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With regard to antimicrobial uses in animals, as a first step, on November 18, 1998, FDA made available to the public a draft guidance document, "Evaluation of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals."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 That draft guidance announced that FDA believes that evaluating the human health impact of the microbial effects associated with all uses of all antimicrobial new animal drugs in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 The draft guidance provides that in assessing the human health impact of such uses, two separate but related factors should be evaluated: 1) the quantity of antimicrobial drug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 soon

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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.

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 noted between fluoroquinolone resistance in *Salmonella Typhimurium* DT-104 and the approval

[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.

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.

Based on an evaluation of these two factors, FDA believes that proposed uses of antimicrobials in

[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.

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 meet any of the following criteria:

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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.

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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