An Approach for Establishing Thresholds in Association with the Use of Antimicrobial Drugs in Food-Producing Animals

A Discussion Document

FDA Center for Veterinary Medicine

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EXECUTIVE SUMMARY

The Center for Veterinary Medicine (CVM) 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. The selection of antimicrobial resistant bacterial populations is a consequence of exposure to antimicrobial agents and can occur from human, animal, and agricultural uses. Food animals are administered antimicrobial drugs for therapeutic, preventive, and production purposes. The use of antimicrobial drugs in food-producing animals is necessary to maintain their health and welfare. However, food-producing animals can become reservoirs of bacteria capable of being transferred in or on food. Food carrying resistant bacterial pathogens can cause illness in people consuming the food or contribute to the human reservoir of resistant bacteria. The use of antimicrobial drugs in food-producing animals may cause bacterial pathogens to become resistant to drugs that may also be used to treat human illness, potentially making human illness more difficult to treat.

CVM recognizes that minimizing the emergence of antimicrobial-resistant bacteria in animals and their subsequent spread to humans through the food supply is a complex problem requiring a coordinated multifaceted approach. Accordingly, CVM has expended considerable effort to identify and support those programs and activities that will reduce the risk to the public. Where mitigation strategies were identified that lie outside the regulatory authority of CVM, support has been enlisted from other Federal agencies, international agencies dedicated to public and animal health, and stakeholder organizations. CVM believes that, taken together, these steps will have a substantial impact in controlling the emergence and spread of resistant bacteria from animals to humans through the food supply.

Despite these preemptive measures, there may occur situations in which the approved use of an antimicrobial drug in animals gives rise to resistant bacteria that in turn pose a risk to human health. In these situations, and as an added measure of human health protection, CVM is considering the establishment of regulatory thresholds intended to arrest the further emergence of resistant foodborne pathogens. As required by the Federal Food, Drug, and Cosmetic Act (FFDCA), CVM has applied the reasonable certainty of no harm standard to human safety considerations associated with the use of antimicrobial drugs in food-producing animals. CVM believes that implementation of an approach as outlined in this paper could be consistent with this standard, but is exploring the impact of the approach under the current standard, whether modifications to the approach or an alternative approach could also meet the standard, or whether legislative change to the standard should be considered.

This discussion document describes a possible approach to the establishment and use of thresholds. The approach describes two types of thresholds, a human health threshold and a resistance threshold. The human health threshold is the unacceptable prevalence of infections in humans that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable to the use of an antimicrobial drug in animals. Based on the current safety standard, the "unacceptable prevalence" is considered that level at which there is no longer reasonable certainty that there is no harm to human health. The human health thresholds discussed in this document focus on enteric or systemic illness in humans. The resistance threshold is the maximum allowable prevalence of resistant bacteria isolated from animal-derived food, that is, the level of such resistant bacteria at which there would still be reasonable certainty that the human health threshold would not be crossed. The resistance threshold is derived through an epidemiology-based model that relates the prevalence of resistant bacteria in food to an impact on either enteric illness (EI) or systemic illness (SI) in humans. The scope and complexity of the implementation and use of thresholds is described with the intent to stimulate constructive discussion.

If this threshold approach is implemented, when post-approval surveillance indicates that bacterial susceptibility to specific antimicrobial drugs is decreasing, the prevalence of resistant bacteria is increasing, or that the prevalence of resistant bacteria has exceeded the resistance threshold level, a range of actions may be taken. For example, if changes are observed, but the resistance threshold has not been reached, voluntary mitigation strategies by groups such as the pharmaceutical industry, food animal production groups, and the veterinary community (e.g., education, labeling changes, use restrictions, etc.) may be implemented to curtail further loss of susceptibility. However, if surveillance data indicate that the resistance threshold has been exceeded, CVM would initiate procedures to withdraw from the label any animal species that has reached or exceeded its threshold.

Introduction

The Center for Veterinary Medicine (CVM) 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. Food animals are administered antimicrobial drugs for therapeutic, preventive, and production purposes. CVM recognizes that the use of antimicrobial drugs in food-producing animals is important in helping to promote animal health, welfare, and productivity. However, food-producing animals can serve as reservoirs of pathogenic bacteria that may be transferred to humans by consumption of contaminated food products. With the use of antimicrobial drugs in food-producing animals, these bacterial pathogens may become resistant to drugs that may also be used to treat human illness, potentially making human illnesses more difficult to treat. In addition, bacteria pathogenic to humans can acquire resistance traits from non-pathogenic bacteria originating in food animals by mechanisms that allow the exchange of their genetic material in the human gastrointestinal tract.

Antimicrobial resistance is a complex human health issue with multiple contributing factors. The selection of antimicrobial resistant bacterial populations is a consequence of exposure to antimicrobial drugs and can occur from human, animal, and agricultural uses. Recently implemented food safety monitoring programs are still developing in response to the evolving needs of agencies such as the FDA. As a consequence, the human health impact due to the use of antimicrobial drugs in food-producing animals can be difficult to assess. It requires the ability to attribute human health impacts (in whole or in part) to the domestic (i.e., U.S.) use of antimicrobial drugs in animals. This association is complicated by other sources of resistance, including the use of the same or similar antimicrobial drugs in human medicine, people contracting resistant bacterial infections while traveling outside of the United States, illness in people consuming imported foods or foods from imported animals, and epidemics of multi-drug resistant pathogens. Antimicrobial drug resistance has been linked to resistance against other antimicrobial drug classes, disinfectants, and other compounds such as heavy metals. The use of unrelated drugs can result in the co-selection of multiple drug resistance. Additionally, cross-drug resistance occurs from the use of a particular antimicrobial drug when the mechanism of resistance affects more than one class of antimicrobial drug.

CVM recognizes that minimizing the emergence of antimicrobial-resistant bacteria in animals and their subsequent spread to humans through the food supply is a complex problem requiring a coordinated multifaceted approach. Accordingly, CVM has expended considerable effort to identify and support those programs and activities that will reduce the risk to the public. Where mitigation strategies were identified that lie outside the regulatory authority of CVM, additional support has been enlisted from other Federal agencies, international agencies dedicated to public and animal health, and stakeholder organizations. The CVM strategy for addressing antimicrobial resistance is one component of more broad reaching strategies being developed at the Agency level by the Food and Drug Administration and at the interagency level in the form of the Public Health Action Plan to Combat Antimicrobial Resistance.[1] Copies of this plan are available at http://www.cdc.gov/drugresistance/actionplan/.

It is important to understand the legal framework within which CVM must operate. For a new animal drug to be approved for use in food animals, the sponsor must demonstrate to CVM that there is reasonable certainty that no harm to human health will result from the proposed use of the drug. Therefore, since the standard to be met is reasonable certainty rather than absolute certainty, the sponsor does not have to demonstrate zero risk. CVM believes that the presence of antimicrobial resistant human pathogens in or on animal-derived food as a consequence of antimicrobial drug use in animals is a safety concern that is subject to the reasonable certainty of no harm standard.

This discussion document does not attempt to define the minimum criteria for what would constitute “harm”. However, as described in this document, the relevant human health concern is considered to be an unacceptable increase in the prevalence of human infections that are treated with the antimicrobial drug of concern and that are caused by bacteria resistant to that drug due to the use of an antimicrobial drug in animals. Based on the current safety standard, an "unacceptable increase" is considered that level at which there is no longer reasonable certainty that there is no harm to human health.

CVM recognizes that meeting this standard is difficult, and may have significant impact on the availability of drugs to treat animal illness. CVM wishes to foster debate on the best policies and science to meet the reasonable certainty of no harm standard, as well as on the implications to animal health of meeting the statutorily-required standard. CVM recognizes that there are times in which the allowed use of an approved antimicrobial drug leads to the development of resistance in pathogens in food from animals treated with the drug. In those circumstances, the agency needs a way by which it and the sponsor know when a level of resistance has been reached that violates the standard of reasonable certainty of no harm, that is, when the use of the animal drug is no longer shown to be safe. That is the goal of the approach for establishing thresholds described in this document.

The CVM strategy that includes a number of contributing components, described in brief below, is a regulatory approach that CVM believes is protective of the human health. The threshold concept provides an added measure of human health protection by establishing a clearly defined point at which CVM would initiate procedures for withdrawing the approval of a particular antimicrobial drug use in animals. This action would be triggered in the event that the approved use of the drug in animals is found to give rise to resistant bacteria that in turn present an unacceptable risk to human health. As noted above, CVM is required by the FFDCA to apply the reasonable certainty of no harm standard to human safety considerations associated with the use of antimicrobial drugs in food-producing animals. CVM believes that implementation of an approach as outlined in this paper could be consistent with this standard, but is exploring the impact of the approach under the current standard, whether modifications to the approach or an alternative approach could also meet the standard, or whether legislative change to the standard should be considered. The threshold concept is but one component of a multifaceted approach for assuring that the use of antimicrobial drugs in food-producing animals is safe with regard to human health. The various components of this multifaceted strategy are briefly described below.

National Antimicrobial Resistance Monitoring System (NARMS)

CVM believes that the safety assessment of antimicrobial drugs must include monitoring for the development of resistance. Monitoring is done through the National Antimicrobial Resistance Monitoring System (NARMS).

NARMS was initiated in l996 as a collaboration between the FDA, the Centers for Disease Control, National Center for Infectious Diseases (CDC), the United States Department of Agriculture Agricultural Research Service, and Food Safety and Inspection Service. NARMS monitors development of antimicrobial resistance of zoonotic enteric pathogens from human and animal clinical specimens, from healthy farm animals, and from carcasses of food-producing animals at slaughter.[2] NARMS current partners include 17 state and local public health laboratories and 8 veterinary sentinel sites. Its purpose is to prospectively monitor the antimicrobial resistance of human, animal, and animal product isolates of selected enteric bacteria.

Concerns associated with the approval of antibiotics important to human medical therapy for use in food animals was the driving force for the development of NARMS. Prior to NARMS there was no antibiotic resistance surveillance system that was national in scope, continuous, and that monitored within the same system resistance development among isolates from both humans in the community setting and from animals.

The goals of NARMS are to provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in enteric organisms from the human and animal populations; provide timely information to veterinarians and physicians; prolong the life span of approved drugs by promoting the prudent use of antimicrobial agents; identify areas for more detailed investigation; and guide research on antimicrobial resistance. The majority of the animal isolates are obtained from raw product collected from federally inspected slaughter and processing plants. The human isolates are collected from state health department partners. The seventeen NARMS sites (CA, CT, CO, FL, GA, KS, Los Angeles County, MA, MD, MN, NJ, New York City, NY, OR, TN, WA, and WV) represent 100 million people, or approximately one-third of the U.S. population.

