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Antibiotic resistance: FDA approach/implication of current proposals

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Introduction

Food-producing animals are administered antimicrobial drugs for therapeutic, preventive, and production purposes. 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-producing animals by mechanisms that enable the exchange of their genetic material in the human gastrointestinal tract.

Antimicrobial resistance is a complex issue. The selection of antimicrobial-resistant bacterial populations occurs as a consequence of the combined impact of antimicrobial drug use in human, animal, and agricultural settings. As a consequence, the human health impact resulting specifically from the use of antimicrobial drugs in food-producing animals is difficult to assess. 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.

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 control program. The CVM strategy for addressing antimicrobial resistance is one component of more far 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].

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[2]. 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 the number of bacteria in animals that are pathogenic to humans.

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) strategies for managing the potential risks associated with the use of antimicrobial drugs in food-producing animals[3]. The Framework Document discussed both pre-approval and post-approval approaches. The strategies include:

- revision of the pre-approval antimicrobial resistance safety assessment for new animal drug applications;
- categorization of antimicrobial drugs based on the importance of the drug for human medicine;
- post-approval monitoring for the development of antimicrobial drug resistance;
- the collection of food animal drug use data; and
- the establishment of regulatory thresholds.

Pre-approval assessment of antimicrobial drugs

As noted previously, CVM announced with Guidance for Industry #78 its intentions to consider as part of its safety evaluation of antimicrobial drugs the potential human health impact associated with the emergence of antimicrobial resistance. The use of pre-approval study information to characterize safety in terms of the rate and ex-

tent of resistance development in food-producing animals was discussed at a public workshop in February 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.

The new animal drug approval process includes the conduct of studies designed to demonstrate the safety and effectiveness of the proposed drug product, including studies aimed at determining the safety of food derived from food-producing animals treated with an animal drug. Chemical residues associated with animal-derived foods are evaluated for their toxic properties using a battery of well-established animal and laboratory methods. Unfortunately, no such predictive models currently exist to estimate with precision the rate and extent of bacterial resistance that may emerge from the use of antimicrobial drugs in food-producing animals. Despite the current lack of such models, CVM believes that certain information can be generated to support a pre-approval antimicrobial resistance safety assessment.

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. The categorization process is an integral part of assessing safety in that it provides some mechanism for characterizing the potential human health impact resulting from treatment failure owing to resistance. The categorization process also serves to focus the greatest level of attention on those antimicrobial drugs of greatest importance to human medical therapy.

Post-approval monitoring

A critical component of the general strategy outlined in the Framework Document is a mechanism for monitoring for the emergence of resistance. The National Antimicrobial Resistance Monitoring System (NARMS) was initiated in 1996 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 for the emergence of antimicrobial resistance among zoonotic enteric pathogens from human and animal clinical specimens, from healthy farm animals, and from carcasses of food-producing animals at slaughter[4]. Its purpose is to prospectively monitor the antimicrobial resistance of human, animal, and animal product isolates of selected enteric bacteria.

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; and 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 for susceptibility to 17 antimicrobial agents. *Campylobacter* isolates are tested for susceptibility to 8 antimicrobial agents. *Enterococci* isolates are identified to species level and tested for susceptibility to 27 antimicrobial agents. Results are entered into a SAS database for analysis.

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. Pilot studies involving retail foods were initiated in 2001 and will be expanded in 2002.

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.

Regulatory thresholds

The concept of establishing thresholds was originally introduced 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 thresh-

old was considered to represent an early warning signal of resistance development.

The concept of establishing thresholds was further refined in the December 2000 discussion document entitled "An Approach for Establishing Thresholds in Association with the Use of Antimicrobial Drugs in Food-Producing Animals"[5]. The approach outlined in the December 2000 "Threshold Document" also proposes the establishment of two types of thresholds, a human health threshold and a resistance threshold. The human health threshold described 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 to the use of an antimicrobial drug in animals.

The resistance threshold described in the Threshold Document is the maximum allowable level of resistance prevalence in bacteria isolated from the food-producing 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.

From a practical standpoint, the human health threshold simply represents a predetermined point at which human health is believed to be unacceptably impacted. A model (described in the Threshold Document) is used to relate that predetermined point to a level (prevalence) of resistance in animals. That model-derived prevalence of resistance in the animal would then be defined as the *resistance threshold*. The prevalence of resistance would be monitored in the animal through the NARMS program to determine if the levels are approaching or have exceeded the threshold. As noted in the Threshold Document, CVM would initiate procedures to withdraw from the label any animal species that has reached or exceeded its threshold.

