FDA RESPONSE TO COMMENTS

on

A Proposed Framework for Evaluating and Assuring the Human Food Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals

Food and Drug Administration (FDA)
Center for Veterinary Medicine (CVM)
December 1999

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Introduction and Background

1. Introduction

In the Federal Register of November 18, 1998 (63 FR 64094), Food and Drug Administration (FDA) published a notice of availability of a draft guidance document entitled "Guidance For Industry: Evaluation of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals" (GFI #78). This Guidance For Industry (GFI) can be found at http://www.fda.gov/cvm/fda/TOCs/final13.htm. The publication of this draft GFI was the first step in the Agency's consideration of the issues related to the use of antimicrobial new animal drugs in food-producing animals. It lays out the agency's rationale for its current thinking about its authority under the Federal Food, Drug, and Cosmetic Act (the Act) to consider the human health impact of the microbial effects associated with the use of antimicrobial new animal drugs in food-producing animals.

In the Federal Register of January 6, 1999 (64 FR 887), FDA announced the availability of a Framework Document entitled "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals" (Framework Document). This Framework Document was the second step in the agency's consideration of issues related to the use of antimicrobial new animal drugs in food-producing animals. FDA made the Framework Document available to the public to initiate discussions with the scientific community and other interested parties on the agency's thinking about appropriate underlying concepts to be used to develop microbial safety policies protective of the public health. This Framework Document is frequently referred to as the Framework Document. It is related to GFI # 78 in that it sets out a conceptual risk-based framework for evaluating the microbial safety (related to human health impact) of antimicrobial new animal drugs intended for use in food-producing animals.

On January 25 and 26, 1999, the FDA held a meeting of the Veterinary Medicine Advisory Committee (VMAC) on the Framework Document to allow members to publicly consider answers to specific questions. The goal of the meeting was "to find the balance that protects human health and gives veterinarians the tools they need to treat animals."

FDA stated that it would review the transcript of the VMAC meeting and any comments on the Framework Document that were submitted to the Dockets, and publish the analysis. This is the agency analysis of the transcript and comments.

FDA received more than 50 comments to Dockets 98D-0969 and 98D-1146 (the Dockets for GFI #78 and the Framework Document). These comments originated from a number of sources including individual members and committees of Congress (3), individual physicians, microbiologists, and hospitals (6), individual citizens and organizations representing consumers (16), animal drug and feed industries (3), individual veterinarians and organizations representing veterinarians (5), environmental organizations (3), individual producers and organizations representing producers (14), and another federal agency (1).

2. Background

The issue of antimicrobial use in food animals has been controversial for more than three decades. The FDA first called for several restrictions on antimicrobial use in feed in 1977. That proposal has generated several studies and reports. Definitive answers about the safety of antimicrobial use in animals remain scientifically challenging, but we are continuing to uncover more truths and, more importantly, have begun updating FDA's process for determining whether antimicrobial products can be safely used in food animals.

The use of antibiotics to treat disease in food-producing animals started in the mid-1940s. The scientific debate over the possible public health risks posed by such use started more than 30 years ago, when researchers first reported that the addition of streptomycin to chicken feed increased the rate of growth of the chickens. The introduction of antibiotics in commercial feed for cattle, pigs, and chickens started in the early 1950s. Soon after livestock producers began using antimicrobials in food-producing animals, scientists began studying the possible effects of long-term use of antibiotics.

In recent years, concerns about the use of antimicrobial products in food-producing animals have focused on human food safety because foods of animal origin are identified as vehicles of food borne disease in humans. As a result of treatment of the animal with antibiotics, food borne microbes may also be resistant to the antibiotics used to treat human disease. These concerns have led to a number of studies.

The following is a brief review of the studies and reports to date.

1960 Netherthrope Committee
It was formed in the UK to consider possible human health implications from the use of subtherapeutic antibiotics in livestock and concluded that there was no evidence of a human health hazard associated with the use.

1969 Swann Committee
Also formed in the UK, the committee reported no hazard to humans or animals from the use of antibiotics in poultry or swine. However, it linked an outbreak of salmonellosis in humans to the therapeutic use of antibiotics in sick calves. The committee recommended:

1. Antibiotics used in animals should be divided into "feed" or "therapeutic" classes.
2. The "feed" antibiotic class should not include drugs used therapeutically in humans or animals.
3. "Therapeutic" antibiotics should be available only by prescription.

1970 FDA Task Force
The task force report, "The Use of Antibiotics in Animal Feeds," concluded:

1. The use of subtherapeutic amounts of antimicrobials favored the selection and development of resistant bacteria.
2. Animals receiving antimicrobial treatment may serve as a reservoir of antibiotic resistant pathogens that can produce human disease.
3. The prevalence of multi-resistant bacteria in animals has increased due to the use of antimicrobials.
4. Resistant bacteria are present in meat and meat products.
5. There has been an increase in the prevalence of antimicrobial resistant bacteria in man.

Based on the report's recommendations, CVM (the Center) began requiring microbiological safety studies for non-therapeutic uses. The focus of these studies was to preserve efficacy and safety of antibiotics for animal uses, and the safety evaluation included an evaluation of human health concerns.

1977 FDA Proposal
In 1977, FDA proposed to withdraw the subtherapeutic uses of penicillin and the tetracyclines from animal feeds when used alone or in combination. These two drugs were chosen because of their importance in human medicine.

The proposal was criticized at the time because of a lack of epidemiological evidence to show that the drug-resistant bacteria of animal origin are commonly transmitted to humans and cause serious illness. Critics argued that, while antibiotics used in animals select for resistant bacteria, the transfer of these bacteria from animals to humans is rare. Also, the critics said, no evidence showed that "any transferred organisms actually survive or cause disease in humans." The critics argued instead that the increased antibiotic resistance of bacteria found in humans was a result of the use of antibiotics in human medicine.

1980 NAS Study
As a result of the 1977 proposal, several studies were started. In 1978, FDA began to work with the National Academy of Sciences (NAS) to study the issue. In 1979, the Congress required FDA to spend $1.5 million of its appropriations for a study of the antibiotic issue, to be conducted by NAS. The NAS study was finished in 1980. It concluded that existing data had neither proved nor disproved the potential hazards to human health from subtherapeutic antimicrobials use in animal feeds.

1984 NRDC Petition
In 1984, the Natural Resources Defense Council, Inc., (NRDC) petitioned the Department of Health and Human Services (HHS) to suspend immediately approval of the subtherapeutic use of penicillin and tetracyclines in food animals by invoking the imminent hazard provision of the Act, 21 U.S.C. Sec. 360b(e)(1). That provision authorizes the Secretary of HHS to suspend approval of an application for the use of a new animal drug if an imminent hazard exists to the health of man or to the animals for which the drug is intended. NRDC based its case on several studies, two by Holmberg, et al., at the Centers for Disease Control and Prevention (CDC) in

Atlanta, GA and one published by Thomas O'Brien, et al., in the *New England Journal of Medicine*. However, in November 1985, HHS denied the petition on the basis that an "imminent hazard" had not been demonstrated. This decision was based on an analysis of the NRDC's evidence as well as scientific evidence, information, and opinions coming out of the January 1985 public hearing and other relevant data collected and analyzed by FDA.

1984 King County Study

In 1981, the House Appropriations Committee provided money in FDA's budget for a definitive epidemiological study of the antibiotics in animal feeds issue. The Committee stated that FDA should hold in abeyance any implementation of the proposed withdrawal pending completion of the studies and reevaluation of FDA's concerns. FDA contracted with the Communicable Disease Control Section of the Seattle-King County Department of Public Health to review the possibility of the movement of bacteria from chickens to humans. The study focused on poultry workers, slaughterhouse workers, and consumers. The report, "Surveillance of the Flow of *Salmonella* and *Campylobacter* in a Community," found that *Campylobacter jejuni* was more common than *Salmonella* on poultry. Also, it found that *C. jejuni* "does appear to flow from chickens to man via consumption of poultry products." The report stated that the "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."

1987 FDA Report

In its report, "Antibiotics in Animal Feeds: An Assessment of Scientific Data Concerning Their Safety," FDA concluded that the therapeutic use of antibiotics would not significantly contribute to the frequency of resistant organisms because of the pattern of use of these products. Therapeutic use is typically for a select number of animals and for a short duration, situations that are not likely to lead to antibiotic resistance, the report said.

1988 IOM Review

In 1988, the Institute of Medicine (IOM) again reviewed all the information about the antibiotic resistance issue available. An expert Committee was convened to determine the human health risks associated with the practice of feeding subtherapeutic levels of penicillin and tetracyclines to animals for growth promotion, feed efficiency, and disease prevention. In the report, "Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed," the Committee developed a risk-analysis model, using data only on *Salmonella* infections that resulted in human death. The Committee found a considerable amount of indirect evidence implicating both subtherapeutic and therapeutic use of antimicrobials as a potential human health hazard, but did not find data demonstrating that use of subtherapeutic penicillin or tetracycline directly caused a human to die from salmonellosis. The Committee strongly recommended further study of the issue.

1995 ASM Report

The American Society of Microbiology (ASM), which includes members who specialize in medical and animal microbiology, issued a report in 1995 that cited grave concerns about both human and animal antibiotic use and the rise in antimicrobial resistance. The report advocated a significant increase in resistance monitoring in the U.S., more education about the use and risks

of antimicrobials, and more basic research designed to develop new antimicrobials and vaccines and disease prevention measures. The report criticized overuse of antibacterials in human medicine, but also pointed out the large use in food production, which was partly attributed to the consolidation of farms to facilities with large numbers of confined animals. The report made it clear that the antibiotic resistance problem is global. The ASM report was a precursor to involvement by the United Nation's World Health Organization (WHO).