Since 1996, NARMS has conducted surveillance for antimicrobial resistance among isolates of non-typhoidal *Salmonella* and *Escherichia coli* O157:H7. In 1997, surveillance was expanded to include human isolates of *Campylobacter*. Currently, NARMS surveillance also includes *enterococci* isolated from human stool samples and animal products, *Campylobacter* isolated from animal products, as well as human isolates of *Shigella* and *Salmonella* Typhi.

Isolates are tested for susceptibility using minimum inhibitory concentrations, or MICs. *Salmonella, Shigella* and *E. coli* are tested with Sensititre (Trek Diagnostics, Westlake OH) a semi-automated system, for susceptibility to 17 antimicrobial agents. *Campylobacter* isolates are tested using the E-test system (AB Biodisk, Solna Sweden) for susceptibility to 8 antimicrobial agents. *Enterococci* isolates are identified to species level and tested by Sensititre and microbroth dilution for susceptibility to 27 antimicrobial agents. Results are entered into a SAS database for analysis.

Since 1996, NARMS has provided data that have been used to initiate field investigations of outbreaks of illness marked by a pathogen which displayed an unusual antimicrobial resistance pattern, provided the data for a risk assessment of the human health impact of fluoroquinolone use in poultry, stimulated research in molecular characteristics of resistance emergence and transfer, improved our knowledge of risk factors associated with the development of an antimicrobial-resistant infection, and triggered broader research projects of prudent antimicrobial use in animals and the role of the environment in the emergence and spread of antimicrobial resistance.

The NARMS program continues to expand by adding new test sites, bacterial pathogens and antimicrobial drugs for evaluation. Plans are currently underway to include the resistance profiles of enteric pathogens isolated from a wide variety of retail foods. This dynamic, national monitoring system will be an integral part of the threshold monitoring process.

Pathogen Reduction Programs

Recently implemented food safety programs such as USDA's pathogen reduction program are critical contributors to CVM's overall strategy for managing human health risks associated with resistant foodborne pathogens. The USDA program that is based on the principles of Hazard Analysis and Critical Control Point (HACCP) appears to be having a positive effect on reducing the overall incidence of foodborne pathogens. However, surveillance data indicate that pathogens continue to be present on animal-derived food products.[3] CVM recognizes the importance of this program in that reducing the incidence of pathogens on food will reduce human exposure and, in turn, reduce the incidence of foodborne related human illness. Any gains achieved in reducing the overall incidence of foodborne disease will serve to reduce the potential human health impact experienced as a consequence of foodborne disease that is associated with a resistant pathogen. CVM also recognizes that the USDA pathogen reduction program is essential in that it serves as a critical source of isolates for the NARMS program. This collaboration between agencies is critical to the success of the program.

Framework Document

CVM announced with the publication of Guidance for Industry #78, "Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals", a regulatory change with regard to the safety evaluation of antimicrobial drugs.[4] Although CVM had previously considered such effects for certain uses of antimicrobial drugs, the guidance stated CVM's intention to consider the potential 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. The microbial effects of concern include the impact of antimicrobial drug use in animals on the rate and extent of resistance emergence and on the quantity of bacteria in animals that are pathogenic to humans.

Given that the regulatory approach then in use did not adequately address these concerns, CVM outlined in a 1998 discussion document titled, "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.e., the Framework Document) several coordinated strategies to the management of risk associated with antimicrobial use in food-producing animals.[5] The Framework Document discussed both pre-approval and post-approval approaches. The strategies include: 1) revision of the pre-approval safety assessment for antimicrobial resistance for new animal drug applications to assess all uses for microbial safety; 2) categorization of antimicrobial drugs based upon the importance of the drug for human medicine; 3) post-approval monitoring for the development of antimicrobial drug resistance; 4) the collection of food animal drug use data; and 5) the establishment of regulatory thresholds.

Drug categorization: A key component of the Framework Document is the concept of categorizing antimicrobial drugs according to their importance for treating disease in humans. The Framework Document discusses three categories with the most important drugs being considered Category I. CVM believes that this categorization process is an integral part of a safety assessment in that it provides some initial indication of the potential human health impact resulting from treatment failure due to resistance. The categorization process also focuses the greatest level of attention on those antimicrobial drugs of greatest importance to human medical therapy. As outlined in the Framework Document, pre-approval and post-approval requirements would likely be greatest for those antimicrobial drugs that are highly important for treating disease in humans. As a consequence, greater emphasis would likely be placed on developing drugs for animal use that are of lower importance for human therapy.

Pre-approval Assessment of antimicrobial drugs: As noted previously, CVM announced with Guidance for Industry #78 its intentions to include in its safety evaluation of all antimicrobial drugs intended for use in food-producing animals a consideration of the potential human health impact associated with the emergence of antimicrobial resistance. CVM has held discussions on the subject of using pre-approval study information to characterize safety in terms of the rate and extent of resistance development in food-producing animals (i.e., public workshop held February 22-24, 2000). The transcripts of the February 22-24, 2000, public meeting and copies of the speaker presentations are available at http://www.fda.gov/cvm/antimicrobial/oldmeet.htm. Such studies would be used to provide CVM with information to assess whether antimicrobial susceptibility changes of human health concern would occur, or would occur at an unacceptable rate. The Center intends to issue further guidance on this aspect of a microbiological safety assessment in the future. The current document discusses the type of data that may be provided as part of an assessment of the microbiological safety of an unapproved antimicrobial new animal drug.

During the evaluation of antimicrobial drugs prior to their approval, CVM considers all available relevant information pertaining to food safety including the potential of the drug to promote the emergence or spread of resistant food borne pathogens. Traditionally, where there was concern, CVM relied on restrictive measures as a means of managing risk. Such restrictions included limiting the sale and distribution to prescription only channels, specifying a dose or dose range sufficiently large to minimize the emergence of resistant pathogens, specifying the conditions under which the drug could be used, and prohibiting extra label use when deemed appropriate

CVM can only approve drugs for food animals which, in its best judgment, meet the standard of reasonable certainty of no harm. With respect to antimicrobial resistance, CVM would not approve a drug intended for use in food animals if it had reason to believe that the approval would lead in a relatively short period of time, to development of antimicrobial resistance at a level that would pose a risk to human health such that it would preclude a finding of reasonable certainty of no harm. Unfortunately, unlike chemical residues which are evaluated for their toxic properties using a battery of well-established animal and laboratory methods, CVM is aware of no such predictive models to estimate with precision the rate and extent of bacterial resistance that may emerge from the use of antimicrobial drugs in food animals.

Thresholds: FDA can only approve drugs for use in food animals for which the sponsor has established, among other things, that there is a reasonable certainty that no harm attributable to use of the drug will come to people from eating food from the animal species administered the drug according to approved label conditions. The agency recognizes that there can be no absolute certainty that use of the drugs will not ultimately lead to adverse human health effects. Therefore, as an added safeguard to protect human health in the event that resistance among bacterial isolates in humans results from the use of a drug in food animals, CVM is considering the establishment of resistance thresholds. Through the establishment of resistance thresholds, CVM hopes to define predetermined endpoints which, if reached, would indicate that the antimicrobial drug is no longer shown to be safe for use in a given food animal species. The threshold, therefore, would serve as the regulatory trigger for initiating immediate withdrawal from the label of the animal species that has reached its resistance threshold, recognizing that actually accomplishing such withdrawal takes time because of due process requirements, and that antimicrobial resistance may continue to increase during that time.

Although the overall concept is the same, it should be noted that the threshold approach outlined in this document differs from that initially proposed in the Framework Document. A description of how the approach discussed in this document differs from that in the Framework Document is provided later in the *Threshold Concept Background*.

Drug use information: CVM currently requires the submission of certain drug sales information as part of the annual drug experience report for approved drug products. The Framework Document identified the need for the pharmaceutical industry to submit more detailed antimicrobial drug sales information as part of its annual report. CVM believes that this additional information is needed to monitor drug use patterns in relation to the antimicrobial susceptibility data being monitored through the NARMS program. The ability to correlate use patterns with changing antimicrobial susceptibility would allow implementation and assessment of intervention or mitigation strategies. CVM is moving forward on developing new requirements for antimicrobial drug use information through a notice and comment rule-making process.

Judicious Use of Antimicrobial Drugs

Antimicrobial resistance is of concern when the same or related antimicrobial drugs are used in both animal agriculture and in human medicine. Guidelines for the judicious use of antimicrobial drugs have recently been prepared by the American Veterinary Medical Association (AVMA) and provide guidance to veterinary practitioners on ways to maximize the efficacy of antimicrobial drugs, while minimizing the development of antimicrobial resistance.[6] Initiatives are also underway in many producer associations to develop similar guidelines and / or recommendations. CVM has participated with a number of these organizations in developing these principles and has provided support for developing educational materials. CVM has also provided support for several ongoing studies to evaluate the impact of judicious use practices on the emergence of antimicrobial resistance.

Research Initiatives

CVM recognizes that additional research is needed on the relationship between antimicrobial use in food animals and the associated human health impact related to antimicrobial resistant bacteria. The importance of the issue and the need for interagency collaboration is highlighted in the Draft Public Health Action Plan to Combat Antimicrobial Resistance.[1] Copies of the draft are available at http://www.cdc.gov/drugresistance/actionplan/.

CVM has initiated its own intramural and collaborative research efforts to investigate factors associated with development, dissemination, and persistence of bacterial antibiotic resistance in both the animal production environment and food supply. Microbiologists from CVM's Office of Research are currently conducting or are participating in projects specifically targeted to gathering data on such issues as: (1) the current background level of bacterial antibiotic resistance in retail animal-derived food products; (2) the development and persistence of bacterial antibiotic resistance from aquaculture and animal production environments; (3) characterization of mechanisms of resistance dissemination and transfer among pathogenic and commensal bacteria associated with food-producing animals and aquaculture environments; (4) determining the roles that animal feeds and feed commodities play in the dissemination of antibiotic resistance and pathogen carriage; and (5) co-selection of antibiotic resistance phenotypes associated with the use of sanitizers and other antimicrobial drugs in animals. In addition, CVM is a contributing laboratory to CDC's PulseNet molecular fingerprinting network involved in the molecular epidemiology of foodborne outbreaks. The CVM laboratory provides the only source of data on animal-associated bacterial pathogens into the PulseNet system.

In addition to the intramural research, CVM also collaborates in extramural research grants and funds extramural research activities through cooperative agreements. This extramural research is designed to complement and augment the intramural research program. Six of the projects are designed to elucidate the prevalence and risk factors associated with the dissemination of antibiotic resistant *Salmonella, E. coli* O157:H7, and enterococci within the animal production environment. Another study seeks to adapt and validate for use in the animal production environment microbial detection methods developed for human food.

