Draft Guidance

#209

The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

U.S. Department of Health and Human Services
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Center for Veterinary Medicine

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This draft guidance is intended to inform the public of FDA's current thinking on the use of medically important antimicrobial drugs in food-producing animals.

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Additional copies of this draft guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either http://www.fda.gov/AnimalVeterinary/default.htm or http://www.regulations.gov.

The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

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I. Executive Summary

Antimicrobial drugs have been widely used in human and veterinary medicine for more than 50 years, with tremendous benefits to both human and animal health. The development of resistance to this important class of drugs, and the resulting loss of their effectiveness as antimicrobial therapies, poses a serious public health threat. Misuse and overuse of antimicrobial drugs creates selective evolutionary pressure that enables antimicrobial resistant bacteria to increase in numbers more rapidly than antimicrobial susceptible bacteria and thus increases the opportunity for individuals to become infected by resistant bacteria. Because antimicrobial drug use contributes to the emergence of drug resistant organisms, these important drugs must be used judiciously in both animal and human medicine to slow the development of resistance. Efforts have been made to promote the judicious use of these drugs in humans (see http://www.cdc.gov/getsmart/index.html) as well as in animals (see http://www.avma.org/issues/default.asp). Using these drugs judiciously means that unnecessary or inappropriate use should be avoided. The focus of this document is on the use of medically important antimicrobial drugs[1] in food-producing animals. Based on a consideration of the available scientific information, FDA is providing a framework for policy regarding the appropriate or judicious use of medically important antimicrobial drugs in food-producing animals. This framework includes the principles of phasing in such measures as 1) limiting medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health; and 2) limiting such drugs to uses in food-producing animals that include veterinary oversight or consultation. Developing strategies for reducing antimicrobial resistance is critically important for protecting both public and animal health. Collaboration involving the public, the public health, animal health, and animal agriculture communities on the development and implementation of such strategies is needed to assure that the public health is protected while also assuring that strategies are feasible and that the health needs of animals are addressed.

[1] The term "medically important antimicrobial drugs" generally refers to antimicrobial drugs that are important for therapeutic use in humans.

II. Introduction

Antimicrobial resistance[2], and the resulting failure of antimicrobial therapies in humans, is a mounting public health problem of global significance. This phenomenon is driven by many factors including the use of antimicrobial drugs in both humans and animals. In regard to animal use, this document addresses the use of medically important antimicrobial drugs in food-producing animals for production or growth-enhancing purposes. These uses, referred to as production uses in this document, are often also referred to as "nontherapeutic" or "subtherapeutic" uses. Such uses are typically administered through the feed or water on a herd- or flock-wide basis and are approved for such uses as increasing rate of weight gain or improving feed efficiency. Unlike other uses of these drugs in animals (e.g., for the treatment, control, and prevention of disease), these "production uses" are not directed at any identified disease, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products (e.g. increasing rate of weight gain or improving feed efficiency). This document summarizes some of the key scientific reports on the use of antimicrobial drugs in animal agriculture and outlines FDA's current thinking on strategies for assuring that medically important antimicrobial drugs are used judiciously in food-producing animals in order to help minimize antimicrobial resistance development.

III. Key Scientific Reports on the Issue

Questions regarding the use of antimicrobial drugs in food-producing animals have been raised and debated for many years. A variety of scientific committees, task forces, and organizations have studied the issue. We have briefly summarized below the findings and recommendations from some of the key reports addressing this issue. These reports provide context to FDA's current deliberations on this issue, and highlight the longstanding concerns that have been the subject of discussion in the scientific community as a whole. Unless otherwise indicated, the page numbers cited in this section refer to the relevant page numbers in the referenced report. A complete list of the reports summarized in this section is provided at Section IX of this document.

<u>1969 Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine</u>

In July 1968, a Joint Committee was established in the United Kingdom to obtain information regarding the use of antibiotics in animal husbandry and veterinary medicine, particularly with respect to antibiotic resistance. This report, often referred to as the "Swann Report," was presented to Parliament in November 1969 by the Secretary of State

[2] The term "antimicrobial" refers broadly to drugs with activity against a variety of microorganisms including bacteria, viruses, fungi, and parasites. Antimicrobial drugs that have specific activity against bacteria are referred to as antibacterial or antibiotic drugs. However, the broader term "antimicrobial," commonly used in reference to drugs with activity against bacteria, is used in this document interchangeably with the terms antibacterial or antibiotic. Antimicrobial resistance is the ability of bacteria or other microbes to resist the effects of a drug. Antimicrobial resistance, as it relates to bacterial organisms, occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals, or other agents designed to treat bacterial infections.

for Social Services, the Secretary of State for Scotland, the Minister of Agriculture, Fisheries and Food, and the Secretary of State for Wales. The report concluded that the administration of antimicrobials to food-producing animals, particularly at subtherapeutic levels, poses a hazard to human and animal health.

