous and sometimes conflicting," and said it could not establish the existence of a human health hazard.

- ***National Institute of Health***, 1987, conducted a worldwide survey of the prevalence of resistance to antibiotics. The results as they related to the issue of farm use were inconclusive, and sometimes confusing. For example, evidence turned up that antibiotic resistance was more prevalent in less developed countries, where their use in agriculture was uncommon. In all, the report found no evidence that farm use added to any human health problems connected with resistance.

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Monitoring Impact of Antibiotic Use

Many groups agree on the need for more information about pathogens that may be becoming less responsive to antibiotics. From farmers to medical doctors, makers of animal medicines to veterinarians and regulators, there is agreement that the lack of solid, scientific information on this important issue leaves everyone in the dark. The core messages of the President's Food Safety Initiative are surveillance, monitoring, and education to reduce the incidence of foodborne illness. These same three strategies can be applied to the issue of bacterial antibiotic resistance, an important subject that suffers from misinformation and seriously inadequate data. One of President Clinton's initiatives calls for expanding the ongoing national surveillance of antimicrobial resistance from food-producing animals to better determine the impact of antibiotic drug use on farms.

The National Antimicrobial Susceptibility Monitoring Program began in January 1996. It was supported by numerous groups, including antibiotic manufacturers, which recognized the importance of collecting data on the emergence of antibiotic resistant bacteria. Coordinated by the Food and Drug Administration, the Centers for Disease Control and Prevention and the U.S. Department of Agriculture, the program aims to provide objective information and analysis about trends in antibiotic resistance in animal bacteria. The data base is important for drawing conclusions and making comparisons between data sets. For example, monitoring systems that rely on samples taken from diagnostic centers that receive their samples from diseased animals are not reflective of the healthy animal population entering the food chain and should not enter the data base.

Results from the government's testing program in 1997 show that "Salmonella with increased resistance to new classes of antibiotics are rare or non-existent," according to scientists at USDA/Agriculture Research Service. To date, no resistance has emerged to ciprofloxacin, a fluoroquinolone used in human medicine. Less than 1% of all isolates were resistant to nalidixic acid, an earlier generation quinolone antibiotic, and a less potent relative of the fluoroquinolones. Increased levels of resistance to other commonly used and older antibiotics were noted.

At a recent World Health Organization (WHO) meeting, participants questioned current monitoring programs for tracking resistance in bacteria. WHO said the monitoring programs do not provide sufficient information to determine how frequently people contract resistant bacterial infections. WHO says more accurate data need to be collected . This recommendation is also supported by public health, veterinary, farm and industry groups – all of which seek to work with the United States and international regulatory bodies to develop comprehensive data.

The federal government is currently working to expand its monitoring program and better coordinate it with data on emergence of resistance of salmonella and campylobactor isolates in human medicine. In 1998, testing of campylobacter and generic E. coli will be added to the monitoring program. Because resistance tracking occurs throughout the world, however, there also need to be other improved methods for global standardization of testing, data collection and data summary. Only through the development of a widespread, objective tracking system can answers to the real questions about possible risks to human health from the use of antibiotics in

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Fast Facts

- Antibiotics were first approved in 1951 by the Food and Drug Administration as feed additives for farm animals.

- A 1998 National Research Council report concluded that "the use of drugs in the food-animal production industry is not without some problems and concerns, but does not appear to constitute an immediate public health concern."

- The average amount of antibiotic in medicated feed is less than two ounces per TON of feed.

- Animal drugs enter the market only after extensive data has been presented to the Food and Drug Administration's Center for Veterinary Medicine to demonstrate their safety and efficacy. After a drug has been approved, monitoring and surveillance continue. The National Antimicrobial Susceptibility Monitoring Program provides objective information and analysis about trends in antibiotic resistance in animal bacteria. Results from 1997 show that "Salmonella with increased resistance to new classes of antibiotics are rare to non-existent."

- The benefit to human health in the proper use of antibiotics in food animals is related to the ability for these drugs to combat infectious bacteria that can be transferred to human by either direct contact with the sick animal, consumption of food contaminated with pathogens from animals or proliferation into the environment.

- Most scientists agree that the increase of bacterial resistance to antibiotics in humans is largely the result of over-reliance on antibiotics in human medicine. Researchers at the Centers for Disease Control and Prevention have estimated that some 50 million of the 150 million outpatient prescriptions for antibiotics every year are unneeded.

- Not all antibiotics work on all pathogenic (disease-causing) microbes. Some are naturally resistant. For example, penicillin does not work at all on Salmonella and never has.