Alternatives to antimicrobial drugs

CVM is interested in evaluating products that may be considered alternatives to antimicrobial drugs. As an example, CVM approved the first competitive exclusion product in 1999 "for the early establishment of intestinal microflora in chickens to reduce *Salmonella* colonization." CVM would support the development of other products that would have a positive human health impact. In addition, CVM acknowledges the importance of continued advances in vaccine development and other management practices that may reduce reliance on the use of antimicrobial drugs in food-producing animals.

Threshold Concept Background

This discussion document describes a possible approach for establishing thresholds as a means of assuring the safe use of antimicrobial drugs in food-producing animals complimentary to the approval process itself. Such thresholds are intended to provide an added measure of protection should the emergence of antimicrobial resistance as a consequence of antimicrobial drug use in food-producing animals pose an unacceptable risk to human health, that is, that there was no longer reasonable certainty that no human health harm would result from an approved use of the drug. This document provides a detailed technical description of the proposed methodology for the purpose of stimulating discussion at an upcoming scientific public meeting.

The current document provides a more detailed discussion of the threshold concept introduced in the Framework Document and describes a possible approach for establishing thresholds. It should be noted that the approach outlined in this document differs from that initially proposed in the Framework Document. The Framework Document discussed two thresholds, a resistance threshold and a monitoring threshold, that would be established prior to the approval of a new animal antimicrobial drug for use in food-producing animals. The resistance threshold was described as the upper limit for the level of resistant bacteria that can be transferred from animals to consumers and still be considered safe for the consumer. Exceeding the resistance threshold was considered to represent an unacceptable human health risk. The monitoring threshold was described as a level of resistance for the food animal species that would allow industry to monitor the development of resistance to the antimicrobial and identify when intervention and mitigation programs should be implemented. Exceeding the monitoring threshold was considered to represent an early warning signal of resistance development.

The approach outlined in this document also proposes the establishment of two types of thresholds, a human health threshold and a resistance threshold. The human health threshold described in this document represents the unacceptable prevalence of infections in humans that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals. Based on the current safety standard, the "unacceptable prevalence" is considered that level at which there is no longer reasonable certainty that there is no harm to human health.

The resistance threshold described in this document is the maximum allowable level of resistance prevalence in bacteria isolated from the food animal that does not pose an unacceptable risk to human health. This resistance threshold is derived through an epidemiology-based model that describes the relationship between the human health threshold and resistance levels in animals. Therefore, exceeding a resistance threshold would be considered a level of resistance at which there is no longer reasonable certainty that there is no harm to human health.

The approach described in this paper does not include the establishment of "monitoring thresholds" as an early warning system. However, given that the proposed resistance threshold is based on a measurable endpoint in animals, CVM believes that resistance thresholds will allow industry to monitor the development of resistance to the antimicrobial and identify when intervention and mitigation programs should be implemented. A monitoring system that utilizes thresholds, such as that described in this document, would provide a timely warning of the emergence of bacterial resistance among pathogens of human health concern. At this time, the approach included in this discussion paper addresses the establishment of thresholds for foodborne pathogens only. However, CVM intends to apply a similar risk-based approach to the establishment of resistance thresholds for non-pathogenic bacteria such as enterococci. CVM is in the process of developing a risk assessment on enterococci that should be helpful in further refining an approach to establishing thresholds for non-pathogenic bacteria.

CVM believes that resistance thresholds would need to be determined for certain antimicrobial products prior to approval. CVM envisions that resistance thresholds will 1) encourage industry participation in monitoring for the development of resistance to an antimicrobial product; 2) identify when intervention and mitigation programs might be implemented by the pharmaceutical industry, producer organizations, or CVM; 3) identify when procedures should be initiated by CVM to withdraw from the label the approval of a particular food animal species; and 4) assist in prolonging the effectiveness of antimicrobial drugs in humans and food animals. If it is determined that resistance thresholds do not have to be established for certain drugs or drug classes, it may also help the pharmaceutical industry to target classes of drugs for development for animal use.

AN APPROACH FOR ESTABLISHING THRESHOLDS

Overview

The approach outlined in this document discusses the establishment of two types of thresholds for certain antimicrobial products intended for use in food-producing animals. The first type of threshold, referred to as the human health threshold (T(x)), is the unacceptable prevalence of infections in humans that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals. These human health thresholds specifically focus on the incremental effects on existing enteric illness or systemic illness in humans as a consequence of the causative bacteria being resistant to the antimicrobial drug the affected persons are expected to receive. Based on the current safety standard, the "unacceptable prevalence" is considered that level at which there is no longer reasonable certainty that there is no harm to human health.

The second type of threshold discussed is referred to as the resistance threshold. The resistance threshold (t(x)) is the maximum allowable prevalence of resistant bacteria isolated from animal-derived food that does not pose an unacceptable risk to human health. The resistance threshold is derived through an epidemiology-based model that relates the prevalence of resistant bacteria in food to an impact (as described above) on either enteric illness (EI) or systemic illness (SI) in humans. Isolates are defined as resistant if their minimum inhibitory concentration (MIC) reaches or exceeds the resistance breakpoint established for the related drug used in human medicine. Therefore, a resistance threshold (i.e., prevalence of resistance in animals) would be established for a particular antimicrobial drug in animals that correlates to the human health threshold. If changes in susceptibility or changes in the prevalence of resistance among animal isolates are observed via monitoring, but a resistance threshold is not exceeded, voluntary mitigating actions may be implemented. However, if a resistance threshold were exceeded, this would be considered a level of resistance at which there is no longer reasonable certainty that there is no harm to human health. .

This document outlines an approach for assessing when the establishment of thresholds would be needed for the approval of an antimicrobial drug in animals. This determination could be made through the completion of a Microbiological Safety Assessment by the animal drug sponsor. Through this process, it may be determined that the proposed antimicrobial product does not pose a human health concern and, therefore, the establishment of resistance thresholds would not be needed prior to approval in a food-producing animal.

If the Microbiological Safety Assessment concludes that establishment of resistance thresholds are necessary for approval, this document describes an epidemiology-based model that could be used to derive such thresholds. The epidemiology-based model is intended to relate the prevalence of resistant bacteria in food to an impact on either enteric illness (EI) or systemic illness (SI) in humans. This document outlines two alternative methods by which the resistance thresholds could be derived. The determination of which method to use would be driven by data availability. Although the two methods presented are very similar in concept, one method uses an estimate of the maximum human health impact in its calculations (i.e., makes assumption that all human cases attributed to animal species were due to bacteria resistant to drug of concern), whereas, the second method uses current human health impact information (i.e., uses current data to determine proportion of animal-related human cases that were due to bacteria resistant to drug of concern). The advantage of using the maximum possible human health impact is that it permits calculation of the resistance threshold (t(x)) without the data required for the second method.

Following the establishment of the resistance thresholds and subsequent approval of the antimicrobial new animal drug, the pertinent bacterial pathogen(s) (for which thresholds were established) would be monitored post-approval with regard to susceptibility to the related drug of importance to human medicine. As discussed above, observed shifts in susceptibility (that do not exceed the resistance threshold) may trigger certain voluntary actions. However, if the prevalence of resistance exceeds the threshold, CVM would initiate procedures to withdraw from the label any animal species that has reached or exceeded its threshold. An overall outline of this approach for establishing thresholds is presented in Figure 1.

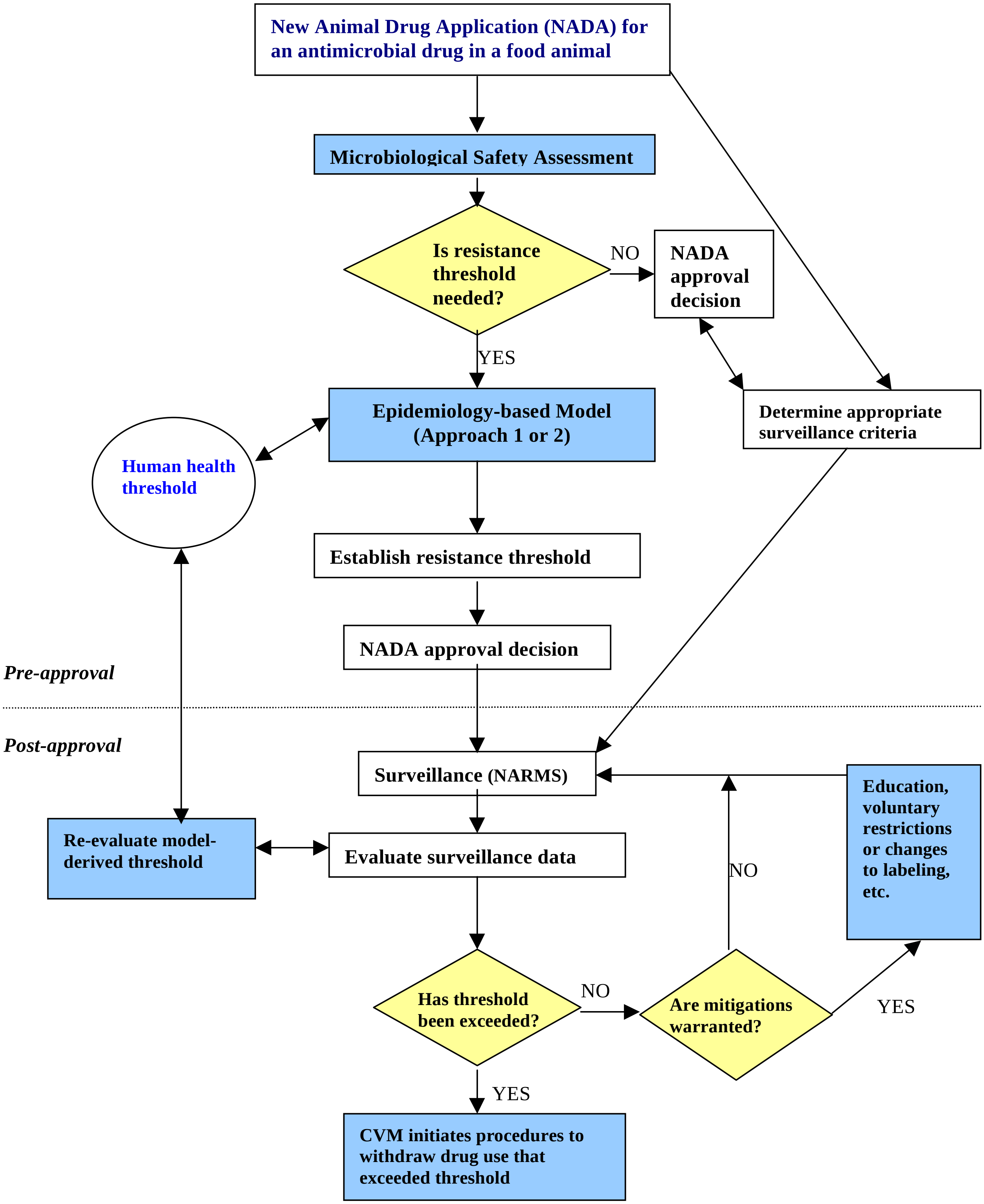

Figure 1: Overview of the approach for establishing thresholds described in this document.