The report stated, "It is clear that there has been a dramatic increase over the years in the numbers of strains of enteric bacteria of animal origin which show resistance to one or more antibiotics. Further, these resistant strains are able to transmit this resistance to other bacteria. This resistance has resulted from the use of antibiotics for growth promotion and other purposes in farm livestock" (*Ref. 1*, p. 60). The report also noted, "There is ample and incontrovertible evidence to show that man may commonly ingest enteric bacteria of animal origin" (*Ref. 1*, p. 60).

The report provided a number of recommendations including that only antimicrobials which "have little or no application as therapeutic agents in man or animals and will not impair the efficacy of a prescribed therapeutic drug or drugs through the development of resistant strains of organisms" should be used without prescription in animal feed (*Ref. 1*, p. 61). Furthermore, the report concluded that antimicrobials used for therapeutic purposes in food-producing animals should remain available but only under veterinary supervision.

1970 FDA Task Force Report, "The Use of Antibiotics in Animal Feed"

In April 1970, FDA established a task force of scientists to undertake a comprehensive review of the use of antibiotics in animal feed. The task force included ten specialists on infectious diseases and animal science from FDA, the National Institutes of Health, the U.S. Department of Agriculture, and the Centers for Disease Control and Prevention, as well as five consultants from universities and industry.

This task force acknowledged that the understanding at the time it conducted its study was that the use of antimicrobials in food-producing animals, especially in subtherapeutic amounts, was associated with the development of resistant bacteria, and that treated animals might serve as a reservoir of antimicrobial-resistant pathogens that could produce human disease.

The recommendations of the Task Force included that antimicrobial drugs used in human clinical medicine that failed to meet certain guidelines established by the Task Force should be prohibited from growth promotion and any subtherapeutic use in food-producing animals by certain dates. Furthermore, those antimicrobials that failed to meet the guidelines should be limited to short-term therapeutic use and use only by a veterinarian or on a veterinarian's prescription.

As a consequence of the 1970 Task Force report, requirements for data to address microbiological safety concerns for subtherapeutic uses of antimicrobials in food-producing animals were outlined in the Code of Federal Regulations (21 CFR 558.15). Sponsors of antibiotic products administered in animal feed for subtherapeutic purposes were required to submit study results demonstrating that their product did not promote bacterial drug resistance. Depending on the class of drug, sponsors were required to submit all information

to the agency on the impact of their drug on enteric salmonella in treated animals by specific dates.

1980 National Academy of Sciences Report, "The Effects on Human Health of Subtherapeutic Use of Antimicrobial Drugs in Animal Feeds"

In 1977, FDA proposed to withdraw the new animal drug approvals for subtherapeutic uses of penicillin and tetracyclines in animal feed on the ground that evidence showed that these drugs, when used for such purposes in animal feed, had not been shown to be safe. These two drugs were chosen because of their importance in human medicine. The proposal was criticized because, at that time, there was not adequate epidemiological evidence (or only just-emerging evidence) to show that drug-resistant bacteria of animal origin were commonly transmitted to humans and caused serious illness. Subsequently, Congress directed FDA to conduct further studies related to the use of antimicrobials in animal feed and to hold in abeyance the implementation of the proposed antimicrobial withdrawal actions pending the outcome of these studies.

In accordance with Congress' directive to conduct further studies, FDA contracted with the National Academy of Science to conduct a study of the safety issues related to the use of antimicrobials in animal feed. In particular, FDA asked the National Academy of Science to: 1) study the human health effects of the subtherapeutic use of penicillin and tetracycline in animal feed; 2) review and analyze published and unpublished data relevant to assessing human health consequences of such use; 3) assess the scientific feasibility of additional epidemiological studies; and (4) make recommendations about additional research needed.

The National Academy of Sciences issued a study report in 1980. The study report concluded that a very limited amount of epidemiological research had been completed on either the subtherapeutic or therapeutic use of antimicrobials in animal feed. According to the study report, much of the information available on the subject involved "poorly controlled studies of small numbers of subjects for brief periods" (*Ref. 3*, p. 52). Based on a consideration of available evidence, the report concluded that existing data could neither prove nor disprove the postulated hazards to human health from subtherapeutic antimicrobial use in animal feed. However, the report cautioned that "The lack of data linking human illness with subtherapeutic levels of antimicrobials must not be equated with proof that the proposed hazards do not exist. The research necessary to establish and measure a definitive risk has not been conducted and, indeed, may not be possible" (*Ref. 3*, p. 53).