1997 WHO Meeting

In October 1997, WHO convened a meeting of experts in Berlin, Germany, to review the question of whether the use of antimicrobials in animals leads to antimicrobial resistance in humans. The experts sought to define potential medical problems that could arise from antimicrobial use in livestock and to recommend actions that the WHO should take. The group of experts recommended against using antimicrobials for growth promotion if those antimicrobials are also used in human medicine or can induce cross-resistance to antimicrobials used for human medical therapy. The group also recommended that research be conducted on non-antimicrobial growth-promoters and urged that the risk to human health from use of antimicrobials in food animals be accurately assessed. The group called for enhanced monitoring of resistance among isolates of enteric bacteria from food animals and food of animal origin. In addition, the group recommended managing risk at the producer level through the prudent use of antimicrobials.

1998 WHO Meeting

In June 1998, the WHO held another meeting, this time in Geneva, Switzerland, to specifically address the use of quinolones in food-producing animals. The participants agreed that the use of antimicrobials will cause resistance to develop and that there is a potential human health hazard from resistant *Salmonella*, *E. coli*, and *Campylobacter* organisms transferred to humans through the food supply. However, the experts also agreed that antimicrobial drugs, including quinolones in certain instances, are needed to treat sick animals, and urged more research on the possible human health effects from the use of these drugs in animals.

1998 CSPI Report

In May 1998, the Center for Science in the Public Interest (CSPI), in a coalition that included 15 other health and consumer groups, produced a comprehensive report on the antibiotic resistance problem. The focus of the report was on human antimicrobial use; however CSPI made several recommendations regarding the use of antimicrobials in veterinary medicine. The report recommended that FDA ban all subtherapeutic uses of antimicrobial agents that are used in human medicine or might select for cross resistance to antimicrobials used in human medicine. The organization also expressed concerns about new human antimicrobials that may be at risk due to use of the same class of drugs in agriculture, at either subtherapeutic or therapeutic levels. Development of resistance to certain classes of drugs that are considered vital in human medical therapy, such as the fluoroquinolones, would cause particular concern. For this reason, CSPI recommended that FDA repeal approval of fluoroquinolones in poultry and allow additional approvals of fluoroquinolones only if the drug sponsor can show that those uses would not reduce the drug's effectiveness for human medical therapy.

1998 NRC Report
In July 1998, the National Research Council (NRC) produced a report reviewing antimicrobial resistance issues in broad terms. The NRC recommended establishing national databases to support scientific process and policy development for approval and use of antibiotics in food animals. The NRC 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."

1998 EU Action
The European Union (EU) recently took action to minimize the agricultural use of antimicrobial drugs. In December 1998, health ministers for the EU voted to ban four antibiotics that are widely used at subtherapeutic levels to promote animal growth. The ban on using bacitracin zinc, spiramycin, tylosin, and virginiamycin in animal feed became effective for the fifteen member states of the EU on July 1, 1999.

1999 GAO Reports
In April 1999, the General Accounting Office (GAO) published two reports on antibiotic resistance. These are FOOD SAFETY The Agricultural Use of Antibiotics and Its Implications for Human Health (GAO/RCED-99-74 Food Safety) and ANTIMICROBIAL RESISTANCE Data to Assess Public Health Threat From Resistant Bacteria Are Limited (GAO/HEHS/NSIAD/RCED-99-132).

In the FOOD SAFETY report, GAO notes that the use of antibiotics in agriculture is only one of several factors that contributes to antibiotic resistance in humans for pathogens that are not foodborne and that the debate extends to antibiotics used on plants. GAO acknowledges the complexity of the antimicrobial resistance issue and reports that FDA recently proposed a framework for evaluating the safety of antibiotics used in food-producing animals. GAO encouraged the Departments of Agriculture and Health and Human Services to 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.

Based on the GAO findings, the House and Senate Appropriations Committees direct the Secretaries of Agriculture and Health and Human Services to implement the GAO report's recommendation and develop a joint strategy for addressing resistance. The USDA and FDA are to report to Congress by January 2000 on that strategy. (H. Rep. No. 106-157 (1999), S. Rep. No. 106-80 (1999), and H. Rep. No. 106-354 (1999)).

In the ANTIBIOTIC RESISTANCE report, GAO states that the full extent of the antibiotic resistance problem remains unknown. While a number of federal and federally funded agencies are collecting information about different aspects of antibacterial resistance, there is little information about, e.g. antibacterial use, particularly in animals, and antibacterial residues in places other than food.

Current Work in the CVM

Since 1988, CVM has approved new therapeutic antimicrobials for use in animals as prescription-only products. This prescription-only policy is based on the need to assure the proper use of antimicrobials through precise diagnosis and correct treatment of disease to minimize animal suffering and to avoid drug residues in food. Antimicrobial products for use in animals have to meet FDA's standards for safety, efficacy, and quality to be approved in the United States.

When antimicrobial products are intended for use in food-producing animals, safety considerations include the evaluation of data to ensure that residues in food derived from treated animals are safe for human consumption. In the past, microbiological safety studies were required only for antimicrobials to be used in feed for more than 14 days. These studies examined resistance patterns and pathogen load.

In the 1990s, several scientists raised concerns about the therapeutic use of fluoroquinolone antibiotics in food-producing animals. The scientists said the use could lead to enteric disease in humans associated with fluoroquinolone-resistant zoonotic pathogens. Adding to that concern were reports of a temporal association between the approval of fluoroquinolones for therapeutic use in poultry in Europe and the emergence of a fluoroquinolone-resistant *Campylobacter* spp. from humans.

To further investigate the public health concerns regarding the potential impact of fluoroquinolone use in food-producing animals and to determine whether the 1987 FDA report (which concluded that therapeutic antimicrobials used for short duration were safe) was still valid, FDA held a Joint Advisory Committee meeting in 1994 that included the CVM Veterinary Medicine Advisory Committee (VMAC) and the Center for Drug Evaluation and Research's Anti-infective Drugs Advisory Committee. The joint committee recommended that fluoroquinolones for poultry be approved, but that the use of the drugs should be limited to prescription only, that no extra-label use should be allowed, and that resistance should be monitored after the product was approved.

CVM created a Fluoroquinolone Working Group to address the points raised by the joint committee. The Working Group offered seven recommendations, all of which were accepted by CVM, and subsequently the use of fluoroquinolones was approved for poultry. As suggested in the recommendations, the sponsors agreed to provide baseline susceptibility information and to conduct continuing monitoring of target animal pathogens through the post-approval monitoring program.

More recently, scientists have detected a new multi-resistant pathogen, *Salmonella enterica* serotype Typhimurium Definitive Type 104 (DT104). The organism carries chromosomally integrated resistance to ampicillin, chloramphenicol, streptomycin, sulphonamides, and tetracycline. This chromosomally integrated resistance is unique and raises concerns about the establishment of a reservoir of multi-drug resistant organisms that are zoonotic enteric pathogens that may become endemic in food-animal microbial populations. In addition to the chromosomally borne penta-resistance, the organism seems to be losing its susceptibility to

quinolone and trimethoprim antibiotics and has been recently shown to carry additional florfenicol and spectinomycin resistance.

A report from the UK suggests that infections caused by DT104 may be associated with greater morbidity and mortality than other infections by *Salmonella*. An association has been noted between loss of susceptibility to fluoroquinolones among DT104 isolates and the approval and use of a fluoroquinolone for veterinary therapeutic use in the UK. This organism has also been identified in livestock and poultry in the U.S. Human disease caused by DT104 in the U.S. has been associated with unpasteurized dairy products and direct contact with livestock.

DT104 is currently epidemic in human and animal populations in Great Britain and has been isolated from most countries in Europe. The organism more recently has been found in the U.S. The most notable outbreak of zoonotic DT104 occurred on a dairy farm in Vermont.

The DT104 findings caused FDA to aggressively move ahead with plans to change its regulatory approach for approving antimicrobial products. The discovery of DT104 was a turning point for FDA, and led to the development of a proposed regulatory course for the Agency.

Reports from the scientific and public health communities, both domestically and internationally, have identified concerns about the relationship between the approval of fluoroquinolones for therapeutic use in food-producing animals and the development of fluoroquinolone resistance in *Campylobacter*. The approval of these drugs in food-producing animals in the Netherlands, the UK, and Spain temporally preceded increases in resistance in *Campylobacter* isolates from humans. Despite several restrictions placed on the use of the two approved poultry fluoroquinolone products in the U.S., ciprofloxacin-resistant *Campylobacter* were recently isolated from 20% of domestic retail chicken products sampled. Molecular subtyping revealed an association between resistant *C. jejuni* strains from chicken products and *C. jejuni* strains from domestically acquired human cases of campylobacteriosis.

Framework Document

FDA's concept of an appropriate regulatory approach for antimicrobial approvals was made public in the "Framework Document," ("A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals"). It is available on the CVM Home Page at http://www.fda.gov/cvm/fda/infores/vmac/antim18.htm or http://www.fda.gov/cvm/fda/infores/vmac/antim18.pdf.