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Pre-approval Microbiological Safety Assessment

As outlined in Guidance for Industry #78, "Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals", CVM intends to consider the potential 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.[4] CVM believes that consideration of this concern may be facilitated by a Microbiological Safety Assessment. Such an assessment would collect and organize all pertinent data and information relevant to the potential human health impact associated with the proposed antimicrobial drug use in animals. Data, provided by the drug sponsor, that may be necessary for this evaluation may include, but are not limited to:

- Information regarding the proposed conditions of use of the product that would help characterize the potential for human exposure to zoonotic enteric bacteria associated with the treated animal.
- Baseline prevalence of appropriate zoonotic enteric bacteria in the target animal species and in humans.
- Baseline susceptibility of appropriate zoonotic enteric bacteria to the relevant drug used in human medicine obtained from animal isolates and human community isolates.
- Information to determine the level of concern for the proposed animal drug use as it may impact human medicine.
- Antimicrobial susceptibility breakpoints for the relevant human drugs in the appropriate zoonotic enteric bacteria.
- Pharmacokinetic and pharmacodynamic information for the new animal drug in the food animal.
- Information regarding the mechanism of action and mechanism(s) of resistance.

The information included in the Microbiological Safety Assessment may be used to evaluate the potential human health impact associated with the proposed use and may be used to make a determination as to whether it was necessary to establish a resistance threshold at the time of approval. CVM anticipates that a resistance threshold would likely be required for those drugs considered highly important to human medicine. For those antibiotics that are not used in human medicine and are not cross-resistant to drugs used in human medicine, a resistance threshold may not be required. The extent to which thresholds should be established for the other drugs, and how those thresholds might be set, are issues that require further discussion.

CVM also believes that the Microbiological Safety Assessment would help to guide the establishment of the appropriate post-approval surveillance criteria for the proposed product. As noted above, CVM envisions that all proposed uses of antimicrobial drugs in food animals would be required to undergo this assessment. The information provided in this assessment may be used to make a determination as to whether post-approval surveillance is warranted, and if so, what should be the appropriate criteria for such surveillance.

Pre-approval Microbiological Safety Assessment
Data input

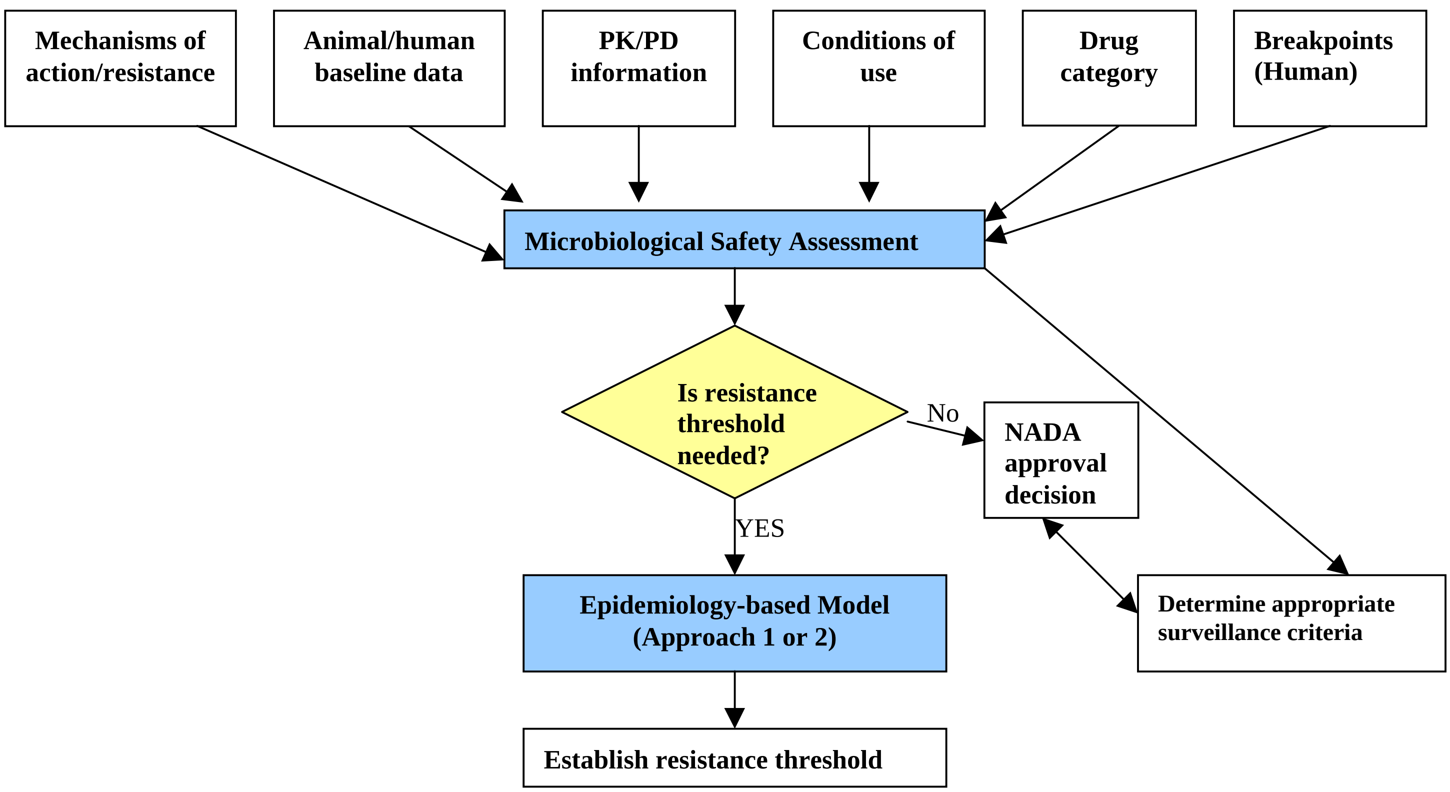


Figure 2: Summary of type of data that may be included in a pre-approval Microbiological Safety Assessment.

Establishment of Thresholds

Overview

This section contains two subsections. The first subsection, Setting Human Health Thresholds, discusses the concept of setting human health thresholds. The human health threshold is defined as the unacceptable prevalence of infections in humans that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals.

The second subsection, Establishing Resistance Thresholds, describes an epidemiology-based model that is used to derive resistance thresholds. The resistance threshold (referred to later in this document as t(x)) is the maximum allowable prevalence of resistant bacteria isolated from animal-derived food that does not pose an unacceptable risk to human health. The resistance threshold is derived through an epidemiology-based model that relates the prevalence of resistant bacteria in food to a particular impact on either enteric illness (EI) or systemic illness (SI) in humans.

The association between the human health and the resistance thresholds is based on certain epidemiological information. In particular, an association is made between the annual prevalence of people affected by enteric or systemic foodborne-related illness and the quantity of food animal commodity containing resistant bacteria to which the population was exposed during the year. The calculations provided in the following sections demonstrate that the threshold of material can be reduced to an expression of the threshold prevalence of resistance among bacterial isolates from the food animal commodity. The resistance threshold is that prevalence associated with a particular preset human health threshold. A resistance threshold can be set to correspond to a measurable human health impact, or through safety factors (see Appendix 2) to avoid any human health impact.

Setting Human Health Thresholds

There is a wide spectrum of potential human health impacts associated with treatment failure due to antimicrobial resistance. This document focuses on foodborne-related enteric or systemic illness in humans and the potential associated incremental health impact experienced as a consequence of antimicrobial resistance in the causative bacteria. CVM considers that enteric and systemic illnesses are possible endpoints that could be used in the regulation of the antimicrobial animal drug.

1. **Threshold for impact on enteric illness:** In a given year, a certain proportion of the U.S. population will experience enteric foodborne illness and will be treated with an antimicrobial drug. Some cases may be due to bacteria that are resistant to the drug administered. Therefore, the threshold for impact on enteric illness is defined as the unacceptable prevalence of cases of enteric illness in the U.S. population that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to

the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals. Such cases would be expected to experience decreased or loss of effectiveness of their antimicrobial drug treatment.

2. **Threshold for impact on systemic illness:** In a given year, a certain proportion of the U.S. population will experience systemic foodborne illness and will be treated with an antimicrobial drug. Some cases may be due to bacteria that are resistant to the drug administered. Therefore, the threshold prevalence of cases of systemic illness impacted is defined as the unacceptable prevalence of cases of systemic illness in the U.S. population that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals. Such cases would be expected to experience decreased or loss of effectiveness of their antimicrobial drug treatment.

The symbol T(EI) is used for the human health threshold for enteric illness. The symbol T(SI) is used for the human health threshold for systemic illness. A symbol of T(x) may be used to represent the human health threshold without specifying a particular end point such as enteric illness or systemic disease.

The threshold concept is one component of a multi-pronged strategy for managing antimicrobial resistance. As stated previously, CVM has issued guidance (Guidance for Industry #78) indicating that the safety evaluation of new animal drug applications for antimicrobial drugs for food-producing animals should include a consideration of the potential impact of antimicrobial resistance on human health. CVM believes that thresholds provide a mechanism for taking appropriate action should post-approval monitoring efforts indicate that an antimicrobial drug used in animals is no longer shown to be safe. Implementation of a threshold concept, such as that discussed in this document, necessitates that a certain human health impact(s) be identified as a means of monitoring the continued safety of antimicrobial drug use in animals. Based on current safety standards, such thresholds would be used to indicate the point at which there is no longer reasonable certainty that there is no harm to human health.

CVM anticipates considerable discussion regarding the selection of the appropriate human health impacts to measure and establishment of the unacceptable threshold prevalence for that human health impact. This document is intended to stimulate discussion on these points. CVM seeks further input on setting human health thresholds.

Establishing Resistance Thresholds

Description of Model for Deriving Resistance Thresholds

Model proportionality factor (k-res): The basis for determining a resistance threshold is a modeled rate or proportionality factor, k-res. This factor links a measurable level of human health impact (H(x)) to a quantity of animal-derived food (Q) containing bacteria resistant to an antimicrobial drug of interest. The factor, k-res, is a key component of the approach outlined for deriving resistance thresholds in that it is intended to approximate the relationship between exposure to resistant bacteria (i.e., Q) and some effect on human health (i.e., H). The ability to calculate k-res is dependent on the availability of data to derive values for the parameters H and Q. If such data are not available (e.g., in the case of a new drug where no resistance has been documented), some other means of approximating k-res would be necessary. This may include applying the k-res factor derived for other drug/bacteria situations.