1984 Seattle-King County Study: "Surveillance of the Flow of Salmonella and Campylobacter in a Community"

As noted above, Congress directed FDA to hold in abeyance any implementation of the proposed withdrawal of new animal drug approvals for the subtherapeutic uses of penicillin and tetracyclines in animal feed, pending completion of additional studies related to the use of antimicrobials in animal feed. Therefore, in addition to the National Academy of Sciences study described above, the FDA also contracted with the Seattle-King County

Health Department to complete a study intended to provide additional information regarding potential public health concerns regarding the use of antimicrobial drugs in animal feed. Under the contract, the Communicable Disease Control Section of the Seattle-King County Health Department was tasked with studying the relationship between the occurrence of Salmonella spp. (*Salmonella*) and Campylobacter jejuni (*C. jejuni*) in foods of animal origin and the occurrence of human illness caused by those two organisms. These two organisms, *Salmonella* and *C. jejuni*, were chosen to serve as models to estimate the flow of potentially pathogenic bacteria from animals to man through the food chain. The study involved a two-pronged surveillance system that included sampling of retail meats over a 20 month period and simultaneous investigation of *Salmonella* and *C. jejuni* enteritis cases in humans. Bacterial isolates from food and human cases were subjected to antibiotic susceptibility testing, plasmid analysis, and serotyping. In 1984, the Seattle-King County Health Department prepared a report summarizing the results of the study. The 1984 study report found that *C. jejuni* was a more common cause of enteritis than *Salmonella*. Also, it concluded that *C. jejuni* "does appear to flow from chickens to man via consumption of poultry products" (*Ref. 4*, p. 3). The report stated, "isolates from human cases and those from retail poultry had similar antibiotic susceptibility patterns, including prevalence of 29.7% and 32.8%, respectively, for tetracycline resistance, which was found to be plasmid-mediated" (*Ref. 4*, p. 3).

1988 Institute of Medicine (IOM) Report: "Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed"

In 1987, FDA asked the IOM to conduct an independent review of the human health risks associated with the subtherapeutic use of penicillin and tetracycline in animal feed. IOM established a committee and directed it to perform "a quantitative risk assessment" of these human health consequences and to "assess the adequacy of the existing human health data and use such data to arrive at an estimate of risk" (*Ref. 5*, p. iii). If quantification of human health risks was not possible due to inadequate data, the Committee was to evaluate the scientific information that had become available since the 1980 National Academy of Science report cited above.

The Committee developed a risk-analysis model, using data only on *Salmonella* infections that resulted in human death. However, the Committee was unable to find a substantial body of direct evidence demonstrating that the subtherapeutic use of penicillin or tetracycline in animal feed posed a human health hazard. Nonetheless, the Committee's 1988 report found a considerable body of indirect evidence implicating both subtherapeutic and therapeutic use of antimicrobials as a potential human health hazard. The Committee also strongly recommended further study of the issue.

1997 World Health Organization (WHO) Report, "The Medical Impact of Antimicrobial Use in Food Animals"

In October 1997, the WHO convened a meeting of experts to examine the question of whether the use of antimicrobials in livestock production, including through use in animal feed, contributes to the escalation of antimicrobial resistance in humans. The findings of the meeting, which were summarized in a report, included the conclusion that all uses of

antimicrobials lead to the selection of resistant forms of bacteria. Furthermore, the report stated that "low-level, long-term exposure to antimicrobials may have greater selective potential than short-term, full-dose therapeutic use" (*Ref. 6*, p. 5). The report found that the selection of resistant bacteria has adverse consequences for preventing and treating disease in humans, animals, and plants.

The WHO expert committee recommended that the use of antimicrobial drugs for growth promotion in animals be terminated if these drugs are also prescribed for use as anti-infective agents in human medicine or if they are known to induce cross-resistance to antimicrobials used for human medical therapy. The Committee also recommended the development of a systematic approach towards replacing growth-promoting antimicrobials with safer non-antimicrobial alternatives. The expert committee called for enhanced monitoring of resistance among isolates of enteric bacteria from food animals and food of animal origin. In addition, the Committee recommended managing risk at the primary production level through measures that promote the prudent use of antimicrobials, including enforcement of relevant laws pertaining to antimicrobial use, education for prescribers and producers, and requiring that use of antimicrobials for treatment of infections in animals be prescribed by veterinarians.