CVM recognizes the complexities of establishing and implementing a threshold approach, but believes that the potential utility of such an approach warrants that the idea be given careful consideration.

Implementation of the Framework Document

CVM is currently drafting guidance for industry that incorporates the concepts previously described in the framework document and outlines a general strategy for regulating the use of antimicrobial drugs in food-producing animals. The overall strategy attempts to incorporate the various strategies/concepts discussed above into a single coordinated and comprehensive plan. To envision the plan from the standpoint of implementation, it may be more practical to describe it in relation to CVM's primary functional areas including pre-approval product review, post-approval activities, and research. A fourth additional and important component involves CVM's coordination and collaboration with other agencies and with stakeholders.

Pre-approval product review

Antimicrobial resistance safety assessment

Consistent with the risk-based approach outlined in the framework document, CVM envisions that applications for antimicrobial drugs for food-producing animals would include an antimicrobial resistance safety assessment. Such assessments would bring together a broad set of information regarding the drug and the proposed drug use under consideration. This assessment could serve to help characterize the proposed drug product in regards to the potential for resistance to emerge in animals, the potential that such resistance would "transfer" from animals to humans, and with regards to the relative importance of the drug (or related drug) to human medical therapy. These factors taken together could be used to characterize the overall level of concern that antimicrobial resistance would emerge (in association with the proposed use of the drug in animals) and cause an unacceptable human health impact.

Antimicrobial resistance risk management

The recognition that the use of antimicrobial drugs exerts selection pressure on antimicrobial-resistant bacteria focuses attention on the issue of appropriate or judicious use of antimicrobial drugs versus their misuse or overuse. A principle consistent with the judicious use concept is the idea that certain drugs (or certain drug use conditions) are more (or less) likely than other drugs (or drug use conditions) to exert pressures favorable to resistance emergence.

This risk-based approach to characterizing antimicrobial drugs is consistent with the basic concepts outlined in the Framework Document. That is, that the regulatory strategy may not be a "one-size-fits-all" approach, but rather an approach that is scaled to account for differing levels of risk associated with certain drugs and certain drug use conditions. An antimicrobial resistance safety assessment, such as discussed above, could serve as a mechanism for characterizing the product in question as to the level of potential risk associated with its use. The next step, theoretically, would be to determine how most appropriately to manage that risk. From an animal drug application standpoint, the two "risk management" options are either for CVM to refuse to approve the drug or for CVM to approve the drug under appropriate conditions of use. Although "appropriate use conditions" have not been specifically discussed as risk management tools in this context, it is not inconsistent with the approval process to

apply certain use limitations to certain products when it is deemed necessary. For example, "use condition" restrictions could include limitations regarding such factors as product marketing status, extra-label use provisions, or dosage and administration instructions.

Post-approval activities

As previously discussed, the NARMS program is currently in place and generating data for various pathogens of human health concern. This program is a key component of CVM's strategy and various program enhancements are being considered. NARMS is relied upon as the source of data for monitoring trends or shifts in antimicrobial susceptibility. As such, this database would be used, when and if thresholds are established, to determine if the threshold has been reached or exceeded. In addition, thresholds in conjunction with monitoring data could be used to serve as an early warning indicator for when resistance may be increasing and approaching the threshold. This could help to identify when intervention and mitigation steps, other than withdrawal action, might be implemented by the pharmaceutical industry, producer organizations, or FDA/CVM.

In addition to monitoring for antimicrobial resistance, CVM intends to expand its activities with regard to monitoring the quantity of antimicrobial drug products marketed for use in food-producing animals. CVM intends to issue a notice of proposed rule-making in the near future in order to establish new requirements for expanded drug sales information.

CVM has also been developing methods for conducting antimicrobial resistance risk assessments. A quantitative risk assessment has been completed with regard to fluoroquinolone use in poultry, and a second risk assessment on the use of virginiamycin has been initiated. CVM is considering how the models developed in these risk assessments might be applied to other antimicrobial drugs that may in the future be determined to be of concern.

Research activities

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. Such research is important for guiding CVM in further developing its pre-approval and post-approval activities related to the issue.

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.

In addition, CVM is a contributing laboratory to CDC's PulseNet '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.

Other collaborative activities

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.

Next Steps

In developing draft guidance for implementing the Framework Document, CVM is considering all relevant comments recorded at the various public meetings on the subject as well as those received in writing. In addition to this general guidance document, CVM anticipates that other, more specific guidance documents as well as new or amended rules may be necessary to implement the Framework Document concepts. CVM intends to publish all guidance documents as drafts in order to seek additional public comment. Proposals for new or amended rules will be subject to a notice and comment rule-making process.

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