As noted above, the factor, k-res, attempts to link drug-related human health effects to exposure to animal-derived food containing bacteria resistant to that drug. Therefore, when considering data to derive the factor, k-res, it should be noted that, based on current safety standards, existing information relevant to drug-related human health effects must not preclude a determination of reasonable certainty of no harm.

Uncertainty distributions: Point estimates of quantities will be discussed in the process of explaining the data and the steps used to calculate resistance thresholds. It should be noted, however, that the resistance thresholds derived from the model would have attendant uncertainty distributions. The 95th percentile of the distribution of the estimated number of people affected and the associated prevalence of resistance in animals could be used rather than the mean of the distribution. Alternatively, the 5th percentile of the distribution of the resistance threshold derived from the model could be used.

Measurable human health impact (H(x)): As discussed in this document, a measurable human health impact (H(x)) represents the current measured prevalence of infections in humans that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals. Additionally, exposure is associated with meat containing drug-resistant bacteria whose resistance was attributed to the use of antimicrobial drugs in the food animal species that produced the meat.

One way to estimate the prevalence of people impacted (H(x)) is as follows:

H(x) = estimate of the total prevalence of cases of disease
×
proportion of total cases due to exposure to animal-derived food commodity
×
proportion of cases with resistance attributed to animal-derived food commodity
×
proportion of cases expected to be treated with the antimicrobial drug of interest

The estimated total prevalence of cases is determined annually for foodborne pathogens in FoodNet, Foodborne Diseases Active Surveillance Network, by the CDC. Periodically, the CDC also conducts case-control studies and surveys that provide more detailed information. Such information includes the prevalence of people impacted by infections caused by drug-resistant bacteria for which they sought care and received an antibiotic to which the bacteria were resistant. In the case of antimicrobial drugs for which transmission of resistance from animals to humans would primarily be expected to occur through foodborne pathogens, resistance thresholds would be established only for a few bacteria, perhaps *Campylobacter* and *Salmonella*. CDC provides annual estimates of the total number of campylobacteriosis and salmonellosis cases in the U.S. With attention focused mainly on a few foodborne pathogens, it will be possible to develop estimates of the proportion of all cases and from this, the number of cases, attributable to various animal species. Scientific panels may also be useful in determining estimates for parameters that are difficult to measure directly. These estimates would need to be reviewed periodically. Once in place, the estimates would be used during the pre-approval process in the establishment of resistance thresholds using one of the approaches described in the following sections.

It should be noted that the current measurable level of human health impact (H(x)) must be lower than the human health threshold (T(x)) which, as stated earlier in this document, is the level at which there is no longer a reasonably certainty of no harm to humans.

Measurable level of exposure (Q): This document describes a measurable level of exposure as the number of pounds of a particular food animal commodity containing drug-resistant bacteria.

While number of pounds of product containing resistant bacteria may be the most practical way to discuss the measurable level of exposure, Table 1 illustrates that the quantity is not measured directly. Instead, a measurable quantity to which the population is exposed (Q) would typically be a product of several terms. The total number of pounds of food animal commodity consumed is known from USDA records. The portion of the total number of pounds containing any of the bacteria of interest is estimated from the USDA data. The prevalence of antimicrobial resistance among bacterial isolates is determined through the NARMS program.

Therefore, Q could be estimated as follows:

Q = total pounds of product consumed
×
proportion of sampled pounds containing bacteria
×
proportion of samples from which resistant bacteria are isolated

Calculating Resistance Thresholds

The proportionality relationship between the measurable human health impact (H(x)) and the associated observable exposure (Q) is expressed,

$$H(x) = [k\text{-res}] * Q. \qquad \text{(Equation 1)}$$

Now, assuming all underlying factors in the system modeled remain stable over the period of interest, this relationship is considered stable over that period. During such a stable period, the relationship allows a linear prediction of the prevalence of people impacted from the quantity of food animal commodity containing resistant drug-resistant bacteria to which the population is exposed. If the level of exposure associated with the human health threshold, T(x), is designated $Q_t(x)$, it is also true that for the specific threshold values, T(x) and $Q_t(x)$,

$$T(x) = [k\text{-}res] * Q_t(x). \qquad \text{(Equation 2)}$$

Taking equations (1.) and (2.) in combination it follows that,

$$[k\text{-}res] = \frac{H(x)}{Q} = \frac{T(x)}{Q_t(x)} \qquad \text{(Equation 3)}$$

This relationship permits solution for a resistance threshold t(x), expressed as the prevalence of resistance among isolates from samples of the food commodity containing the bacteria of interest. A resistance threshold (t(x)) is associated with a set human health threshold value (T(x)), given measurable values of impact H(x), and proportion of all isolates from food samples from which resistant isolates are obtained (h). To illustrate as in Equation 3 above, write:

$$\frac{H(x)}{Q} = \frac{H(x)}{\text{total weight in pounds} * \text{proportion contaminated with bacteria} * h}$$

and

$$\frac{T(x)}{Q(x)} = \frac{T(x)}{\text{total weight in pounds} * \text{proportion contaminated with bacteria} * t(x)}$$

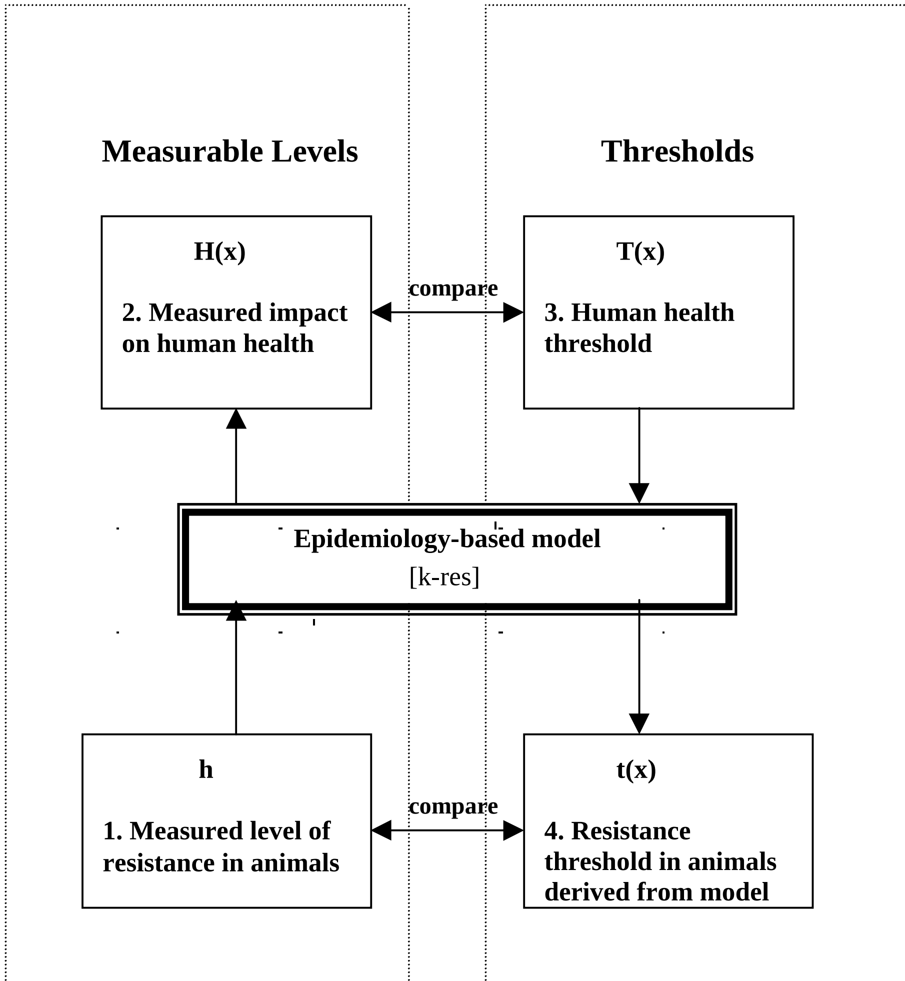
Then when the total weight in pounds and proportion contaminated with bacteria are cancelled from both sides in Equation 3, it can be seen that the solution for the resistance threshold specified in terms of prevalence of resistance is:

$$t(x) = \frac{T(x) \times h}{H(x)} \qquad \text{(Equation 4)}$$

We would consider using the prevalence of carcasses from which resistant bacteria are isolated at slaughter (or from products at retail for situations in which slaughter data will not be collected).

The essential strategy of the proposed quantitative approach outlined above is illustrated in Figure 3. There are four quantities represented here:

- H(x) – The current measured prevalence of infections in humans that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals.
- h – A consistent measure of the current prevalence of animal-derived foods containing resistant bacteria.
- T(x) – The unacceptable prevalence of infections in humans that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals.
- t(x) – The resistance threshold (t(x)) is the maximum allowable prevalence of resistant bacteria isolated from animal-derived food that does not pose an unacceptable risk to the human health.



x = {enteric illness or systemic illness}

Figure 3: Diagram illustrating the relationship between human health thresholds, resistance thresholds, measured levels of resistance in animals, and measured impacts in human health. A measured level of resistance (1.) is linked to a measured human health impact (2.) by Equation 1 through [k-res], based on an epidemiology-based model. The human health threshold (3.) is linked through [k-res] to the resistance threshold (4.). After approval the measured prevalence of resistance (h) is compared to the resistance threshold [t(x)] set prior to approval. The measurable human health impact [H(x)] is compared to the set human health threshold [T(x)] level for confirmation. The relationship between observable human health impact and observable prevalence of resistance is examined to determine if [k-res] needs to be adjusted.

Two Alternative Methods for Deriving Resistance Thresholds

Two methods are described in the following sections for using the proposed epidemiology-based model for deriving resistance thresholds. The methods differ mainly in the amount of data required to perform the calculations to establish the resistance thresholds. Coincident differences in assumptions are required.