1999 National Research Council (NRC) Report: "The Use of Drugs in Food Animals – Benefits and Risks"

The Panel on Animal Health, Food Safety, and Public Health, jointly sponsored by the NRC's Board on Agriculture and IOM's Food and Nutrition Board, initiated a project to review the issues and relevant information regarding the use of drugs in food-producing animals and to make recommendations about such use. The panel convened the Committee on Drug Use in Food Animals to examine the benefits and risks associated with drug use in food-producing animals and to prepare a report and make recommendations.

The Committee's 1999 report included a review of the issues related to antibiotic use in food-producing animals and provided a number of recommendations. The report recommended establishing national databases to support scientific process and policy development for the approval and use of antibiotics in food-producing animals. The report also recommended that FDA use interdisciplinary panels of experts so that "further development and use of antibiotics in both human and animal medicine have oversight by an interdisciplinary panel of experts composed of representatives of the veterinary and animal health industry, the human medicine community, consumer advocacy groups, the animal production industry, and the regulatory agencies" (*Ref. 7*, p. 11).

1999 United States Government Accountability Office (GAO) Report – "Food Safety: The Agricultural Use of Antibiotics and Its Implications for Human Health"

In response to a request from Congress, the GAO initiated a study in May 1998 to examine: "1) how antibiotics are used in agriculture and the implications of that use for human health; 2) federal roles and responsibilities for overseeing the use of antibiotics in agriculture; and 3) issues surrounding the debate over whether to further regulate or restrict the use of antibiotics in agriculture" (*Ref. 8*, p. 1).

In its study report, dated April 1999, GAO concluded that although research has linked the use of antibiotics in agriculture to the emergence of resistant foodborne pathogens, "there are no current comprehensive estimates of the extent to which antibiotic-resistance strains have resulted in illness and deaths" (*Ref. 8*, p. 1). GAO concluded that the debate over whether antibiotic use should be restricted in agriculture centers around the risk antibiotics pose to human health relative to their benefits to agriculture. The GAO report recommended that "the departments of Agriculture and Health and Human Services work together to develop and implement a plan with specific goals, time frames and resources needed for determining the safe use of antibiotics in agriculture."

1999 European Commission Report, "Opinion of the Scientific Steering Committee on Antimicrobial Resistance"

Due to the public and animal health concerns associated with the increasing rate of antimicrobial resistance development, the European Commission, Directorate-General XXIV, asked that organization's Scientific Steering Committee to "scientifically evaluate the current position regarding the prevalence and development of antimicrobial resistance, examine its implications for human and animal health, particularly with regard to the development and management of infections" (*Ref. 9*, p. 7).

The Committee's report concluded that actions should be taken promptly to reduce the overall use of antimicrobials. Four primary recommendations were forwarded: (1) antimicrobial drugs should be used prudently; (2) infections should be prevented and resistant organisms contained; (3) research for new modalities of prevention and treatment of infections should be undertaken; and (4) the effects of such interventions should be monitored and evaluated.

2000 World Health Organization (WHO) Expert Consultation: "WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food"

The Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) participated in the June 2000 WHO expert consultation, the purpose of which was to develop global principles for minimizing the negative public health impact associated with the use of antimicrobial agents in food-producing animals while providing for their safe and effective use in veterinary medicine.

The principles were part of a comprehensive WHO global strategy for the containment of antimicrobial resistance and provided a framework of recommendations to reduce the overuse and misuse of antimicrobials in food-producing animals for the protection of human health. The principles strengthened and endorsed earlier WHO recommendations such as the need to terminate the use of antimicrobial growth promoters pending comprehensive human health safety evaluations, the need to ensure that all antimicrobials for animal use are only supplied through authorized outlets (e.g., by veterinary prescription), and the need to establish surveillance systems on antimicrobial drug consumption.

2003 Report, "Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific assessment"

In December 2003, the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE), and the World Health Organization (WHO) convened a workshop to "perform a scientific assessment of the antimicrobial resistance risks arising from non-human usage of antimicrobials and to formulate recommendations and options for future risk management actions to be considered by the Codex Alimentarius Commission (Codex) and OIE" (*Ref. 11*, p. 1).

The expert panel's findings from the workshop were documented in a report which contained a number of conclusions, including: 1) "there is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials;" 2) "the amount and pattern of non-human usage of antimicrobials impact the occurrence of resistant bacteria in animals and on food commodities and thereby human exposure to these resistant bacteria;" 3) "the foodborne route is the major transmission pathway for resistant bacteria and resistance genes from food animals to humans, but other routes of transmission exist;" and 4) the "consequences of antimicrobial resistance are particularly severe when pathogens are resistant to antimicrobials critically important in humans" (*Ref. 11*, p. 1).