The document was released to the public December 9, 1998, and the comment period was open until April 6, 1999.

General Comments on the Framework Document

General comments received in support of the Framework Document applauded the agency in its effort to address antimicrobial resistance and to establish a new policy by which antibiotics for food-producing animals are reviewed, approved and monitored as part of the agency's mission to protect the public health. One comment strongly supported the approach taken by FDA and considered both the guidance and Framework Document to be major steps forward. Some of the comments indicated a shared concern that antimicrobial resistance in humans is a serious emerging problem and use of antimicrobials in food-producing animals contributes to the problem. Efforts to preserve the effectiveness of antibiotics against infections in humans are a shared public health goal achievable through collaborative efforts of industry, academia, consumers and government. Other comments supported FDA for including new criteria in the approval process and for considering antibiotic resistance in pre-approval review. Several comments, although supportive of the Framework Document, expressed concern that the agency needed to progress towards an implementation phase before the strategy would have any real meaning. One comment suggested that the Framework Document be translated to regulation with added enforcement measures before a public health crisis arises.

Negative comments were received that described weaknesses in the Framework Document. One comment interpreted the document as a general statement of overreaction by the agency. The document was too uncertain, complex, and restrictive in comparison to the actual public health risk. It was noted to be a solution to a poorly understood problem, making faulty assumptions and not supported by scientific evidence. One comment reported that the document was not a conceptual risk-based document but rather a hazard-based Framework Document based on potential risk. It was suggested that the document have a more flexible approach. It was interpreted that the food animal industry must prove that use in animal agriculture is not the cause of human harm. A comment suggested that more data be collected and analyzed before recommendations are made and implemented.

Many of the comments expressed concern that antibiotic use in food animals threatens the effectiveness of antimicrobials in humans. Some comments stated that FDA should restrict or ban antimicrobials that are used in humans, those that select for cross resistance in humans, and/or all antibiotics used in humans from administration in animal feeds. Other comments stated that FDA should ban all Category I drugs from use in animals. Another comment suggested that FDA prohibit the use of any human-use antimicrobial drugs if there is evidence of an increase in antimicrobial resistance within the food animal population. Another comment stated that FDA should focus its limited resources on reviewing and eliminating existing approvals that pose a threat to public health. Some comments stated that FDA's regulatory oversight should be consistent with WHO's and CDC's recommendations to remove antimicrobials from animal feeds.

A few comments expressed specific concerns about the use of fluoroquinolones in food-producing animals that ranged from repealing the poultry approvals to collecting and evaluating data from the post-approval monitoring studies prior to taking regulatory action.

Another comment stated that the Framework Document should be made stronger in order to protect the efficacy of antibiotics vital to human health. One comment noted that the Framework Document limits but does not ban essential drugs for human use from animals. Another comment stated that the document relies on developing information for which the agency does not have reasonable methods of discovery. The document establishes required decisions and policies that require subjective judgements by the agency.

Several comments were received that recommended CVM use the current human drug approach (prudent use, education, and monitoring) instead of a complicated regulatory process and incorporate judicious use and current food safety efforts (to include producers, Hazard Analysis Critical Control Point (HACCP), and improved food processing technologies such as irradiation). These comments asked that the Agency fund educational programs directed at veterinarians and food producers to promote judicious therapeutic use of antimicrobials for food-producing animals.

Several of the comments asserted that because serious human health dangers are caused by subtherapeutic use of antimicrobials that are also used in humans, the Framework Document must identify and eliminate non-essential antimicrobial drug use, regardless of category. Antibiotics should be used to treat sick animals only. Some of the comments referred to the fact that the EU recognized the important role of veterinary use of antibiotics in the development of antibiotic resistance and has banned the use of specific growth promoters based on their impact to human medicine. FDA was urged to also ban the use of antimicrobials for subtherapeutic use and growth promotion. The Framework Document was seen as favoring agriculture and animal production at the expense of human health.

Several comments expressed a commitment to work with FDA to reduce the emergence of antimicrobial resistance.

The VMAC concluded that "the proposed Framework Document to protect public health by ensuring that the efficacy of human antimicrobial therapies is not compromised due to the use of antimicrobials in food animals, while providing for the safe use of antimicrobials in food animals, provides a basis for achieving this goal. A sound scientific basis for the Framework Document must be put together, utilizing a diverse group of experts working in microbiology from government, industry and academia. This should be done quickly."

FDA Response:

The majority of the general comments on the Framework Document agreed that the agency needs to address the issue of use of antimicrobial drugs in food-producing animals. However, the suggested approaches are conflicting. FDA agrees that ideally more data should be collected to more clearly determine the extent of the impact on human health caused by antimicrobial use in food-producing animals and therefore intends to continue funding surveillance and research programs concerned with antimicrobial resistance. FDA also supports programs, initiated by veterinary and producer organizations and the Agency, that promote judicious use of antimicrobials and has funded several projects on prudent use

and education. However, FDA is responsible for ensuring that there is a reasonable certainty that the use of antimicrobial drugs in food-producing animals does not result in adverse health consequences to humans. FDA agrees with the comments stating that the scientific evidence is robust enough to further evaluate the microbial safety of antimicrobial drugs intended for use in food-producing animals.

It is important to note that the Framework Document itself does not represent regulatory action. Instead, it lays out a conceptual risk-based strategy for evaluating the microbial safety of antimicrobial drugs intended for use in food-producing animals. FDA intended the document to initiate discussions with the scientific community and other interested parties on the agency's thinking about appropriate underlying concepts to be used to develop policy protective of the public health.

Although the agency recognizes that the use of antimicrobial drugs in food-producing animals is important to animal health, FDA's primary public health goal must be to protect the public health by preserving the long-term effectiveness of antimicrobial drugs for treating diseases of humans. At this time, FDA believes there is sufficient evidence concerning the impact of antimicrobial use in animals to require that applicants who petition the agency for approval of new animal drug applications for antimicrobials to be used in food-producing animals address the issue of microbial safety. GFI #78 and the Framework Document state that FDA believes it is necessary to evaluate the human health impact of the microbial effects associated with all uses of all antimicrobial new animal drugs in food-producing animals. The public health concerns are not limited to the growth promotion or feed uses of antimicrobials but also extend to therapeutic and prophylactic uses. All uses can be significant contributors to the pool of resistant microorganisms that enter the food chain.

2. Scientific Basis of the Framework Document

Several comments asserted that the agency has not adequately characterized the risk to humans and has not presented the science that demonstrates the probability of human disease occurrence resulting from that resistance. One comment refers to a FDA survey conducted 20 years ago that found no correlation between antibiotic resistance and antibiotic usage in food animals. Additional comments asked that the agency propose a research agenda. Other comments stated that the document was based on sound principles and scientific evidence. One of the comments stated that the strength of the proposed Framework Document is that it permits "science–based evaluation of individual animal drugs without requiring broad *a priori* consensus on risk to humans." Another comment purported that the Framework Document offers a consistent scientific international approach to the use of certain antibiotics.

Several comments asserted or imply that the basic premise of the Framework Document is speculative with weak, controversial scientific underpinnings and does not support such a broad regulatory program. One comment asks for evidence that human antibiotic-resistant infections of clinical significance have been acquired from federally inspected food. Other comments stated that evidence that a public health hazard exists from the use of antimicrobials in food-

producing animals has been accumulating for years and the agency has been extremely lax in not regulating the matter.

Several comments disagree with scientific statements or assumptions in the Framework Document or indicate that more data are needed to support assumptions. These comments disagree with such things as the cause of vancomycin-resistant enterococci, choosing to distinguish between enteric and non-enteric human pathogens in the categorization scheme, and the implied assumption that quantitative viable counts of pathogens above a normal baseline will present a greater risk to public health. Several other comments referenced numerous scientific publications and reports that support the validity of a public health risk from the use of antimicrobials in food-producing animals.

Specific comments on antibiotic resistance indicate opposing views. On the one hand, a comment asserted that the transfer of resistance does not respect the boundaries between animals, people, and the environment. Several comments expressed the view that current data do not indicate that antibiotic use in animal agriculture is a major culprit in increasing antibiotic resistance among microbial pathogens in humans. For example, one comment stated that antibiotic resistance (including multiple resistance) is very common in people on or off antibiotics. How much of it is related to human use, agricultural use, or veterinary use is unknown. Another stated that there is no documented case of treatment failure resulting from a foodborne disease caused by an animal drug.

A few comments asserted that the major resistance problem is the abuse of antibacterial drugs in humans. Additional comments expressed opposition to the Framework Document approach unless the agency takes steps to regulate inappropriate antibiotic use in humans, which is believed to have a significant role in the loss of effectiveness of these drugs in humans. Another comment stated that recent approvals of new human antimicrobials, which contradicts the predictions of a dire emergency, permit the availability of alternative treatments to life-threatening diseases and, if necessary, the FDA can expedite approvals of important new drugs for humans.

Several comments expressed concern about the use of scientific references in the Framework Document. The comments asserted that there is a lack of balance in the references cited in the document, that the document contained insufficient data to support the regulatory changes proposed, and that a thorough evaluation of the scientific literature is needed. One comment criticized specific articles and reports cited in the Framework Document. The comment stated that related data, had it been available to the authors of the Framework Document, might have altered the interpretation of some studies. This comment also notes that advisory committees in the US and Europe determined that some of these studies did not indicate a health risk from the use of certain drugs in animals. Other comments agreed with the agency's interpretation of the available scientific literature and mentioned other references, which supported the agency's position but were not mentioned in the Framework Document.