Method 1: *Maximum Human Health Impact Method of Establishing t(x)*

In the case of antimicrobial drugs for which transmission of resistance from animals to humans would primarily be expected to occur through food borne pathogens, resistance thresholds would likely be established for *Campylobacter* and *Salmonella*. *Campylobacter* and *Salmonella* are commonly isolated from food animals at slaughter[7-14] and represent the predominant bacterial pathogens isolated from cases of enteric illness for those pathogens under surveillance in FoodNet[15]. CDC provides annual estimates of the total prevalence of cases of campylobacteriosis and salmonellosis in the U.S. in FoodNet reports. To use Method 1, it is necessary to know the total prevalence of cases of illness in humans attributable to the animal species of interest. The total prevalence of illness is multiplied by the attributable fraction to determine the prevalence of cases attributed to the animal species. The assumption is made that when there are no resistant bacterial isolates among isolates from a given animal species, no human cases with resistant bacteria are attributable to that animal species. Similarly, the assumption is made that when all isolates from an animal species are resistant; all human cases attributable to that animal species will be caused by resistant bacteria.

This maximum prevalence of cases with resistant infections is multiplied by the fraction of those cases expected to be treated with the antimicrobial drug of concern to yield the maximum human health impact that would be expected if 100 percent of the animal isolates are resistant. A line drawn between these two points, the zero value and the prevalence of cases attributable to the animal species who would be given the antimicrobial drug of interest, is a first approximation of the relationship between the human health impact and the prevalence of resistance among isolates from the food animal commodity of interest. The maximum prevalence of cases who were given the antimicrobial drug to which the bacteria causing their infections are resistant constitutes a measurable health impact (H(x)), denoted $H_{max}(x)$. Its associated value of prevalence of resistance among isolates in the animal species is h = 1. As mentioned in the previous section, these two values and the set value T(x) may now be used to solve for the resistance threshold (t(x)) in the animal species:

$$t(x) = \frac{T(x)}{H_{max}(x)} \qquad \text{(Equation 5)}$$

Note that this method implies that the prevalence of resistance among isolates in the food animal commodity is the same as the prevalence of resistance among isolates from people with illness attributed to the food animal commodity. This method is quite simple to apply and beneficial in the situation where there are little data on resistance in the food animal, such as when a novel animal drug is in the review process. This method assumes that the likelihood of the pathogen to cause an infection in humans is the same for susceptible and resistant strains. It also assumes that the distribution of the total numbers of bacteria that are found on units of a food-animal commodity is the same regardless of the prevalence of resistance among the bacteria. An example calculation using Method 1 is provided in Appendix 1.

Method 2: ***Current Human Health Impact Method of Establishing t(x)***

Calculating t(x) by Method 2 requires data on the prevalence of cases with disease caused by resistant bacteria for which resistance is attributable to use of an antimicrobial drug in a food animal species, and on the prevalence of resistance among isolates from the food animal commodity of interest. This prevalence is not estimated under the current surveillance system, which estimates only the total prevalence of cases caused by each pathogen. The total prevalence must then be translated into the prevalence of cases caused by resistant bacteria attributable to the food animal commodity by applying an estimated proportion of resistant cases among all cases attributable to the food animal commodity. Until the prevalence of cases caused by resistant pathogens attributable to the food animal commodity is estimated directly, Method 2 requires the data required by Method 1 plus an estimate of the proportion of cases with resistant bacteria attributable to the food animal commodity. Despite the additional data requirements, Method 2 has an advantage over Method 1 because it assumes linearity only over a narrow range around the current estimate rather than over the entire range from 0 to 100% resistance prevalence in the isolates from the food animal commodity.

The current human health impact is an estimation of the prevalence in the U.S. population of some particular health effect in the current year. The two prevalences offered for consideration in this document are:

1. **Current impact on enteric illness**: In any given year, a certain proportion of the U.S. population will experience enteric foodborne illness and will be treated with an antimicrobial drug. Some cases may be due to bacteria that are resistant to the drug administered. The current impact on enteric illness is defined as the current prevalence of cases of enteric illness in the U.S. population that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals. Such cases are expected to experience decreased or loss of effectiveness of their antimicrobial drug treatment.
2. **Current impact on systemic illness**: In any given year, a certain proportion of the U.S. population will experience systemic foodborne illness and will be treated with an antimicrobial drug. Some cases may be due to bacteria that are resistant to the drug administered. The current impact on systemic illness is defined as the current prevalence of cases of systemic illness in the U.S. population that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of

an antimicrobial drug in animals. Such cases are expected to experience decreased or loss of effectiveness of their antimicrobial drug treatment.

Just as was the case for each threshold prevalence where there is an associated expected human health impact T(x), there is a current human health impact estimate associated with each current prevalence. These are the values H(x) introduced in the section above entitled, **Description of Model for Deriving Resistance Thresholds**. Risk managers compare estimates of the current prevalences with the threshold prevalences, or the corresponding values of H(x) to T(x), to determine whether an unacceptable human health risk has been or is about to be reached. The following offers some suggestions on how these values could be determined and then how the resistance threshold is calculated.

Calculating Resistance Thresholds Using Current Impacts

This measure of risk (H(x)) will normally be the most easily estimated impact, since it will usually be the most frequent human health effect.

H(x) = current total prevalence of people with illness (x = EI or SI)
×
the attributable fraction for the food animal species
×
current prevalence of resistance in cases attributed to food animal commodity
×
proportion expected to receive antimicrobial drug of concern

Assuming the current prevalence of resistance in cases attributed to food animal commodity is known, the resistance threshold associated with the human health threshold is calculated as follows:

$$t(x) = \frac{T(x) \times h}{H(x)} \qquad \text{(Equation 6)}$$

Summary of Establishing Resistance Thresholds

A resistance threshold set under the approach in this document would be established prior to the approval of certain antimicrobial products for use in food-producing animals. As discussed above, the resistance threshold would be linked to the human health threshold through a proportionality relationship between a measurable human health impact and the exposure to food animal product containing resistant bacteria associated with that human impact. The graph shown in Figure 4 illustrates that the maximum human health impact and the current human health impact are two conveniently understood points among the many possible points that comprise the relationship between human health impact and resistance among animal isolates.

This document describes two methods for using a model to derive resistance thresholds. The availability of data partially dictates how estimates for required quantities are derived. Table 1 lists the type of information used in the model and compares the information needed for the two methods described.

The benefit of using Method 1, the maximum health impact method, is that it permits calculation of t(x) without requiring data on the prevalence of resistance in cases attributed to the food animal commodity. This would be particularly useful in situations where a product is the first new animal drug in its class. In such situations, there presumably would be no data on the prevalence of resistance to the drug in the food animal commodity attributable to animal drug use at the time of the review of the new animal drug application. Method 1 derives the resistance threshold by making the assumption that all human cases of foodborne disease attributed to the food animal species would be due to bacteria resistant to the drug of concern. The advantage of using Method 2, the current health impact method, is that it allows CVM to adjust the calculation of k-res from that based on the assumptions in Method 1. That is, Method 2 uses current data to determine the proportion of animal-related human cases that would be due to bacteria resistant to the drug of concern. Of course, in such situations, approvals for new uses could only occur in circumstances in which the existence of animal-related human cases due to bacteria resistant to the drug of concern would not preclude approval of such drug for additional uses.

The 5^{th} percentile of the uncertainty distributions for the modeled resistance threshold would be more protective of human health than would be the mean of the distribution. See Appendix 1 for example calculations of resistance thresholds for individual animal species and extensions to multiple species as discussed later in this document. The example calculations are not modeled values. They are presented to illustrate the logic used in modeling resistance thresholds.

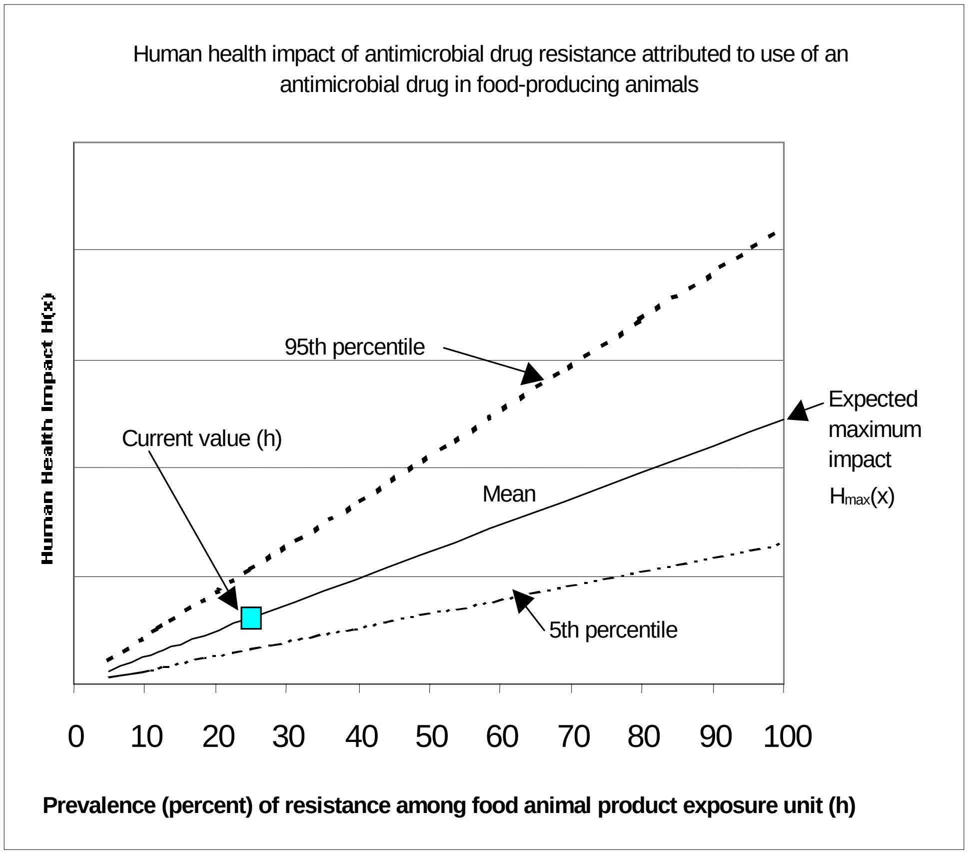


Figure 4: Indicates the proportional relationship between human health impact (H(x)) and resistance among animal isolates (h) showing current and maximum human health impact ($H_{max}(x)$)estimates. The expected maximum impact used in Method 1 is the prevalence of infections in humans that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable to the use of an antimicrobial drug in animals. It is called the maximum impact because it is calculated assuming all disease cases attributable to the animal species are resistant. A line connects the maximum to (0,0) and [k-res] is the slope of that line. Using Method 2, the ratio of the current human impact (y-axis) to the prevalence of resistance among food animal product associated with the current human impact (x-axis) is [k-res].

Table 1. Types of data and information that may be needed in the epidemiology-based model. Data and sources are listed for example purposes and are not intended to be an exhaustive list.