The expert panel recommended that WHO appoint a group of experts to define which antimicrobials are considered critically important in humans. In addition, the panel commented on the need to further develop risk assessment approaches that adequately address the broad range of potential human health impacts and encouraged OIE to continue its work on risk analysis in coordination with FAO and WHO. Finally, the panel recommended that Codex collaborate with OIE to define a more efficient risk management system for addressing the risks.

2003 Institute of Medicine (IOM) Report, "Microbial Threats to Health: Emergence, Detection and Response"

The Committee on Emerging Microbial Threats to Health in the 21st Century was charged by the IOM to "review the current state of knowledge on the emergence of infectious diseases; assess the capacity of the United States to detect and respond to microbial threats to public health; and identify potential challenges and opportunities for public health actions, both global and domestic, to strengthen capabilities in prevention, detection, and response" (*Ref. 12*, p. 3).

The Committee's report discussed thirteen factors[3] that account for the emergence of new or enhanced microbial threats. The report noted "the convergence of any number of factors can create an environment where infectious diseases can emerge…" (*Ref. 12*, p. 4).

[3] The thirteen factors included 1) microbial adaptation and change, 2) human vulnerability, 3) climate and weather, 4) changing ecosystems, 5) economic development and land use, 6) human demographics and behavior, 7) technology and industry, 8) international travel and commerce, 9) breakdown of public health measures, 10) poverty and social inequality, 11) war and famine, 12) lack of political will, and 13) intent to harm.

In addition, the Committee provided a number of recommended actions for responding to the increasing infectious disease rates prompted by these emergence factors. One of the recommendations was to "more finely target the use of antimicrobials" including expanding efforts to decrease the inappropriate use of antimicrobials in human medicine (*Ref. 12*, p. 6). In addition, the committee recommended that "FDA ban the use of antimicrobials for growth promotion in animals if those classes of antimicrobials are also used in humans" (*Ref. 12*, p. 15).

2004 Report, "Second Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management Options"

As summarized above, a preliminary scientific assessment of the antimicrobial resistance risks arising from non-human usage of antimicrobials was conducted by the first Joint Expert Workshop on Non-Human Antimicrobial Usage in December 2003 in Geneva. The outcome of the first workshop, plus other relevant information, formed the basis for consideration by this second workshop. The report of this second workshop included suggestions to Codex, FAO, WHO, and OIE for moving forward on the issue.

Some of the key conclusions and recommendations in the report included: 1) the risks associated with non-human antimicrobial use and antimicrobial resistance should be part of human safety assessments for regulatory decisions relating to veterinary antimicrobials, 2) the concept of "critically-important" classes of antimicrobials for humans should be developed by WHO, 3) good agricultural practices can reduce the necessity for antimicrobials, 4) there is a need for capacity building and networking to help implement antimicrobial resistance surveillance systems in various countries, and 5) a Codex/OIE Task Force should be established to develop risk management options for antimicrobial resistance related to non-human use of antimicrobials.

2004 United States Government Accountability Office (GAO) Report – "Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risks to Humans from Antibiotic Use in Animals"

In response to a request from Congress, GAO initiated a study in May 2003 to "examine 1) scientific evidence on the transference of antibiotic resistance from animals to humans and extent of potential harm to human health, 2) agencies' efforts to assess and address these risks, 3) the types of data needed to support research on these risks and extent to which the agencies collect these data, 4) use of antibiotics in animals in the United States compared with its key agricultural trading partners and competitors, and 5) information on how use has affected trade" (*Ref. 14*, p. 3).

In its study report, dated April 2004, GAO concluded that antibiotic-resistant bacteria have been transferred from animals to humans. GAO also stated that many of the studies reviewed as part of GAO's research found that this transference from animals to humans poses significant risks for human health. According to GAO's findings, studies have shown two types of evidence related to the transfer of antibiotic-resistant bacteria from animals to humans. First, some studies have provided evidence of associations between changes in antibiotic use in animals and resistance to antibiotics in human bacteria. For example,

researchers have found that antibiotic-resistant *Escherichia coli* (*E. coli*) and *Campylobacter* increased in humans as use of the antibiotics increased in animals.

Second, GAO concluded that studies that have examined the genetic makeup of the bacteria have provided stronger scientific evidence that antibiotic-resistant *Campylobacter* and *Salmonella* bacteria are transferred from animals to humans. In those studies, strains of antibiotic-resistant bacteria infecting humans were indistinguishable from those found in animals, leading researchers to conclude that the animals were the source of human infection.