FDA Response:

The agency agrees that regulatory policies should be based on sound science whenever possible. FDA is in the process of assessing the risk to human health for resistant campylobacteriosis associated with the use of fluoroquinolones in broiler chickens. This risk assessment will be discussed at a public meeting in Rockville MD on December 9 and 10, 1999 and will be available for public comment. Based on its evaluation of available surveillance data and the current scientific literature, FDA believes that there is adequate scientific evidence to move forward and implement new requirements to evaluate the development of antimicrobial resistance in enteric bacteria associated with the use of antimicrobials in food-producing animals.

FDA has also proposed a multi-year research agenda under the National Food Safety Initiative that addresses many aspects of antimicrobial resistance. Several projects are currently underway; more specific information can be obtained from the FDA homepage at http://www.fda.gov/cvm).

The FDA does not agree with the comments indicating that the scientific evidence to support the Framework Document is weak and controversial. There is a great deal of scientific information concerning the development of resistant bacteria following use of drugs in food-producing animals to challenge previously accepted assumptions concerning the impact of animal uses of antimicrobial drugs on human health.

Selective pressure resulting from widespread antimicrobial use is the underlying force in the development of resistance. FDA agrees that the development of resistant bacteria that cause human infections or compromise human medical therapy that are not foodborne is primarily the result of use of antimicrobial drugs in humans. However, for foodborne pathogens, especially for those pathogens such as *Salmonella* that are rarely transferred from person to person in industrialized countries, the predominant source of antibiotic resistance is use of antimicrobials in food-producing animals. For example, susceptible nontyphoidal salmonellosis in humans in the United States is acquired primarily through contaminated foods of animal origin. This has been demonstrated through several different types of foodborne disease follow-up investigations, including laboratory surveillance, molecular subtyping, outbreak investigations, and studies on infectious dose and carriage rates (Ref 1,2,3).

Epidemiologic evidence supports the conclusion that resistant foodborne pathogens are present on animals as a result of drug use in animals. In the United States, 13.5% of the *Campylobacter* isolated from chicken carcasses are fluoroquinolone resistant (1998 data from the U.S. National Antimicrobial Resistance Monitoring System (NARMS) at http://www.fda.gov/cvm). Holmberg, et al. were the first to document an outbreak of salmonellosis in people caused by multi-drug-resistant *Salmonella* from eating hamburger originating from South Dakota beef cattle fed subtherapeutic chlortetracycline for growth promotion (Ref 1). The Centers for Disease Control and Prevention published an extensive review of epidemiology studies that focused on human foodborne infections caused by drug-resistant *Salmonella* and concluded that the resistant infections were acquired through contaminated foods of animal origin (Ref 4,5).

Much of the current scientific literature, primarily that published in the last 10 years, provides evidence to substantiate this position.

Recent emergence of a resistant foodborne pathogen that has a food animal reservoir is illustrated by DT104. DT104 is a multi-drug resistant pathogen that is currently epidemic in human and food animal populations in Great Britain and has been isolated from several countries in Europe (Ref 6,7,8). DT104 carries chromosomal integrated resistance to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracycline. A report from the UK suggests that infections caused by DT104 may be associated with greater morbidity and mortality than infections by less resistant serotypes of *Salmonella* (Ref 9). An association has been noted between loss of susceptibility to fluoroquinolones among DT104 isolates and the approval and use of a fluoroquinolone for veterinary therapeutic use in the UK (Ref 10,11,12). This organism has also been identified in livestock and poultry in the United States (Ref 13,14,15). Human disease caused by DT104 in the United States has been associated with unpasteurized dairy products and direct contact with livestock (Ref 15).

Reports from the scientific and public health communities, both domestically and internationally, have identified a relationship between the approval of fluoroquinolones for therapeutic use in food-producing animals and the development of fluoroquinolone resistance in *Campylobacter* in animals and humans. The approval of these drugs in food-producing animals in the Netherlands (Ref 16,17), the United Kingdom (Ref 18) and Spain (Ref 19,20) temporally preceded increases in resistance in *Campylobacter* isolates from treated animals and ill humans. Despite several restrictions placed on the use of the two approved poultry fluoroquinolone products in the United States, fluoroquinolone-resistant *Campylobacter* were recently isolated from 20 percent of domestic retail chicken products sampled (Ref 21). Molecular subtyping revealed an association between resistant *C. jejuni* strains from chicken products and *C. jejuni* strains from domestically acquired human cases of campylobacteriosis (Ref 21).

There have been reports that the use of the glycopeptide avoparcin as a growth promoter created a reservoir of vancomycin-resistant *Enterococcus faecium* in food-producing animals in Europe that was subsequently transferred to humans. Until recently, there was no effective antimicrobial therapy available for many vancomycin-resistant enterococci (VRE) (Ref 22) and these infections have been associated with increased mortality (Ref 23). Recently, FDA approved Synercid® (quinupristin and dalfopristin) and some comments make reference to other new entity antimicrobial drugs that are in early stages of development. In Europe, colonization with VRE, a precursor of infection, occurs in the community, possibly from foodborne sources (Ref 24). In the United States, colonization has been demonstrated only in the hospital setting (Ref 25). It has been postulated that undetected community VRE transmission may be occurring at low levels (Ref 26).

Epidemiology studies in several countries in Europe have shown an association between the recovery of VRE from food animals, primarily poultry, and the use of avoparcin at subtherapeutic doses for growth promotion (Ref 27,28,29,24,30). A comparison of conventionally reared poultry flocks that used avoparcin to organically reared poultry flocks that used no growth promoters found no VRE in organically reared birds and VRE in the majority of the conventionally reared flocks (Ref 27). Because conventional and organic production differs

in several respects other than growth promoter usage, the investigators next compared conventional swine and poultry flocks that used and did not use avoparcin. The investigators reported a strong, statistically significant association between the presence of VRE in the animals and the use of avoparcin as a growth promoter (Ref 29). As a result of these studies, Denmark banned avoparcin use at subtherapeutic levels in 1995, followed by Germany in 1996, and subsequently by the entire European Union (Ref 31,32,33). Avoparcin is not approved for any use in the US.

3. Conclusions by Other Scientific Organizations

Several comments asserted that the Framework Document reaches conclusions not supported by scientific bodies studying the available evidence and data. According to one comment, multiple scientific bodies have said the human risk of animal uses of antimicrobials has not been quantified and there are no imminent hazards. One comment references an independent study entitled *Emergence of a Debate: Antibiotic Growth Promoters and Human Health*, which states that epidemiological data do not show that the use of antibiotic growth promoters compromised the use of related antibiotics in human medicine. Also mentioned is a press release from a 1998 WHO meeting that stated that there is a lack of documentation on the impact of fluoroquinolone use in livestock. Because of the lack of consensus, or the lack of data, a few comments suggest further multi-disciplinary research.

Other comments mentioned that numerous scientific organizations have recognized, and reported on, the threat to human health from resistant bacteria that have food animal origins, beginning with the Swann Committee report in 1969. Additional reports since that time have generally concluded that there is a public health hazard associated with the use of antimicrobials in food-producing animals that must be addressed.

FDA Response:

FDA acknowledges that the many authoritative bodies and committees that have studied the issue of the use of antimicrobial drugs in food animals and its impact on human health have reached various conclusions and that virtually all have called for more data and research. The literature also contains conflicting reports, which is a common phenomenon when interpreting issues on which new scientific findings continue to be reported. However, the weight of the evidence, particularly that published in the last 10-15 years, indicates that therapeutic as well as growth promoting uses of antimicrobials in food-producing animals can select for resistant bacteria of public health concern. The scientific evidence taken as a whole is sufficient for FDA to find it necessary to evaluate the human health impact of the antimicrobial effects associated with all uses of all Categories of antimicrobial new animals drugs intended for use in food-producing animals and to request drug sponsors to address the issue of microbial safety as discussed in GFI #78.

FDA agrees with the comment that an imminent threat to human health has not been demonstrated. However, in concert with its mission to protect the safety of the food supply,

FDA routinely initiates regulatory activity long before an imminent threat to human health is evident. With respect to the hazard presented by resistant foodborne pathogens, it is especially important to take action early since the nature of the problem is dynamic. Unlike a static situation such as that which exists with residues of antimicrobial drugs in the tissues of food-producing animals, the development of resistant pathogens is the result of selective pressure from antimicrobial use and thus can be expected to increase over time rather than remain stable.

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Risk Assessment

1. Importance of Risk Assessment

Many comments asserted that the Framework Document is not based on a sound risk-based scientific assessment. Rather, according to one comment, it is a broad research agenda of data needed to understand the risk to the public of antimicrobial resistance. Common themes expressed among these comments were that increased regulatory action should not be implemented until a risk assessment demonstrates a significant impact on public health, and regulatory action should be proportional to actual risks to public health.

Several comments express the opinion that antimicrobial resistance is a potential hazard that does not always translate into a risk. Several comments recommend that the agency base its decisions on a significant and detailed formal risk analysis using sound scientific evidence. The comments indicate that the risk assessment should quantify the potential human health impact of an antimicrobial use in veterinary medicine. One comment suggests the agency should seek funding to conduct such a risk assessment. A few comments remarked that the Framework Document is a risk management tool that lacks the prerequisite risk assessment.