- In the U.S. and internationally, principles on the judicious use of antibiotics are being drafted. Once approved, these general guidelines will serve as a template for the development of more detailed guidelines appropriate for specific species and diseases.

- In one year, America produces food to feed the world through 7.5 billion chickens, 293 million turkeys, 109 million cattle, 92 million pigs, and nearly 1 million sheep. With the world's population expected to increase by more than 50 percent over the next 30 years, the need for products to keep animals healthy, as well as preserve natural resources, will increase.

- There is no documented case where antibiotic use in animals has caused treatment failure in people.

11/12/98

Sample Labeled Indications for Antibiotics

DOGS, CATS, HORSES

Respiratory

- Bronchitis
- Pneumonia
- Secondary Bacterial Infection
- Tracheobronchitis
- Rhinitis

Skin/soft tissue

- Abscesses
- Foot wounds
- Eye wounds
- Soft tissue infections
- Deep Pyoderma (canine)
- Superficial Pyoderma (canine)

Oral Infections

- Gingivitis
- Periodontitis
- Stomatitis

Bones

- Open Fractures
- Osteomyelitis

Urinary/Reproductive/Other

- Bladder Stones (Secondary to Infection)
- Kidney Stones
- Prostatitis
- Hepatitis
- Septicemia
- Endometritis
- Cystitis
- Pyelonephritis

Otitis

- Acute Suppurative Otitis

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Defining Prudent Use of Antibiotics

When is antibiotic use in veterinary medicine appropriate, and how do farmers and veterinarians ensure that these products are used carefully?

Public health officials, veterinarians, government regulators, farmers and makers of animal medicines agree that information about the proper use of antibiotics on the farm is important to ensure that these products are used prudently. Before a product is ever approved, companies conduct thorough tests to determine an appropriate dose of a product needed to maximize effectiveness, which thereby minimizes chances of resistance. Label instructions for using the product safely are also carefully determined and reviewed by the Food and Drug Administration.

And over the past decade, all of animal agriculture's major livestock producer groups in the U.S. have developed comprehensive quality assurance programs, to provide guidance on all aspects pertaining to the proper handling and raising of farm animals – including the safe use of antibiotics.

Companies that make medicines for animals, together with veterinarians and food producers, are working with international groups to develop guidelines for the prudent use of antibiotics in animals. In the United States and internationally, draft principles on the judicious use of antibiotics have been developed and are currently being reviewed by veterinary groups, government agencies, producers, farmers and industry. Once approved, these general principles will serve as a template for the development of more detailed guidelines appropriate for specific species and diseases. The animal health industry is also reviewing how food producers and veterinarians receive information on the use of antibiotics in animals to ensure that products are used safely and prudently.

By following recommendations outlined in the quality assurance programs, producers have become more adept at ensuring that the correct antibiotic has been selected, that it has been administered properly, and that withdrawal times have been adhered to. These quality assurance programs offer an excellent opportunity to learn more about the successes and pitfalls of prudent-use education programs on the farm.

Quality assurance programs include information on:

• Working with veterinarians and other health care experts to establish a herd-health management plan that focuses on preventing disease from occurring;

• Understanding veterinarian-client-patient relationships to ensure that the best care is given to each animal;

• Safe storage of animal health products;

• Understanding the difference between FDA-approved over-the-counter and prescription-only products;

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Questions and Answers

Why are antibiotics used in animals?

Antibiotics are used in animals to control and treat disease and improve animal productivity. Antibiotics not only keep dogs and cats healthy by treating wounds, infections, pneumonia and other illness, but keep food animals healthy by reducing the incidence of infectious bacterial disease. They are used on the farm to treat animal illnesses such as pneumonia, mastitis, bladder infections, infectious hepatitis, salmonellosis, cholera, and many other diseases. Using antibiotics in animals to treat disease is important to prevent animal suffering, as well as the spread of disease to humans through food, which helps assure that only healthy animals enter the food chain.

What is antibiotic resistance?

Antibiotic resistance is the ability of certain bacteria, which are normally destroyed by a particular antibiotic, to survive exposure to that antibiotic. Doctors prescribe antibiotics that are known to kill or inhibit the growth of the specific bacteria causing a particular disease. Many bacteria, however, are naturally insensitive to some antibiotics. "Resistance" means that the bacteria no longer responds to the antibiotic treatment. "Susceptibility" is a term for describing how sensitive bacteria are in responding to treatment with antibiotics. A lot of what people call "resistant" really means "less susceptible."