Data to support human health impact estimate	***Method 1***	***Method 2***
U.S. population (denominator for determining prevalences)	Yes[1]	Yes
FoodNet (or other sample) population	No	Yes
Observed cases enteric/systemic disease in the sampled population	No	Yes
Prevalence of culture confirmed cases reportable to health department (enteric and systemic) in US	Yes	No[2a]
Prevalence of culture confirmed resistant cases reportable to health department (enteric and systemic) in U.S.	No	Yes[3]
Proportion of enteric/systemic disease cases attributable to the animal species	Yes	Yes
Proportion of enteric/systemic disease cases attributed to the animal species and resistant to the antimicrobial drug under study	No	Yes[2b]
Proportion of persons with enteric/systemic disease that seek care and are treated with the antimicrobial drug under study	Yes	Yes
Data to support exposure estimate		
Total prevalence of bacteria among the animal product samples	No	No
Prevalence of antibiotic resistant bacteria among bacteria collected from contaminated animal product samples	No	No
Estimated prevalence of antibiotic-resistant bacteria in animal product	No	Yes
Consumption of animal product from domestically reared animals, per capita (lbs.) in U.S.[4]	No	No
Total consumption of animal product from domestically reared animals in U.S. (lbs.)[4]	No	No
Total consumption of animal product from domestically reared animals contaminated with antibiotic resistant bacteria in U.S. (lbs.)[4]	No	No

1. "Yes" indicates the value is necessary for calculating a resistance threshold by the given method.
2. Information estimated by the current surveillance system.
3. If this information were estimated by the surveillance system, this line would supplant the line containing 2b.
4. Note: Although consumption data are not needed, changes in consumption will alter the value of [k-res], as indicated between Equations 3 and 4.

Risk Management Considerations

After assessing the risk, there may be circumstances where additional factors need to be considered in order to make a decision as to how to manage the risk identified. Such factors may include a consideration of sub-populations that may be at greater risk than the general population. In addition, consideration may be given to the level of uncertainty inherent in the evaluation of the risk. Such uncertainty may be addressed through the application of various safety factors. Also, safety factors could be applied to the model in order that thresholds be set to correspond to a level to preclude a measurable human health impact. These examples of risk management considerations are described in Appendix 2 of this document to stimulate further discussion.

Setting thresholds for multiple food animal species

The approach set out in the document would allow CVM to consider a number of options including the relative contribution to the human health impact from each animal commodity group. CVM believes that there needs to be significant discussion for setting thresholds when a particular antimicrobial drug is or potentially will be approved in more than one food animal species.

One possible approach is to set resistance thresholds based on the relative contribution to human health by each food animal commodity. If an antimicrobial is to be used in multiple species, it may be necessary to provide each animal industry with its own resistance threshold. CVM believes that the use of a specific antimicrobial in animals constitutes the decision option against which the human health risk should be measured. This means that whatever human health thresholds are determined, the risk should be shared among the animal species for which the antimicrobial has been approved such that the combined human health impact from all antimicrobial drug use in food animals will not exceed T(x). This leads to the restriction that for number of species (n),

$$\sum_{i=1}^{n} a_i [t_i(x) * k - res_i] \leq T(x) \qquad \text{(Equation 8)}$$

where a_i is the multiplier used to allocate a portion of the resistance threshold to species i.

A readily calculable method for distributing the allowable risk among species would be to allocate the risk in proportion to the weight of consumable food product contributed by each animal species. The resistance thresholds derived for each animal species (based on that species' contribution to the human health impact) would be divided by the number of species. In this case a_i is 1/n. See Appendix 1 for example calculations of resistance thresholds for multiple species.

Alternatives to this approach would be to share the human health impact equally among all species or to allocate the resistance threshold in proportion to the species contribution to human disease.

Once these human health thresholds are set by species, one needs to determine a measure that estimates the relative proportion of foodborne disease that each species contributes. The model can then determine what the resistance threshold would be for that species to match its human health threshold. If any commodity group exceeds the resistance threshold, CVM would initiate procedures to withdraw from the label the animal species that has reached or exceeded its threshold.

Pharmaceutical companies may seek approval for a new antimicrobial one species at a time. Following the above philosophy, seeking approval for a second, third, etc. species would necessitate reducing the level of resistance allowed in those species already approved.

In the event that it proves impossible to distinguish the proportion of foodborne disease contributed by each species, it would be necessary to monitor the total human health impact and relate that directly to the human thresholds, withdrawing the product globally should the human health threshold be reached.

Reassessment of Thresholds

CVM anticipates that after the approval of a new antimicrobial drug for use in food-producing animals, it will periodically reassess the established threshold to account for new information and data. Data collected through the NARMS program and from other sources after approval will allow a more accurate determination of a resistance threshold for a particular use of an antimicrobial drug. Reconsideration of an established resistance threshold would also be appropriate given changes in the use of the antimicrobial drug or related antimicrobial drug in human medicine, changes in the pathogenicity or virulence of resistant bacteria, changes in hygienic practices leading to greater or fewer foodborne illnesses, changes in consumption patterns of animal-derived foods, and emergence of new foodborne pathogens.

Regulatory Options for Approved Products

CVM envisions the codification of the resistance threshold as part of the approval of a new animal drug application. If the resistance threshold was determined to have been exceeded prior to approval, the new animal drug application would not be approved. The basis for this codification is that the continued use of the new animal drug, when the resistance threshold has been exceeded, contributes to the loss of effectiveness of important human antimicrobial therapies and, as such, causes the use of the new animal drug to be no longer shown to be safe.

If, after antimicrobial drug approval, shifts in susceptibility are observed via the post-approval monitoring program (and the resistance threshold has not been exceeded) voluntary action may be initiated to mitigate further loss of susceptibility. However, if the resistance threshold was found to have been exceeded, CVM would initiate procedures to withdraw from the label any animal species that has reached or exceeded its threshold. This process would not preclude the agency from taking any regulatory steps at any time if human health is at risk because of the use of a new animal drug.

GLOSSARY

ADI - Acceptable Daily Intake. Quantity of the new animal drug that may safely be consumed in the human diet daily for a lifetime.

Breakpoints - Specific values, expressed relative to terms such as Minimum Inhibitory Concentrations (MICs), or zones of inhibition (which can be correlated with MICs using appropriate statistical methods), which categorize bacteria as clinically susceptible, intermediate or resistant.

***Campylobacter* Risk Assessment** - The first probabilistic risk assessment undertaken by the Center for Veterinary Medicine which estimated the human health impact of drug resistant Campylobacter resulting from fluoroquinolone use in poultry. Available at http://www.fda.gov/cvm/antimicrobial/Risk_asses.pdf.

Current impact on enteric illness: In any given year, a certain proportion of the U.S. population will experience enteric foodborne illness and will be treated with an antimicrobial drug. Some cases may be due to bacteria that are resistant to the drug administered. The current impact on enteric illness is defined as the current prevalence of cases of enteric illness in the U.S. population that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals. Such cases are expected to experience decreased or loss of effectiveness of their antimicrobial drug treatment.

Current impact on systemic illness: In any given year, a certain proportion of the U.S. population will experience systemic foodborne illness and will be treated with an antimicrobial drug. Some cases may be due to bacteria that are resistant to the drug administered. The current impact on systemic illness is defined as the current prevalence of cases of systemic illness in the U.S. population that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals. Such cases are expected to experience decreased or loss of effectiveness of their antimicrobial drug treatment.

Drug characterization factor (DCF) - An additional factor to multiply the estimated human health impact of an antimicrobial drug to compensate for the loss of an important human drug therapy. Criteria will be established.

Framework Document - A December 1998 draft document by the Center for Veterinary Medicine that outlines a range of potential regulatory issues affecting antimicrobial drugs to be used in food-producing animals. These issues include pre- and post-approval studies, the significance of the drug to human medicine and regulatory thresholds (See page 1 onto 2). The document is issue oriented and has not resulted in Center guidance at this time. . Available at http://www.fda.gov/cvm/index/vmac/antimi18.html.

Human Health Threshold - The unacceptable prevalence of infections in humans that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals. Human health thresholds specifically focus on the incremental effects on enteric illness or systemic illness in humans as a consequence of the causative bacteria being resistant to the antimicrobial drug the affected persons are expected to receive. Based on current safety standards, the "unacceptable prevalence" is considered that level at which there is no longer reasonable certainty that there is no harm to human health.

K-res - A proportionality constant relating the nominal mean number of cases of illness due to drug resistant bacteria attributable to a particular food-animal species to the estimated amount of food product (derived from given food animal species) consumed that contains drug-resistant bacteria.

h - A consistent measure of the current prevalence of animal-derived foods containing resistant bacteria.

H(EI) - The current level of human health impact of enteric illness resulting from the current level of material containing drug-resistant bacteria.

$H_{max}(x)$ - The maximum level of human health impact resulting from the use of an antimicrobial drug in food producing animals causing 100% resistance to a human antimicrobial drug, given current prescription practices in human medicine.

H(SI) - The current level of human health impact of systemic illness given the current level of material containing drug resistant bacteria.

H(x) - The current measured prevalence of infections in humans that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable to the use of an antimicrobial drug in animals (where x = EI or SI).

Minimum inhibitory concentration (MIC) - The lowest concentration of an antimicrobial drug, expressed in µg/ml or mg/L that, under defined *in-vitro* conditions prevents the growth of bacteria within a defined period of time.

Minimum inhibitory concentration (MIC) distribution - The range of MICs for a given population of organisms when tested against a specific antimicrobial drug under defined *in-vitro* conditions

Mitigation Programs - Actions initiated by CVM, the sponsor, or other groups to alleviate the concern for unacceptable human health impacts resulting from the use of the antimicrobial drug in food animals. These actions may include a wide range of activities such as education, changes in animal production practices, changes to the animal drug label, or initiation of procedures to withdraw the animal drug product.

Model Adjustment Factor (MAF) - A factor to multiply risk estimates to compensate for uncertainty in the model. This may be similar to the uncertainty multipliers commonly used in unit risk estimates from laboratory animals to derive an acceptable daily intake. Criteria and experience will be developed as the Center considers using such factors.

Monitoring - The collection of specific data used for regulatory purposes

NADA - New Animal Drug Application

NARMS - National Antimicrobial Resistance Monitoring Program. Available at http://www.cdc.gov/ncidod/dbmd/narms/

Q - Quantity of product containing bacteria resistant to an antimicrobial of interest.

Resistance - A characteristic of a bacterial strain in which it is not inhibited by the usually achievable systemic concentrations of an antimicrobial agent with normal dosing schedules and/or falls in the range where specific mechanisms are likely (e.g., beta-lactamases), and clinical efficacy has not been reliable in treatment studies.