The GAO report noted that researchers disagree about the extent of the human health risk caused by this transference. According to the report, "many researchers contend that antibiotic use in animals poses significant risk for human health." The GAO report also noted that "a small number of studies contend that the health risks of the transference are minimal" (*Ref. 14*, p. 23).

GAO recommended that "the Commissioner of FDA expedite FDA's risk assessments of the antibiotics used in animals that the agency has identified as critically important to human health to determine if action is necessary to restrict or prohibit animal uses in order to safeguard human health" (*Ref. 14*, p. 48). GAO also recommended that the Secretaries of Agriculture and of Health and Human Services "jointly develop and implement a plan for collecting data on antibiotic use in animals..." (*Ref. 14*, p. 48).

The Department of Health and Human Services (HHS) reviewed and subsequently responded to the 2004 GAO Report on Antibiotic Resistance. In its response, HHS cited 11 additional supporting studies not included in the GAO report, and provided the following comments:

"The draft report presents or refers to significant and growing evidence demonstrating the human health consequences of drug resistant infections related to antibiotic use in agriculture." "These [11 additional] studies, along with those cited in the GAO report, all demonstrate a relationship between the use of antimicrobials in food-producing animals, antibiotic resistance in humans, and adverse human health consequences as a result. We believe that there is a preponderance of evidence that the use of antimicrobials in food-producing animals has adverse human consequences." "There is little evidence to the contrary."

2005 Codex Alimentarius Commission (Codex), "Code of Practice to Minimize and Contain Antimicrobial Resistance" (Code of Practice)

The Code of Practice provides guidance for the responsible and prudent use of antimicrobials in food-producing animals. Its objectives are to minimize adverse impacts on public health associated with the use of antimicrobial drugs in food-producing animals.

The Code of Practice makes a number of recommendations regarding the responsible use of antimicrobials in food-producing animals. For example, the document recommends that responsible use 1) should be controlled by the veterinary profession or other parties with the requisite expertise, and 2) does not include the use for growth promotion of

veterinary antimicrobial drugs that belong to or are able to cause cross-resistance to classes of antimicrobial agents used in humans (or submitted for approval for use in humans) in the absence of an appropriate risk analysis.

IV. Strategies for Controlling Antimicrobial Resistance Are Needed

As summarized above in Section III, the public health concerns associated with the use of medically important antimicrobial drugs in food-producing animals has been the subject of scientific interest for the past 40 years. FDA has reviewed the recommendations provided by the various published reports and, based on this review, believes the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health.

To effectively respond to the public health concerns associated with antimicrobial resistance, FDA believes it is important to broadly consider how antimicrobial drugs are being used. The scientific community generally agrees that antimicrobial drug use is a key driver for the emergence of antimicrobial-resistant bacteria. Since all uses of antimicrobial drugs, including use in both humans and animals, are collectively contributing to the selection pressures that drive antimicrobial resistance development, these drugs must be used judiciously in both humans and animals. It is imperative that strategies for controlling antimicrobial resistance include a consideration of how antimicrobial drugs are being used and measures to address those uses that are injudicious in nature.

V. Current Regulatory Framework

FDA considers the issue of antimicrobial resistance as part of its human food safety review related to new animal drugs used in food-producing animals. FDA considers an antimicrobial new animal drug to be "safe" if the agency concludes that there is "reasonable certainty of no harm to human health" from the proposed use of the drug in food-producing animals. This standard applies to safety evaluations completed prior to new animal drug approvals, as well as to those completed for drugs after approval. If this safety standard is not met before approval, the drug cannot be approved. If safety issues arise after approval, the Federal Food, Drug, and Cosmetic Act (the Act) provides grounds for withdrawal of approval of new animal drug applications for safety reasons. For example, section 512(e)(1)(B) of the Act provides for withdrawal of new animal drug application approvals when new evidence, along with evidence contained in the application, shows that the drug is not shown to be safe under the approved conditions of use. Under this provision, if FDA initiates a withdrawal action, it must produce evidence to show that there is a reasonable basis from which serious questions may be inferred about the ultimate safety of the drug and any substance that may be formed in or on food as a result of use of such drug under approved conditions. Once the agency meets this initial burden, the burden then shifts to the sponsor to demonstrate the safety of the drug (Docket no. 00N-1571, at p. 5, Mar. 16, 2004).

In 2003, FDA implemented new policies for evaluating antimicrobial resistance associated with use of antimicrobial new animal drugs in food-producing animals through the

issuance of Guidance for Industry (GFI) #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern" (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf). This guidance document describes a risk-based assessment process for evaluating antimicrobial resistance associated with the use of antimicrobial new animal drugs in food-producing animals. The guidance also recommends measures for mitigating such risk.