What causes antibiotic resistance?

Unquestionably, resistance to antibiotics is usually a consequence of their use. It is also universally agreed that over-use and misuse of antibiotics speeds up the development of resistance. The answer to why that happens may be several things: 1) in any group of bacteria, there are some that are able to survive despite the presence of antibiotics because they contain genetic material that allows them to grow and reproduce more of their kind; 2) some bacteria are naturally resistant to certain antibiotics; and 3) antibiotic resistance can be transferred from one type of bacteria to another through genetic material.

Does antibiotic use in animals cause antibiotics not to work in people?

There is no documented case where antibiotic use in animals has caused treatment failure in people. Scientists are now attempting to pinpoint sources for bacterial contamination, which involve many steps on the farm, in processing and packing, at the retailer, and through handling, preparation and cooking, as well as sources of resistance. U.S. Department of Agriculture statistics show that animal carcasses inspected just after harvest have very low levels of contamination, which suggests that good farm management programs, including prudent use of antibiotics, keep bacteria counts low.

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Salmonella and Resistance

Salmonella infections are the second most common cause of bacterial foodborne illness. Most of the 2,200 types of salmonella rarely cause disease in humans; two percent of them cause 80 percent of all cases of salmonella infections in the United States. Salmonella bacteria are found commonly throughout the biosphere – in soil, water, and in the gut of humans, birds, rodents, reptiles and deer as well as farm animals. Very high numbers – one million or more bacteria -- are usually necessary to cause illness in humans. Given the proper conditions and temperature, however, salmonella can double their population every 20 minutes, which is why food safety experts focus their consumer advice on proper refrigeration, handling and cooking of foodstuffs.

In general, most salmonella respond to antimicrobial drugs when indicated for their treatment. Current U.S. data show no salmonella that are clinically resistant to fluoroquinolones, but higher incidence of resistance to some of the older antibiotics has developed in some types of salmonella. Enteric (intestinal) salmonella infections are usually self-limiting, and antibiotic therapy is not indicated. Systemic (blood-borne) infections are uncommon and primarily affect vulnerable populations and in most cases may be treated with a number of antibiotics.

Since 1993, numerous articles have been published by various scientists from the Laboratory of Enteric Pathogens (LEP), Central Public Health Laboratory, London, England. The articles focused on a relatively new type of *Salmonella typhimurium* called DT104 and the emergence of isolates reportedly resistant to ciprofloxacin, the fluoroquinolone used in humans. Some in the UK have associated the use of fluoroquinolones in animals with increased "resistance" in people.

Review of the materials and associated data show the initial reports of increasing resistance to be incorrect, based on globally accepted microbiological standards for determining resistance. The data show small shifts in susceptibility with only a few human isolates truly resistant, and the relationship of these shifts to use of fluoroquinolones in farm animals has not been determined:

- ***The authors arbitrarily defined "resistant" isolates as those for which a minimum inhibitory concentration (MIC – the lowest amount of drug that halts bacterial growth) for ciprofloxacin was at least 0.25 micrograms per milliliter (mcg/ml). The standard MIC breakpoint for resistance in Europe and the United States, however, is 4.0 mcg/ml. Why the authors chose a lower MIC to define resistance is not explained. These researchers now use phrases such as "reduced susceptibility" instead of "resistance" for those isolates.***
- ***Using U.S. and European guidelines, over 99 percent of the DT104 isolates termed "resistant" by the British scientists are actually susceptible to ciprofloxacin.***
- ***The most prevalent salmonella in the UK is Salmonella enteritidis, accounting for approximately two-thirds of all types identified. It remains highly susceptible to many antibiotics and the fluoroquinolones.***

OTHER RELEVANT DATA:

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Subtherapeutic Uses of Antibiotics on the Farm

Along with their ability to treat clinically ill farm animals, antibiotics have proven their value in two other ways: they help prevent or control the outbreak of disease, and they help promote enhance performance. Because the dosages used are much smaller than those called for in therapeutic uses, these have historically been grouped as "subtherapeutic" uses. The Food and Drug Administration, however, regulates these uses separately.