Resistance Threshold - The resistance threshold (t(x)) is the maximum allowable prevalence of resistant bacteria isolated from animal-derived food that does not pose an unacceptable risk to human health. The resistance threshold is derived through an epidemiology-based model that relates the prevalence of resistant bacteria in food to an impact on either enteric illness (EI) or systemic illness (SI) in humans.

Exceeding a resistance threshold would be considered a level of resistance at which there is no longer reasonable certainty that there is no harm to human health. For the purposes of this definition, bacteria are considered resistant if their minimum inhibitory concentration (MIC) reaches or exceeds the resistance breakpoint established for the related drug used in human medicine.

Surveillance - The close and vigilant review of data coming from a system used for regulatory purposes.

Susceptible - A characteristic of a bacterial strain in which it is inhibited by the usually achievable systemic concentrations of an antimicrobial agent with normal dosing schedules and/or falls in the range where specific mechanisms are not likely (e.g., beta-lactamases), and clinical efficacy has been reliable in treatment studies.

Threshold for impact on enteric illness: In a given year, a certain proportion of the U.S. population will experience enteric foodborne illness and will be treated with an antimicrobial drug. Some cases may be due to bacteria that are resistant to the drug administered. Therefore, the threshold for impact on enteric illness is defined as the unacceptable prevalence of cases of enteric illness in the U.S. population that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals. Such cases are expected to experience decreased or loss of effectiveness of their antimicrobial drug treatment.

Threshold for impact on systemic illness: In a given year, a certain proportion of the U.S. population will experience systemic foodborne illness and will be treated with an antimicrobial drug. Some cases may be due to bacteria that are resistant to the drug administered. Therefore, the threshold prevalence of cases of systemic illness impacted is defined as the unacceptable prevalence of cases of systemic illness in the U.S. population that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable (in whole or in part) to the use of an antimicrobial drug in animals. Such cases are expected to experience decreased or loss of effectiveness of their antimicrobial drug treatment.

t(EI) - The resistance threshold for enteric illness. It is the maximum allowable prevalence of resistant bacteria isolated from animal-derived food that does not cause an unacceptable impact on enteric illness in humans.

t(SI) - The resistance threshold for systemic illness in humans. It is the maximum allowable prevalence of resistant bacteria isolated from animal-derived food that does not cause an unacceptable impact on systemic illness in humans.

t(x) - The generic resistance threshold (i.e., a resistance threshold derived in relation to a human health impact, x (where x = EI or SI). See above for complete definition of **Resistance Threshold**.

T(EI) - The human health threshold for enteric illness.

T(SI) - The human health threshold for systemic illness.

T(x) - The generic form of the human health threshold, for x={EI or SI}.

REFERENCES

1. FDA, "Public Health Action Plan to Combat Antimicrobial Resistance," June 22, 2000 (65 FR 38832). Available at http://www.cdc.gov/drugresistance/actionplan/.

2. Tollefson, L., Angulo, F. and Cray, P. National Surveillance for Antibiotic Resistance in Zoonotic Enteric Pathogens. (In) Hunt, E., and Tollefson, L. The Veterinary Clinics of North America, Food Animal Practice Microbial Food Borne Pathogens. March 1998. W.B. Saunders Co. Philadelphia, 14(1); 141-150.

3. CDC Preliminary FoodNet Data on the Incidence of Foodborne Illnesses - Selected Sites, United States, 1999. MMWR. March 17, 2000 / 49(10); 201-5. Available at http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4910a1.htm.

4. FDA, "Guidance for Industry: Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals (GFI #78)," 64 FR 72083 and 72084, December 23, 1999. Available at http://www.fda.gov/cvm/guidance/guidad78.html.

5. FDA, "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," January 6, 1999 (64 FR 887). Available at http://www.fda.gov/cvm/index/vmac/antimi18.html.

6. AVMA. Judicious Antimicrobial-Use Principles, Related Proposals Approved by Board. JAVMA 214(2): p167-8

7. United States Department of Agriculture, Food Safety and Inspection Service, Science and Technology Microbiology Division, April 1996 Nationwide Broiler Chicken Microbiological Baseline Data Collection Program, July 1994-June 1995. [available at http://www.fsis.usda.gov/OPHS/baseline/contents.htm] .

8. United States Department of Agriculture, Food Safety and Inspection Service, Science and Technology Microbiology Division, February 1996 Nationwide Beef Microbiological Baseline Data Collection Program: Cows and Bulls, December 1993-November 1994. [available at http://www.fsis.usda.gov/OPHS/baseline/contents.htm].

9. United States Department of Agriculture Food Safety and Inspection Service, Science and Technology Microbiology Division, January 1994 Nationwide Beef Microbiological Baseline Data Collection Program: Steers and Heifers, October 1992-September 1993. [available at http://www.fsis.usda.gov/OPHS/baseline/contents.htm].

10. United States Department of Agriculture Food Safety and Inspection Service, Science and Technology, Microbiology Division, April 1996 Nationwide Federal Plant Raw Ground Beef Microbiological Survey, August 1993- March 1994. [available at http://www.fsis.usda.gov/OPHS/baseline/contents.htm].

11. United States Department of Agriculture, Food Safety and Inspection Service, Science and Technology Microbiology Division, June 1996 Nationwide Pork Microbiological Baseline Data Collection Program: Market Hogs, April 1995-March 1996. [available at http://www.fsis.usda.gov/OPHS/baseline/contents.htm].

12. United States Department of Agriculture, Food Safety and Inspection Service, Science and Technology Microbiology Division, May 1996 Nationwide Raw Ground Chicken Microbiological Survey.

13. United States Department of Agriculture, Food Safety and Inspection Service, Science and Technology, Microbiology Division, May 1996 Nationwide Raw Ground Turkey Microbiological Survey. [available at http://www.fsis.usda.gov/OPHS/baseline/contents.htm].

14. United States Department of Agriculture, Food Safety and Inspection Service, Science and Technology, Office of Public Health and Science, Microbiology Division, August 1998 Nationwide Young Turkey Microbiological Baseline Data Collection Program, August 1996-July 1997, [available at http://www.fsis.usda.gov/OPHS/baseline/contents.htm].

15. Centers for Disease Control and Prevention. FoodNet CDC/FSIS/FDA Foodborne Diseases Active Surveillance Network. CDC's Emerging Infections Program. 1998 Surveillance Results. Preliminary Report. Atlanta, Georgia.

Appendix 1

Example Calculation of Thresholds t(EI) by Method 1

Assume that the current estimated prevalence of an enteric illness caused by animal-derived food is 6.67 cases per 1000 people in the U.S. annually.

Assume that 10 percent of the cases are treated with the antimicrobial drug of concern such that:

$H_{max}(EI) = 6.67*10^{-3} * 0.10 = 6.67*10^{-4}$

Assume that the antimicrobial drug of concern is approved for use in four food animal species and that each species is responsible for causing a proportion of total enteric illness cases such that: Species *A* causes 60 percent of the cases, Species *B* causes 20 percent of the cases, Species *C* causes 15 percent of the cases, and Species *D* cause 5 percent of the cases.

For any given human health threshold (T(EI) expressed as a prevalence), a resistance threshold (t(EI) expressed as percent) can be calculated for each species according to the formula:

$$t_i(EI) = \frac{T(EI)*a_i*}{H_{max}(EI) * S_i} 100\%$$

Where:

a_i = 1/n where n is the number of food animal species for which the antimicrobial drug is approved. In this example, n=4 such that $a_i = 0.25$.

S_i is fraction of the total number of food borne cases caused by the food animal species of concern such that:

$S_A = 0.60$

$S_B = 0.20$

$S_C = 0.15$

$S_D = 0.05$

Appendix 2

Risk Management Considerations

Consideration of sub-populations

If an identifiable sub-population (e.g., certain immuno-compromised people) bears a significantly greater proportion of the risk than the general population it seems appropriate that they should be the focus of protective measures. However, this is provided that the defined sub-population is not able to avoid or manage the risk and receives no significant direct benefits from exposure to the risk that are greater than the population in general. One could argue that these people are shouldering the risk for the entire population and that they should not have to be exposed to any risk imposed on them by the population as a whole that is greater than the population accepts upon itself.

In that case, the current prevalence estimates for enteric illness (EI) and systemic illness (SI) that will be compared with the threshold prevalences for these potential impacts would be modified as follows:

Sub-population current prevalence **(EI)** = Expected cases of enteric illness in sub-population due to resistance in the year and treated with the antimicrobial drug of concern / Size of sub-population.

Sub-population current prevalence **(SI)** = Expected cases of systemic illness in sub-population due to resistance in the year and treated with the antimicrobial drug of concern / Size of sub-population.

For any identified sub-populations, these threshold levels would replace the three population risk estimates (since they will always be more stringent), and used together to determine whether an unacceptable human health impact has or is likely to be reached by comparing them with the threshold prevalences for enteric illness (EI) and systemic illness (SI).

Adjusting the current risk estimate for statistical uncertainty and model uncertainty

Compensating for statistical uncertainty

Models used to estimate current levels of human health impact should account for statistical uncertainty. The resultant estimates therefore have uncertainty distributions that reflect the degree to which one cannot be sure about the true value because of the small amount of data. Picking the 95^{th} percentile of these estimates, or any other appropriately high percentile, as the measure of the risk is a conservative action because it evaluates the risk at a value that we are 95% (for example) statistically certain the true value lies below.

This approach has the limitation that it only considers the uncertainty due to inference about some measure from a set of data. Any inference is based on a mathematical model.

Statistical analysis cannot take into account any inaccuracies arising from a mismatch between the model assumptions used to create the mathematics of the model and physical reality. The model uncertainty can be separately accounted for by multiplying the risk estimates by a ‘model adjustment factor’ described below.

Compensating for model uncertainty

CVM recognizes that the epidemiology-based model set out in this document may overestimate or underestimate the impact of the animal drug on antimicrobial bacterial resistance and changes in human health. A model adjustment factor (MAF) intended to be applied to provide adjustments for unquantified factors may need to be applied to the results of the model to address this concern. CVM will need to develop criteria for the application of this uncertainty factor.

Compensating for potential loss of efficacy of an important drug

CVM recognizes that the epidemiology-based model set out in this document may not address the importance of the drug in human medicine. A drug categorization factor (DCF) may need to be applied to the results of the model to address this concern. CVM will need to develop criteria for the application of this uncertainty factor.

Resistance Threshold Safety Factor

The resistance threshold described in this document is the maximum allowable level of resistance prevalence in bacteria isolated from the food animal that does not pose an unacceptable risk to human health. This resistance threshold is derived through an epidemiology-based model that describes the relationship between the human health threshold and resistance levels in animals, and presumably could contain some safety factor to minimize the likelihood of the human health threshold ever being reached. Further discussion is needed regarding the development and application of such a safety factor.