In general, FDA's GFI #152 is premised on the concept that increasing the exposure of bacterial populations to antimicrobial drugs increases the risk of generating resistance to those antimicrobial drugs. Pursuant to this principle, the administration of medically important antimicrobial drugs to entire herds or flocks of food-producing animals (e.g., for production purposes) would represent a use that poses a qualitatively higher risk to public health than the administration of such drugs to individual animals or targeted groups of animals (e.g., to prevent, control, or treat specific diseases). In addition to factors that impact the potential extent of use of the drug, the guidance also considers such factors as the properties of the drug in question including mechanism of action and mechanism of resistance; the prevalence of zoonotic foodborne bacteria in the food-producing animal species for which the drug is intended, and the importance of the drug in question as a therapy in humans. Risk mitigating factors that are considered include such limitations as restricting use of the drug to use by or on the order of a veterinarian.

Although GFI #152 was developed primarily to assess antimicrobial resistance risks as part of the new animal drug approval process, the underlying concept described above is also applicable to safety evaluations conducted for previously-approved antimicrobial new animal drugs. Therefore, FDA considers this same concept when it conducts safety evaluations for currently approved antimicrobial drugs, including those approved for use in animal feed.

From a practical standpoint, however, some significant differences exist between applying the GFI #152 risk assessment approach to the pre-approval process and applying it to safety reviews of currently-approved products. On the pre-approval side, the GFI #152 assessment process, including the various risk mitigation measures described, is taken into consideration by drug sponsors upstream in the drug development process and, in effect, steer product development in a direction that is most consistent with the guidance. On the post-approval side, FDA may examine certain currently-approved products to determine whether such products appear consistent with GFI #152. However, initiating action to withdraw an approved new animal drug application (NADA), in whole or in part, based on the results of a post-approval safety review would require the agency to make the showing required under section 512(e)(1) of the Act.

Alternatively, concerns associated with approved NADAs can sometimes be addressed through more informal processes. For example, in certain cases FDA has worked collaboratively with the sponsor of an NADA to address concerns raised regarding their product and has initiated steps to permit the sponsor to voluntarily withdraw part or all of the NADA or to revise the product labeling to address the concern. This alternative pathway can

in some cases be an effective and expedient mechanism for resolving issues associated with an NADA.

VI. Status of FDA's Current Activities

In general, the antimicrobial new animal drug applications that FDA is addressing as part of its efforts to evaluate the public health concerns associated with the use of medically important antimicrobial drugs in food-producing animals can be divided into two broad categories: 1) those NADAs submitted after the issuance of GFI #152 in 2003 and for which FDA is assessing the microbiological safety of the new animal drug on a pre-approval basis using the principles outlined in GFI #152; and 2) those NADAs approved before the final version of GFI#152 was issued in 2003. In regard to the first category, FDA believes the approach outlined in GFI #152 for evaluating microbiological safety as part of the drug approval process has been very effective. As noted above, that assessment process and the associated risk mitigation measures are usually taken into consideration by industry during the drug development process. Thus, products that ultimately move forward toward approval are those products that include use conditions that are consistent with the guidance and are intended to minimize the extent to which product use would contribute to resistance development.

FDA believes the approach outlined in GFI #152 is scientifically sound and is protective of the public health. However, FDA recognizes that some aspects of the guidance (e.g., the ranking of drugs as to importance to human health) may now need to be updated to reflect the most current and relevant information. In the near future, FDA intends to seek input from experts and the public on updating the guidance.

The second category of products are those antimicrobial NADAs that were approved prior to the implementation of GFI #152. Some of the products in this category include products that were approved for use in food-producing animals more than 30 years ago. Of particular concern, as discussed in section IV, are those products that are approved for use in animal feed for production or growth-enhancing purposes. Although these products are FDA-approved, their approval occurred prior to implementation of current processes for assessing safety with respect to antimicrobial resistance. Furthermore, the scientific understanding regarding antimicrobial resistance has advanced significantly over this time frame and, as discussed earlier in this document, a number of scientific reports have raised public health concerns regarding the use of medically important antimicrobials in food-producing animals.

As a result, FDA is examining available information regarding medically important antimicrobial drugs currently approved for use in food-producing animals and considering potential steps for agency action.

VII. Recommended Principles Regarding Judicious Use in Animals

The continued availability of effective antimicrobial drugs is critically important for combating infectious disease in both humans and animals. This includes the continued availability of feed and water uses of such drugs for managing disease in animal

agriculture. Therefore, it is in the interest of both human and animal health that we take a more proactive approach to considering how antimicrobial drugs are being used, and take steps to assure that such uses are appropriate and necessary for maintaining the health of humans and animals. Using medically important antimicrobial drugs as judiciously as possible is key to minimizing resistance development and preserving the effectiveness of these drugs as therapies for humans and animals. Although FDA applauds the efforts to date by various veterinary and animal producer organizations to institute guidelines for the judicious use of antimicrobial drugs, the agency believes additional steps are needed.