FDA Response:

The FDA stated at the VMAC meeting and has restated since that the Framework Document was intended as a discussion paper. FDA intended that several guidance documents and, possibly, regulations would be necessary to implement the concepts laid out in the Framework Document. The agency intends that each of these future documents will be presented in draft form and comments will be solicited from all interested parties before finalizing the document, in accordance with the administrative procedure requirements of notice-and-comment rulemaking and/or with FDA's Good Guidance Practices (62 FR 8961, February 27, 1997)). FDA continues to actively solicit public input. The agency held a public meeting on October 4, 1999 to gather input on workshops planned to further develop the concepts laid out in the Framework Document prior to promulgating guidance or regulations.

The agency agrees that regulatory action should be proportionate to the potential impact on public health. To that end, FDA proposed categorization of antimicrobial drugs based on their importance to human medicine. FDA believes that it is crucial to determine the importance of an antimicrobial in human medical therapy before it can determine what effect the development of resistance to that drug from food-producing animal use will have on human health. FDA plans to expend more regulatory oversight on the drugs of high importance to human health. The agency realizes that the categorization will have to be flexible because new antimicrobials will be developed and the importance of existing therapies may change over time due to new medical needs and shifting patterns of antimicrobial resistance.

FDA agrees that agency decisions must be based on science and that a risk assessment is useful to help assess the magnitude of the human health impact of resistant food borne enteric bacteria derived from animals. In consultation with an internationally known expert

on risk assessment[1], FDA has developed a mathematical model relating the prevalence of fluoroquinolone resistance observed in *Campylobacter* isolates from broiler chickens to the level of fluoroquinolone resistance in *Campylobacter* isolates from humans. This model was then used to determine quantitatively the human health impact from resistant human campylobacteriosis attributable to the use of fluoroquinolones in broiler chickens. The risk assessment uses data from published literature and from recently initiated surveillance systems, the Foodborne Diseases Active Surveillance Network (FoodNet)[2] and the NARMS, which monitor the actual incidence of foodborne disease and prevalence of fluoroquinolone resistance in humans and chickens. The risk assessment model will be discussed at "The Risk Assessment and the Establishment of Resistance Thresholds Workshop" to be held on December 9 and 10, 1999. FDA plans to use this risk assessment model as a regulatory tool to assess risk posed by enteric pathogens.

Moreover, because the model cannot be extrapolated to assess the public health risk from commensal bacteria, which may pass resistance determinants or traits to human pathogenic bacteria, FDA plans to conduct a separate assessment of the impact to human health from resistant enterococci. If additional data are needed, the CVM proposes to target its food safety research monies to fill any data gaps.

2. How to Conduct Risk Assessments

A few comments advocated the use of a comprehensive risk assessment or a formal risk assessment that uses the accepted step-wise approaches of hazard identification, exposure assessment, dose response assessment and risk characterization. One of the comments recommended that the agency also address the problem of validation by using alternate models. Other risk assessment models were suggested such as the risk and benefit methodology being developed by Georgetown University's Center for Food and Nutrition Policy.

FDA Response:

FDA has long maintained that there is no provision for consideration of benefits under the safety standards for food. The risk assessment on *Campylobacter*, which the agency recently completed, uses the classic steps of risk assessment methodology. FDA intends to obtain more information on the other issues from stakeholders at "The Risk Assessment and the Establishment of Resistance Thresholds Workshop" to be held on December 9 and 10, 1999.

3. Quantitative vs. Qualitative Risk Assessment

There is disagreement among the comments about what is possible or practical regarding quantitative risk assessment. On the one hand, a comment asserted that there a quantitative risk

[1] David Vose, David Vose Risk Consultancy Limited. La Coutancie, 24320 Nauteuil-Auriac de Bourze, Dordogne, France.

[2] A collaborative effort of the U.S. Department of Agriculture's (USDA's) Food Safety and Inspection Service (FSIS), FDA, and Centers for Disease Control and Prevention.

assessment should be conducted to quantify potential impacts and establish acceptable levels of risk. On the other hand, a working group set up by the European Committee for Veterinary Medicinal Products (CVMP) determined that a quantitative risk assessment of antibiotic resistance would be very difficult to conduct and suggested that a qualitative risk assessment may be acceptable. Another comment suggested the need for a discussion about whether it is possible to conduct quantitative risk assessment and to think about what are the bounds of acceptable risk.

FDA Response:

FDA has conducted an assessment of the risk to humans from fluoroquinolone-resistant campylobacteriosis that is related to the use of fluoroquinolones in broilers and is planning to conduct additional risk assessments. However, experience indicates that these efforts are very resource intensive. The fluoroquinolone in broilers risk assessment cost the agency substantial monies, required additional government resources in terms of personnel and materials, and has taken several months to complete. Therefore, it is not feasible to quickly accomplish a quantitative risk assessment for every antimicrobial-pathogen combination. FDA intends to obtain more information on the use of risk assessment as a regulatory tool to evaluate other antimicrobial-pathogen combinations at "The Risk Assessment and the Establishment of Resistance Thresholds Workshop" to be held on December 9 and 10, 1999.

Resistance and Monitoring Thresholds

1. Basis for Establishing Thresholds

Many of the comments questioned the agency's ability to establish resistance thresholds. One comment stated that the agency is linking all food animal approvals to the creation of thresholds, which it states it does not have data or information to establish. Others stated that there is no proposal on how thresholds will be set. Will they be based on susceptibility shifts or clinical resistance? How will the agency establish thresholds that are conservative enough to protect public health? What are the resistance thresholds that would prompt concern and who will define them? Another comment stated that setting resistance thresholds is more appropriate as a research study than a regulatory document.

One of the comments advised the agency that implementation of a valid process to assess the development of resistance is a very complicated process. There are several questions that are not answered in the Framework Document.

- How many samples are needed to provide assurance of real changes due to antibiotics vs. random changes that occur over time? Are present baselines defined?

- What is the definition of resistance? Is it just any increase in the dose required to inhibit organisms or total resistance to a previously effective antibiotic? If a required dose increases what level is considered resistance?

One comment referred to the NRC recommendation that the emergence of resistance should be evaluated based on antibiotic used, concentration, dosage and blood concentrations achieved, bacteria or strain affected and animal species using the drug.

2. Source(s) of Isolates for Establishing Thresholds

Several of the comments asserted that the thresholds issue is a major roadblock in the Framework Document and those thresholds must be scientifically based and determined on a drug-by-drug basis. Some of the comments advocated the use of human data while others believe that resistance data from human strains derived from animals should be a major determinant of regulatory action for any antibiotic that is the drug of choice or important in treating potentially serious human disease. Others recommended that decreased susceptibility in animal isolates would be an appropriate threshold instead of waiting to see decreased susceptibility develop in human isolates or perhaps clinically significant resistance. Other comments stated that both human and animal data should be used in setting resistance thresholds and that genetic "fingerprinting" could be valuable in validating linkages that may exist between human and animal data.

3. Monitoring Thresholds

One comment stated that resistance surveillance should not be hidden as part of a food safety program but should exist independently and be done for its own sake. Other comments in support of monitoring thresholds stated that any rise in resistance levels related to antimicrobial use in food-producing animals could constitute a public health threat, thus FDA must continually monitor resistance levels associated with animal use of drugs. Data monitoring before, during and after antimicrobial administration would be invaluable in determining resistance trends and should be available to guide public health decisions. Drug companies should be required to submit resistance data on a regular basis to determine conservative resistance thresholds and to monitor resistance trends. Also, monitoring thresholds should be applied to certain currently approved therapeutic and subtherapeutic antibiotics with the same type of corrective actions.

Some of the comments asserted that the Framework Document lacks important details including which bacteria will be monitored. If indicator bacteria are monitored to identify decreasing susceptibility, then foodborne pathogens and commensal organisms that colonize both animals and humans and can be pathogenic in humans should be included. Changes in MICs need to be monitored continuously rather than waiting for changes in resistance or susceptibility.

4. Susceptibility Data/Testing

One comment stated that using in-vitro susceptibility data as a regulatory tool has many drawbacks. It measures in-vitro activity but does not assure therapeutic outcome. It may detect short-term shifts but several years are required to establish trends when used as a monitoring tool. Another comment stated that the NARMS could be relied upon if a problem was detected but was not nearly robust enough to detect early changes in susceptibility to be sufficiently protective of public health.

Another comment suggested that the NCCLS V-AST would provide accepted methodology and quality. The testing methodology provides support of judicious use antibiotic selection to the practitioner via clinical diagnostic laboratories and assures the quality of methodology for surveillance application.

5. Mitigation Action and Withdrawal of Approval

Many of the comments expressed general agreement that a good surveillance system is needed to pick up the first signs of adverse human consequences along with a procedure already in place to mitigate the hazard. One comment stated that there would be less concern about approvals for certain antimicrobials if rates exceeding the established pre-approval resistance thresholds automatically resulted in corrective actions including withdrawal.

Several comments provided suggestions on when and how mitigation should be implemented. Mitigating action should be considered when trends of decreasing susceptibility are noted. The Framework Document lacks important details including which thresholds of resistance or trends of decreasing susceptibility will lead to mitigating action. Some comments suggested that the sponsor could propose mitigation strategies, which may decrease the development of resistance,

and if acceptable to FDA, the product could be reinstated. One comment stated that FDA's proposal to evaluate mitigation measures should be used in the judicious use initiative but can't be justified as part of the regulatory process since no scientific studies have been conducted that demonstrate which mitigation strategies, if any, are successful in controlling or containing resistance.