- *Disease prevention and control*: Farm animals are typically raised in herds or flocks. Therefore, disease in one animal will threaten many others. Good animal husbandry practices require farmers and veterinarians to take quick action if they detect disease in one animal that will spread to others, or there are conditions that frequently lead to the development or rapid spread of disease. In such situations, veterinarians advise farmers to in effect "inoculate" the entire herd or flock to treat sick animals and limit the spread of disease. Antibiotics used to prevent or control disease are usually administered as additives to feed or water and used with the advice of veterinarians. This use of antibiotics is generally credited with eliminating or greatly reducing the incidence of such diseases as ileitis and coccidiosis, which once routinely wiped out whole herds or caused needless suffering. Accordingly, the American Veterinary Medical Association considers the use of antibiotics to prevent and control bacterial disease as a therapeutic use rather than subtherapeutic use. The prudent use of antibiotics for prevention and control of disease lessens the need for the use of high doses of therapeutic antibiotics.

- *Growth promotion*: Researchers have known since the mid 1940s that very small doses of antibiotics – two ounces or less per ton of feed –administered to farm animals at critical points in their growth can make them grow more rapidly and efficiently. Although the precise biological mechanism is not fully understood, these small doses appear to slow down the harmful activity of certain bacteria in the animals' intestinal tract. Growth occurs more efficiently, more rapidly, or both to reduce production times and cost while producing a healthier animal.. Growth promoters provide both an economic and an environmental benefit to farmers and to the general public. Bringing farm animals to market more quickly reduces the costs of raising them – and the retail costs of purchasing animal protein. In addition, s improving animal growth reduces the amount of land needed to raise them and the amount of manure they produce over their lifetime.

The benefits and risks of subtherapeutic use of antibiotics administered in animal feed have been debated for decades. For example, responding to concerns that subtherapeutic use of antibiotics may lead to antibiotic resistance, a British committee recommended in 1969 that restrictions be placed on the use of some antibiotics used in both animal feed (at subtherapeutic levels) and human medicine. Following the release of the British report (the Swann report), England banned the preventive use of tetracyclines and penicillin in food animals. Twenty years later, a 1989 Institute of Medicine report on penicillin and tetracycline use in animals concluded that the

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Antibiotic Use in Farm Animals

A Summary

Antibiotics have been used on the farm along with other animal drugs for almost half a century to treat and control disease in animals, and to improve animal productivity. Antibiotics are one reason why the U.S. food supply is one of the highest quality, most nutritious, safest, and most affordable in the world. The use of antibiotics assures an abundant food supply, and makes it healthier and safer for human consumption.

Antibiotics were first approved in 1951 by the Food and Drug Administration as feed additives for farm animals. It was found that minute amounts of antibiotics added to feed (an average amount of less than 2 ounces per ton of feed) proved helpful in controlling intestinal bacteria that interfered with the animal's ability to absorb nutrients. These microdoses of antibiotics were also found to control infections before they became noticeable. In short, animals became healthier, allowing them to grow faster and stronger.

Antibiotics are also used at therapeutic levels to treat and cure animals that are ill or at high risk of becoming ill. For example, when weather conditions change, large numbers of young cattle are at risk for respiratory illness. Antibiotic therapy helps prevent, as well as treat, the disease. Additionally, chicks are vulnerable to a disease called colibacillosis, and to potentially fatal intestinal infections.

Antibiotics work by killing bacteria or halting their growth. By no means do all antibiotics work on all disease causing microbes. Some bacteria are naturally resistant to certain antibiotics. For example, penicillin doesn't work at all on salmonella, and never has. Bacteria can also develop resistance by random changes in their genetic makeup. Unquestionably, resistance to antibiotics is a consequence of their use. It is universally agreed that over-use and misuse of antibiotics speed up the development of resistance. Whether this hazard is a public health risk remains in question, however.

The animal health product industry shares the concern of public health officials that the injudicious use of antibiotics on the farm can contribute to the increase of antibiotic-resistant bacteria being transferred to people through undercooked food. The industry takes the issue seriously. One way that veterinarians, food producers, antibiotic makers, federal government agencies, and other stakeholder groups are addressing the issue is by participating in the development of new prudent-use guidelines and education programs that further assure antibiotics are used wisely, safely, and responsibly. In addition, the animal health industry is supporting a risk/benefit assessment and enhanced surveillance

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Understanding Antibiotic Resistance

Antibiotics have been used to prevent and treat disease in livestock and poultry for more than 50 years. They are used to control types of animal diseases such as pneumonia, hepatitis, wounds, salmonellosis, cholera, diarrhea and dozens of other bacterial infections in animals that would otherwise be untreatable. The use of antibiotics to treat disease in animals, therefore, is vitally important: Without antibiotics there would be an increased chance that disease could be passed from animals to people through our food supply. There would also be increased animal suffering.