To further address this public and animal health concern, FDA is recommending two additional principles about the appropriate or judicious use of medically important antimicrobial drugs in food-producing animals. These principles are consistent with the recommendations of a number of recent scientific panels or committees referenced earlier in this document including the 1997 and 2000 reports of the WHO, the 2003 IOM Report, and the 2005 Codex Code of Practice.

FDA recognizes the need to collaborate with the animal health and animal producer communities on strategies for phasing in these recommendations. Furthermore, FDA intends to consult with the United States Department of Agriculture (USDA) on such implementation strategies, including the development of a framework for veterinary oversight and consultation requirements. FDA is committed to assuring that the public health is protected while also assuring that the health needs of animals are addressed.

Principle: *The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health.*

In light of the risk that antimicrobial resistance poses to public health, FDA believes the use of medically important antimicrobial drugs in food-producing animals for production purposes (e.g., to promote growth or improve feed efficiency) represents an injudicious use of these important drugs. Production uses are not directed at any specifically identified disease, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products. In contrast, FDA considers uses that are associated with the treatment, control, or prevention of specific diseases, including administration through feed and water, to be uses that are necessary for assuring the health of food-producing animals.

Although some may have concerns that the use of medically important antimicrobial drugs in food-producing animals for disease prevention purposes is not an appropriate or judicious use, FDA believes that some prevention indications are necessary and judicious. . Veterinary involvement in the decision-making process associated with the use of medically important antimicrobial drugs is an important aspect of assuring appropriate use, including judicious preventive use. Important factors to consider when determining the appropriateness of a preventive use include whether there is: (1) evidence of effectiveness, (2) evidence that such a preventive use is consistent with accepted veterinary practice, (3) evidence that the use is linked to a specific etiologic agent, (4) evidence that the use is appropriately targeted, and (5) evidence that no reasonable alternatives for intervention exist.

Principle: *The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation.*

Most of the feed-use antimicrobial drugs are currently approved for over-the-counter use in food-producing animals for purposes that include the treatment, control, and prevention of disease as well as for production purposes (i.e., for growth promotion uses such as increased rate of weight gain). In addition to instituting measures that would limit use of medically important antimicrobial drugs in food-producing animals to uses that are considered necessary to assure the animals' health, FDA also believes it is important to phase-in the practice of including veterinary oversight or consultation in the use of these drugs. As noted above, FDA believes that this practice is an important mechanism for helping to assure appropriate use. Veterinarians can play a critical role in the diagnosis of disease and in the decision-making process related to instituting measures to treat, control, or prevent disease. FDA recognizes that the nature of veterinary involvement can vary due to numerous factors such as geographic location and animal production setting. In fact, there are limited numbers of large animal veterinarians, which can make consultation or oversight challenging in certain situations. For example, some animal disease events require immediate attention.. In some cases, veterinarians may be directly diagnosing and administering therapies, while in other cases they are visiting and consulting with producers periodically to establish customized disease management protocols for that producer's herd or flock. Of key importance to FDA is the fact that, in both of these cases, the veterinarian is involved in the decision-making process regarding antimicrobial drug use. FDA recognizes that increasing veterinary involvement in the use of antimicrobial drugs has significant practical implications for animal producers, veterinary practitioners, and the veterinary profession as whole. Therefore, FDA is particularly interested in receiving comments on strategies for effectively phasing-in such a change.

VIII. Conclusion

In order to minimize the development of antimicrobial resistance, FDA believes that steps need to be taken to ensure the judicious use of medically important antimicrobial drugs in animal agriculture. Such steps should include phased-in measures that would limit medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health and that include veterinary oversight or consultation. Such limitations would reduce overall medically important antimicrobial drug use levels, thereby reducing antimicrobial resistance selection pressure, while still maintaining the availability of these drugs for appropriate use.

FDA is committed to working with animal drug sponsors, the veterinary and public health communities, the animal agriculture community, and all other interested stakeholders in developing a strategy to address antimicrobial resistance concerns in a manner that is protective of both human and animal health. In regard to comments on this draft guidance, FDA is especially interested in hearing from the public and stakeholders on how the agency can best use its regulatory authority and take non-regulatory measures to support the two principles, while minimizing adverse impacts on animal health and disruption to the animal agriculture industry.

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