Other comments provided suggestions for withdrawal procedures. If a resistance threshold is reached or exceeded after an approval is granted, the drug should be withdrawn immediately. FDA must not have to follow a protracted regulatory process to remove the product from the market while the public health is further endangered.

6. Measuring Human Health Impact

Some of the comments questioned how the agency would measure human health impact when there are insufficient data to define specific resistance thresholds below which protection of human health could be assured. How will the FDA measure the rate of resistance transfer in-vivo? What measures of resistance will be used? How will MICs and breakpoints be used to determine human health impact and what is a sufficiently sensitive test?

Other comments posed additional specific questions with regard to human health impact as follows: 1) how will the impact of various threshold levels on human health be measured? 2) What is the relationship between resistance levels measured on the farm and human health and what are the outcome measurements?

VMAC Recommendations:

1. Resistance Thresholds

The VMAC discussed resistance threshold levels in relation to Categories I and II (as addressed on pages 14 to 16, 18 and 20 of the Framework Document) and specifically discussed criteria the agency should use to safely define the acceptable level of resistance transfer, if any, for antimicrobial drugs that fall into these categories.

The committee members generally agreed that for Category I antimicrobials the threshold should be zero or very low. The committee noted potential difficulty in establishing resistance threshold levels for Category II drugs. The background materials and invited speakers did not provide enough data or information on which to base a recommendation for Category II drugs. The Committee agreed with the agency's plans to obtain scientific and public input to the process of threshold development.

2. Monitoring Thresholds

The VMAC discussed the importance and feasibility of monitoring thresholds (as contained on pages 15, 16, 18 and 20 of the Framework Document) and the basis for establishing them. The committee agreed that multiple monitoring thresholds should be established as a means of identifying emerging problems before they become public health concerns. The committee also

agreed that the monitoring threshold levels should be tied to specific public health response activities such as further investigation, development of mitigation or intervention strategies and withdrawal of the drug from the market. It was also emphasized that the monitoring will be a part of existing programs. The Committee's recommendation is as follows:

A) Monitoring threshold levels of antimicrobial resistance is the important for the proposed Framework Document, and assures the human safety of the microbial effect of new animal drugs. We encourage the use of human, food-producing and pet animal, and other environmental data such as slaughterhouse samples, for making these decisions. The levels should be tied to specific actions.

B) Some members felt that a broad range of gram negative and gram positive organisms should be used for monitoring antimicrobial resistance and others felt that we do not have enough data to make statements about what organisms should be the basis for monitoring thresholds. The committee agreed that the sole use of sentinel organisms would be inappropriate.

C) Antimicrobial resistance data should be monitored through NARMS, animal health diagnostic laboratory data, FSIS HACCP program within plants, the quality assurance programs that various associations are implementing, and an independent central laboratory for on-farm data using sentinel farms. Government and industry should support these activities.

FDA Response:

FDA agrees that the concepts of resistance and monitoring thresholds are not yet well defined. FDA plans to gather extensive input into the process of further defining thresholds and how to set them. The agency recognizes the difficulties involved in setting and enforcing thresholds that would adequately protect public health without being so conservative as to prohibit the use of any antimicrobial of human health importance in food-producing animals. Because of the difficulties inherent in establishing thresholds for all uses of all antimicrobials, the agency is considering limiting the requirement for a formal threshold to be established to those products considered most important in human medicine.

The Framework Document proposes that two thresholds, the resistance threshold and the monitoring threshold, be established to ensure that antimicrobial animal drug products used in food-producing animals are safe for consumers. The resistance threshold represents 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. Because the public health risk is different for different antimicrobial products and for different bacteria, the resistance threshold may need to be established for each bacteria of concern. Exceeding the resistance threshold would represent an unacceptable public health risk, and the agency would take action to withdraw or suspend the product approval or otherwise remove the product from the market until the public health threat decreases.

Before a resistance threshold can be established, the agency must establish a risk standard that expresses a quantitative definition of safety. Once the risk standard is developed, the risk threshold can be calculated with the aid of a standardized risk assessment model.

Drugs in Category I represent those of highest public health hazard. In order to meet any risk standard, the agency believes that human exposure to resistant bacteria from animals must be avoided or extensively minimized to assure that these drugs remain effective for treating human disease. Thus, the resistance threshold would be zero or very low. The agency believes that it may be possible in certain cases to define a level of resistant bacteria in animals for Category I drugs that would result in no or insignificant transfer of resistance to human pathogens.

For all Category I drugs, if a resistance threshold can be established, the agency would also establish monitoring thresholds for resistance development in animals. The monitoring thresholds would be established so that they serve as an early warning system signaling when loss of susceptibility or resistance prevalence is approaching a level of concern. The monitoring threshold would be used as a predictor of the number of resistant bacteria of public health concern that are likely to develop over time due to the approved use of the drug. Surveillance of foodborne pathogens in food-producing animals would need to be continually monitored to detect when resistance prevalence reaches the monitoring threshold.

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

As previously stated, the agency will seek expert and public input into the most appropriate basis for establishing resistance and monitoring thresholds. The agency is also exploring its legal options to ensure the best legal basis for establishing a threshold that will facilitate timely withdrawal actions, if necessary to protect public health. The establishment of thresholds will be introduced at a scientific workshop scheduled for December 9-10, 1999 on risk assessment and the establishment of thresholds.

Pathogen Load

Some of the comments questioned the basis for this requirement. These comments asked how the agency would establish pathogen load and how it would relate to the microbial effect of an antimicrobial new animal drug in humans. One comment questioned how the changes in the number of enteric bacteria in an animal's intestinal tract that cause human illness would be determined in light of issues such as the mean concentration of total viable bacteria in an animal's intestinal tract, the unknown variable of anaerobe involvement, ranking and percent of isolation of bacteria in humans, virulence factors, and the variable susceptibility of bacteria to antimicrobials.

A few of the comments stressed that pathogen load is a HACCP issue that belongs to USDA-FSIS, not FDA, and that it will be impacted by this program and reduced from current levels. One comment added that the use of HACCP intervention to reduce pathogen load would reflect processing reality.

FDA Response:

The agency recognizes and agrees that pathogen load is an important and complex issue that needs to be addressed and is currently considering whether to include it in the workshop on pre-approval studies scheduled for February 2000, or to address it at a separate workshop.

Categories

1. General Support

Some of the comments endorsed the approach of separating antibiotics by importance of the drug or drug class in human medicine. Other comments suggested that different drugs within a drug class should be categorized differently so as not to lead to undue restrictions. Other comments supported the Category approach but disagreed on which categories would be appropriate for use in food-producing animals. One of the comments stated that the potential for transfer of resistance from commensal to pathogenic bacteria must be considered and another indicated that this consideration should also apply to antibiotics that select for multi-drug resistance.

2. Concerns

Several comments expressed concern that categorization will result in elimination of novel therapies and increase the selective pressure for the emergence of resistance to approved drugs. One comment stated that categorization into 3 categories will be problematic and expressed major concern about the matter of cross-resistance (or associated resistance).

3. Importance to Human and Animal Health

Some of the comments suggested that the risk to human health should be refined to be more specific in terms of subgroups of people that need to be considered. The criteria and the categories regarding the importance of drugs in human medicine are subjective. Measurable objective criteria are needed.

A few of the comments stated that there is nothing in the Framework Document about the importance of antimicrobials in the food animal itself. The importance of the drug to animal health and welfare should be included in the categorization scheme.

4. Category Structure and Criteria

Several of the comments stated that FDA should review the proposed scheme for the three Categories because it does not adequately protect human health. Category I drugs may be used in food animals and such use is likely to result in human deaths (see Comments on Category I below). The comments included suggestions for revising category structure and criteria. The basis for assigning drugs to Category I, II or III is not clear and the system does not provide a means for the drug's category to be changed. The high, medium, and low groups should be eliminated because the number of animals does not relate to potential exposure to humans. There should be a separate Category for drugs that would not be subject to restrictions under the Framework Document such as those that are not used in human medicine or are not cross resistant to drugs used in human medicine.

One comment suggested that the categorization should be based on 3 criteria: importance to humans, likelihood that use in animals will result in resistance and level of exposure to humans from animal use. Other comments reiterated that Category placement should be a transparent

process and it needs to be clear into which Category currently approved drugs would be classified.

5. Category Definitions and Classification

Several comments stated that the categories are not well defined and the classification is very subjective. Category II is ill defined and Category III may include drugs which still pose problems to human health (see Comments on Category II and on Category III below).

There is disagreement on what would be appropriate to handle approvals of antibiotics in certain categories. One comment suggested that approaches for dealing with complex factors such as duration of exposure on individual drugs and multi-drug resistance should to be developed within the Framework Document.

6. Comments on Category I

Many of the comments stated emphatically that Category I drugs should not be approved at all for use in livestock because they would endanger public health. A few comments requested that the use of Category I drugs be allowed in livestock when there is no other effective means to reduce a particular animal disease. However, others felt that this category should be revised so that there would be no approvals for non-therapeutic antibiotics. One comment mentioned that the second criterion under this Category concerns a lesser group of drugs for foodborne diseases that are a) neither life threatening nor serious, b) antimicrobial therapy is contraindicated, or c) the need for antimicrobial therapy is controversial.