Almost from the beginning, however, concerns have been expressed that using antibiotics to make animals healthier might unwittingly create a human health risk: That antibiotic use in animals could lead to foodborne bacteria becoming increasingly resistant, and therefore harder to fight in humans. This concern centers on the hypothesis that extended antibiotic use in animals can cause certain bacteria to become resistant.

The theory goes like this: Antibiotic-resistant bacteria in animals can be transferred to people through improperly cooked food. The foodborne bacteria could then make a person sick, manifesting itself in a mild stomachache or diarrhea. Some people with compromised immune systems could become so sick that they require antibiotics to treat the foodborne infection. The fear is that the subsequent treatment could be unsuccessful because the bacteria already grew resistant to the antibiotic due to exposure on the farm.

It is certainly true that bacteria are prone to developing resistance, whether they are used in animals or humans or both. Some bacteria are naturally resistant to certain antibiotics, which is why physicians and veterinarians culture an infection to better determine which antibiotic to use. Bacteria can also develop resistance by random changes in their genetic makeup. By whatever method, bacteria have proven themselves very resourceful at developing resistance over time.

But the other issues, such as how frequently resistant microbes are actually transferred to people from animals, and how frequently this results in antibiotic treatment failure in humans -- are not as clearly understood. Indeed, these issues have been debated for more than 35 years.

While bacteria can be transferred from food to people, there are no conclusive data showing that animal-to-human transfer of resistant organisms causes illness in people to any significant degree. Scientists are trying to pinpoint sources of bacterial contamination, which involve a complex matrix on the farm, in processing and packing, at the retailer, and through handling, preparation and cooking, as well as sources of resistance. Department of Agriculture statistics show that animal carcasses inspected just after harvest have very low levels of contamination, which suggests that antibiotic use may be a factor in keeping bacteria counts low.

What is known, however, is that direct animal-to-human transfer of resistant bacteria through undercooked food is extremely infrequent. It is also infrequent that a person actually requires an antibiotic to treat foodborne illness. And there is no documented case where an antibiotic used to treat the person proved ineffective because of resistance development from use of the antibiotic in animals.

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World Health Organization

The World Health Organization, the United Nations specialized organization responsible for safeguarding public health, is examining the extent to which using antibiotics to treat farm animals causes them to be less effective in fighting foodborne infections in people.

At a meeting in Berlin in October 1997, WHO gathered 70 representatives from academia, industry and government to review the use of antibiotics as feed additives and therapeutic products in animals. After four days of discussion, WHO agreed that antibiotics are vital for use in animals in helping to eliminate or control certain bacteria. If not controlled, these bacteria could be passed on to people through undercooked food. But WHO also recommended that the use of antibiotics in animals, particularly for enhancing growth in animals, be reduced.

In June 1998, the WHO convened a three-day meeting to review data on the use of fluoroquinolones in animal agriculture and its implications for human health. The international participants concluded that "although no human cases have been documented," there is "concern that there could be treatment failures in humans" if resistance were to increase and spread. Therefore, "further research and data gathering are essential" to fill the gaps in our understanding of antibiotic resistance.

WHO noted that while fluoroquinolones are not used as growth promoters, they are currently used for the treatment of animal disease in many countries of the world and, in some regions, they are also used for disease prevention in animals. Experts said that because the data available on antibiotic usage is scarce, it is difficult to make correlations between quinolone use and the emergence of resistant bacteria. The pharmaceutical industry is working to increase the availability and compilation of data. WHO and the meeting participants welcomed the initiative by COMISA, the world federation of the animal health industry, which provided sales and volume data for the major fluoroquinolones in more than 30 countries.

WHO questioned the applicability of current monitoring programs for tracking bacteria. WHO said the monitoring programs do not provide sufficient information to determine how frequently people contract resistant bacterial infections. WHO said more accurate data needs to be collected. This recommendation is supported by public health, veterinary, farm and industry groups -- all of which seek to work with U.S. and international regulatory bodies to develop a comprehensive data-collection system that will provide for objective, scientific analysis.

Veterinarians, farmers and makers of animal medicines are working with public health officials and government regulators to develop more comprehensive monitoring and surveillance programs to help them draw better conclusions. They also are looking at ways that food producers and veterinarians are educated about how to use antibiotics safely in animals. A thorough assessment of the impacts on human health of using antibiotics in animals (both benefits and potential risks) is being conducted by scientists at Georgetown University. In the meantime, the U.S. and international groups are developing guidelines to ensure that antibiotics are used prudently on the farm.

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