Some comments expressed concern that most new entity antimicrobials would fall into Category I. This would discourage drug sponsors from attempting to develop important new antimicrobials for use in food-producing animals. This would result in reliance on older products and hence more resistance selection. Drugs for swine and poultry would be penalized because there is a bias in the definition of Category I drugs with a high potential for human exposure. One comment stated that the agency should indicate any anticipated cross-resistant categories.

7. Comments on Category II

Several comments stated that Category II drugs should be held to the same restrictions and post-approval requirements outlined for Category I drugs and their use in livestock should not compromise their effectiveness in treating human disease.

8. Comments on Category III

Several of the comments stated that Category III drugs should be subdivided into two categories, so that antibiotics used in human medicine are subject to greater restrictions and post-approval requirements than those not used in human medicine. The antibiotics that are little used in human medicine should be subjected to pre- and post-approval monitoring, detailed drug sales information should be kept on them, and resistance should trigger withdrawal of approval.

Antibiotics that are not used in human medicine should not be held to post-approval studies and monitoring laid out in the Framework Document for Category II drugs, unless new evidence becomes available that suggests their use in animals endangers human health.

VMAC Recommendations

The issue of categorization of drugs based on their importance to human medicine as proposed in the Framework Document was discussed by the VMAC. The discussion included issues involving clarification of the definitions of the categories, the criteria for placing drugs in the different categories and the complexity of the three-by-three concept.

The committee concluded "Categorization of antimicrobial drugs for food animals considering the importance of the antimicrobial drug for human medicine is a workable concept. Antimicrobial resistant microbes as well as the ability of transference of resistance genes from other bacteria of food animals must be considered." The committee heard comments from many members requesting that CVM attempt to simplify the categorization. The committee also voted to have the agency consider adding a fourth category.

The committee recommended that the following sentence from the third paragraph, page 14 of the Framework Document be deleted: "Given our current understanding of the mechanisms of resistance, FDA believes that, generally, it would not appear biologically plausible for resistance to be transferred from animal enteric pathogens to the human respiratory pathogen." Recent scientific studies suggest such a mechanism might exist in nature.

FDA Response:

Many of the comments on categorization favored the concept of reserving Category I for the drugs, which are the most important for use in the treatment of otherwise untreatable human illness. FDA agrees. It is the agency's intention that the number of drugs considered Category I be limited. Thus, it does not agree with the comments expressed that the majority of antimicrobials would fall into Category I. Many comments expressed caution about the immediate adoption of categorization without carefully considering the ramifications to human and animal health. The agency agrees that the development of a categorization scheme must be done carefully and that such a scheme be revisited on a periodic basis to reflect changes in antimicrobial use in human medicine. The agency is reconsidering the proposed division of antimicrobials into three categories in order to simplify the proposed scheme. Furthermore, the agency is considering the suggestion of the VMAC to add a fourth category, which would be reserved for drugs with no utility in human medicine. The agency plans to seek comments from the public on a draft categorization of the antimicrobials used in the treatment and prevention of disease in animals.

As recommended by VMAC, FDA plans to remove the following sentence on page 14 of the Framework Document: "Given our current understanding…to the human respiratory pathogen."

Pre-Approval Studies

One comment stated that requiring drug sponsors to conduct pre-approval studies to demonstrate what level of resistance is safe proposes a standard that can't be met because 1) there is very little correlation between in vitro susceptibility of enteric bacteria from food animals and impact on animal health, 2) resistance development is a natural response and 3) resistance can't be quantified by the methods used to establish drug tolerances.

Another comment supports pre-approval studies (as opposed to post-approval studies) including the *Salmonella* shedding studies and modifications proposed by CVM at the VMAC meeting held on January 25-26, 1999. Other comments stated that there are no quantifiable risk criteria for pre-approval studies in the Framework Document or that resistance thresholds should be established prior to approval in sentinel organisms (e.g., *Salmonella).* However, some of the comments stated that the studies are too closely tied to enteric bacteria as the indicator organism and that enteric organisms should not be the sole indicator species. One comment expressed other pre-approval study concerns about the target animal, drug exposure, points in time for sampling, nature of resistance development, pathogen load and validation of the pre-approval study.

FDA Response:

The agency agrees with the comments supporting the value of pre-approval studies in evaluating the rate and extent of resistance development. However, the agency acknowledges that the design of such studies is scientifically complex and requires further scientific input. The agency plans to gather additional scientific input at its workshop on pre-approval studies for antimicrobial resistance scheduled for February 22-23, 2000. The workshop will provide an open forum to discuss the Center's current thinking on the appropriate design of pre-approval studies to model the rate and extent of resistance development in food-producing animals and seek suggestions for alternative approaches. The three basic areas of concern for microbial safety are 1) transfer of resistant foodborne pathogens; 2) transfer of resistant determinants from a foodborne bacteria to a pathogen within the human gastrointestinal tract; and 3) the increase in pathogen load in the target animal as a result of treatment with a new animal drug. All three areas will be addressed at the February workshop.

CVM's current thinking about the types of pre-approval studies that may be needed to address these concerns are as follows:

- Pre-approval studies to predict the time (weeks, months, years) it will take under approved use conditions to see changes in susceptibility to the drug;

- Pre-approval studies to predict the magnitude of the changes in susceptibility to the drug;

- Pre-approval studies to determine the potential of the drug to increase pathogen load in the target animal.

Although the Framework Document proposed requiring pre-approval studies to assess resistance for all Category I and II products, the agency acknowledges that these studies might be costly to the industry and could increase the overall regulatory burden. However, new studies for estimating resistance may not necessarily be needed for all products. Sponsors may be able to use information from other required studies or published literature to demonstrate that the exposure of the treated animal's enteric bacteria to the antimicrobial would be very limited. Antimicrobials not used in human medicine would not need to submit data unless cross-resistance to a human therapeutic drug is an issue.

The agency intends to further solicit discussion as to when it may be appropriate to not require new studies to address the issue of resistance at its public meeting in February. The agency also intends to solicit discussion of alternatives to new studies, such as use of information from other required studies or published literature, at the same meeting.

Finally, the agency intends to discuss those conditions where it is appropriate to request studies on pathogen load at the upcoming February meeting.

Current Approvals and New Approvals

There was general agreement in the comments that FDA's policy focuses on new therapeutic drugs and that a major weakness of the Framework Document is that it does not address antimicrobials that are already approved. Several of the comments stated that it is essential that existing approved uses of antimicrobials be subject to review under the Framework Document. One comment recommended that the document should state explicitly that it would be applied to previously approved antimicrobials starting with subtherapeutic use of antibiotics as growth promotants. A review of the fluoroquinolone approvals (especially in poultry) should also be among CVM's highest priorities.

Some of the comments asserted that the Framework Document is not a risk-based approach for evaluating uses in food-producing animals unless applied to existing uses as well as new approvals. The greatest risk to human health comes from existing rather than new uses of antibiotics. The post-approval monitoring provisions should include antibiotics currently in use. One comment suggested that the reporting requirement should be extended to apply to manufacturers of old antibiotics so that resistance can be monitored.

One of the comments stated that the regulations should be retroactive and include all antimicrobials used in veterinary medicine (current as well as future uses). However, another comment stated that CVM should resume the approval of new antimicrobials in the review pipeline under the existing regulatory guidelines as the new regulations are being developed.

VMAC Recommendations

The committee encouraged FDA to proceed with the review and approval of new animal drug applications in progress and ask for additional information needed to ensure a safe human antimicrobial therapy. It was also recommended that CVM state how it will handle current and future applications until this process is completed and to make that information publicly available. The committee noted that there is a footnote on page 7 of the Framework Document that states "FDA anticipates that the Framework Document, if implemented, will be part of the approval of new animal drug applications, and as resources permit, will also be used for reviews of existing uses of antimicrobials for food-producing animals."

FDA Response:

FDA agrees with the recommendation by VMAC that it is important to state publicly how current and future applications will be handled until this process is completed. FDA is currently asking all sponsors seeking approval of antimicrobials for use in food-producing animals to address the issue of microbial safety as defined in GFI #78. All original new animal drug applications (NADAs) for antimicrobial products, or supplemental approvals that represent an expansion of a current approval, must consider the issue of microbial safety. However, new studies may not be needed for all applications. These applications will be assessed on a case-by-case basis to determine whether additional information is needed; and when needed, what type of information should be provided. Supplements that do not expand currently approved uses will not need to address the issue of microbial safety at this time.

Generic applications (ANADAs) are not required to address the issue of microbial safety at this time. However, a generic application that includes an innovation (i.e., a hybrid generic application) that expands the conditions of use relative to the pioneer product, must address the issue of microbial safety. Products that are not used in human medicine would need to assess whether resistance to antimicrobials used in human medicine would pose a concern.

CVM encourages individual sponsors to discuss their particular product application with Center staff. The CVM will, to the greatest extent possible, make commitments on protocols agreed to between company and CVM personnel.

FDA agrees with the comments stating that it is important to consider the human health risk of antimicrobials that are currently being marketed for use in food-producing animals. The agency intends that its approach to new approvals of antimicrobials in food-producing animals, once finalized, will also be applied to existing products. However, as stated in the Framework Document, the agency will prioritize its examination of existing products based on those it believes pose a risk to public health. The completion of such review will also be dependent on available resources.

Drug Use Information

General Comments

FDA proposed in the Framework Document that more detailed drug sales information would be necessary to be submitted as part of the drug experience report. There was almost universal agreement with the proposal. Some comments suggested that the drug sales information requirement also include how the antibiotics are being used, in what species, at what dosage, for what purpose and for how long. Some of the comments emphasized that both the drug sales and the drug usage information should be made publicly available to the fullest extent of the law. Other comments stated that the efforts of government and university scientists to correlate the evolution of resistance in bacteria with the use of antimicrobials in agriculture are hampered by lack of information on antibiotic sales and strongly encouraged FDA to require this information. Understanding mitigation strategies and the effects of intervention efforts would be greatly enhanced if drug use information were available. A comment asked that the reporting requirement be included in a regulation so that it has the force and effect of law.

FDA Response:

FDA agrees that sales and volume distribution data for antimicrobial drugs approved for use in animals and sold in the United States are crucial to a complete understanding of the antimicrobial resistance issue. Drug use information would allow more direct correlation between loss of susceptibility or increasing resistance trends observed in NARMS or on-farm monitoring programs with the actual use of both individual drugs and drug classes. FDA notes that this information would also allow more effective implementation and assessment of any intervention or mitigation strategies to be initiated in response to findings of decreased susceptibility or increasing resistance trends over time.

FDA has the authority to obtain information on the quantity of drug marketed. The authority is provided in Section 512(l) of the Federal Food, Drug, and Cosmetic Act as implemented by 21 CFR 510.300(a)(5). After approval of a new animal drug application, the sponsor is required to submit comprehensive information on experience and activities related to the product including promotional activities, adverse experiences reports, literature reports and unpublished reports on experience or studies, as well as marketing activities including active distributors and quantities of product marketed. This information is reported in the annual drug experience report (DER) submissions on the anniversary date of approval. Sponsors typically provide a quantity for each of the dosage forms marketed for each animal drug but the information is not differentiated by animal species or geographic region. There is also no requirement for the sponsor to differentiate between the amount of product marketed domestically and product exported. The FDA is prohibited from providing this information to the public for individual products as it is considered propriety information.

Therefore, in order to make the data useful, expanded information is needed on the amounts of antimicrobial agents used by species, the duration of use, routes of administration, and by claim, e.g., for therapeutic or production purposes. Also the information needs to be submitted in a

consistent format and time frame, e.g., on a calendar year basis and by specific geographic areas. FDA plans to revise the Records and Reports section of the DER regulations to include quantity marketed data to support the Framework Document and other FDA data needs. The agency plans to obtain more input into this process through its development of the regulation and any necessary guidance.

On-Farm Monitoring

1. General Comments

Several of the comments agreed with FDA that on-farm studies are necessary and that monitoring of resistance is integral to the effectiveness of the program. An on-farm program in which resistance and antibiotic use can be monitored is advantageous in that mitigation efforts could also be readily assessed. However, some of the comments stated that on-farm monitoring should be focused and not global and that national on-farm monitoring could be disastrous. Also, while there was support for the advisory committee's comments on post-approval monitoring programs, some stated that these studies should not be mandatory or a condition of approval and should be required for only Category I drugs.

Other comments stated that FDA should evaluate the feasibility of on-farm monitoring. Post-approval monitoring must be sensitive enough to detect even small changes in resistance and include non-foodborne and foodborne pathogens. The monitoring program should take into account the impacts of spreading manure on crop fields.

2. Location(s) for Monitoring Exposure

One comment asserted that FDA has not given adequate consideration to the important aspect of location relating to exposure. Surveillance for resistance is a necessity; however, on-farm isolation and susceptibility testing does not represent the best or most efficient location for assessing exposure. The Framework Document places emphasis on the drug and how it is used on the farm when the most critical factors in determining potential exposure take place after the animal or food products leave the farm. A few comments stated that surveillance and on-farm monitoring raise serious doubts about whether it will provide a true analysis of the risk to consumers. On-farm monitoring will not provide information relevant to the risk transfer potential to humans.

The comments varied on how to address this issue. Some stated that the organisms should be included from all possible sources including the farm. Others stated that the best early warning system to monitor for change is the slaughterhouse and that surveillance of animal isolates at slaughter is more appropriate than on-farm surveys because it is closer to the consumer of meat and poultry. The comment also stated that this type of surveillance must be more extensive than currently performed in order to provide reliable data. One comment stated that because consumers typically have more contact with the food product than the animal, the product that should be evaluated for risk is not at the farm or the processing plant but immediately prior to consumption. Resistance should therefore be assessed at the point of sale to determine risk. Other comments, supportive of on-farm monitoring, asserted that sampling only at the slaughter facility or after processing would miss the opportunity to implement on-farm mitigation strategies if resistance develops.

3. On-Farm Authority, Costs and Logistics

Some of the comments stated that the costs of on-farm testing are prohibitive and questioned whether FDA had given full consideration of the costs and logistics necessary to gather useful data. One comment stated that the scope of testing is beyond even what the federal government is capable of doing based on surveys conducted by FSIS and the Animal and Plant Health Inspection Service (APHIS). There were a few comments espousing that on-farm post-approval monitoring programs create concerns about disease biosecurity issues. Post-approval monitoring means on-farm visits and potential breaches of biosecurity. The health of the animals depends largely on biosecurity of the herd.

One comment posed the question, "How does FDA propose to gather on-farm data?" and questioned the agency's authority to go onto farms. Another stated that before an on-farm monitoring program is established there needs to be more clarity of details on the testing and the following questions need to be addressed:

- Who has the authority to do the testing and collect the samples on the farm?
- Would the data collection be drug specific?
- Which animals will be tested, what will they be tested for and what numbers of samples will be taken to yield significant results?
- What kind of verification procedures would be put in place?
- What will happen and under what time frame, should resistance be found?

4. National Antimicrobial Resistance Monitoring System (NARMS)

Many of the comments generally agreed that an effective monitoring and surveillance system is needed. However, some stated that an alternative to on-farm monitoring is the NARMS for generating pre-approval baseline data and for post-approval studies and monitoring. One comment suggested that NARMS be expanded and enhanced as a monitoring tool for assuring the safety of proposed Category I drugs. Under this scenario, the agency should consider obtaining additional information during the data collection process.

Many comments indicated strong support for NARMS, which focuses on carcass sampling at slaughter facilities to obtain animal isolates. However, other comments stated that NARMS is far too limited in scope and numbers of isolates collected. Concern was expressed that the program currently does not adequately protect the public health because it is limited in its detection capabilities.

The FDA Veterinary Medicine Advisory Committee addressed the issue of on-farm monitoring at a meeting on January 25-26, 1999 in Rockville, Maryland and provided several recommendations. The Committee discussed the feasibility of on-farm post-approval monitoring

programs as referred to on pages 17, 19 and 20 of the Framework Document. FDA proposed in the document that on-farm post-approval monitoring programs would be necessary for all antimicrobials in Category I, Category II high and some Category II medium products. The Committee was also asked to make a recommendation as to whether the monitoring should be instituted immediately post-approval or should it be triggered by a change in the data generated from other sources such as NARMS.

The committee members had different opinions on whether on-farm testing was essential as well as whether it should occur before or after approval. There was also discussion on the legality of requiring sponsors to monitor resistance, especially on farms where it does not directly involve the sponsor's drug as proof of safety and efficacy, whether testing on the farm was the best place to determine exposure to resistant pathogens and who should be responsible for funding the project. The Committee's recommendation is as follows:

> "Slaughterhouse data is of paramount importance to the Framework Document. On-farm antimicrobial resistance programs utilizing on-farm health quality assurance programs would be encouraged (but not required) by the committee to look at post-approval antimicrobial levels for high category antibiotics. Diagnostic laboratory data and development of an accredited central laboratory should be developed utilizing government and industry monies."

FDA Response:

While there was universal support for the expansion of NARMS, the collection of on-farm monitoring was controversial in the comments. NARMS is a key component of FDA's overall strategy on antimicrobial resistance; it is a national surveillance program that monitors resistance among enteric pathogens in both animals and humans. In 1996, the FDA established the National Antimicrobial Resistance Monitoring System: Enteric Bacteria (NARMS) to prospectively monitor changes in antimicrobial susceptibilities of zoonotic enteric pathogens from human and animal clinical specimens, from healthy farm animals, and from carcasses of food-producing animals at slaughter. NARMS is currently monitoring susceptibilities of human and animal isolates of *Salmonella* and *E. coli* to 17 antimicrobials, *Campylobacter* isolates to 8 antimicrobials, and *Enterococcus* isolates to 27 gram positive antimicrobials.

Animal isolate testing is conducted at the USDA Agricultural Research Service Russell Research Center. Human isolate testing is conducted at the CDC National Center for Infectious Diseases Foodborne Disease Laboratory. Seventeen states and local health departments submit human clinical isolates of non-typhoid *Salmonella, E. coli, S. typhi* and *Shigella*. Eight health departments submit *Campylobacter* isolates and in addition four states are submitting *Campylobacter* isolates from poultry retail samples and *Enterococcus* isolates from humans and poultry. Both the CDC and USDA laboratories use a semi-automated system (Sensititre™, TREK™ Diagnostics, Inc., Westlake, Ohio) for testing *Salmonella*, *E. coli* and *Enterococcus* isolates and the E-test (AB Biodisk™, Solna, Sweden) for testing *Campylobacter* isolates. Annual reports summarizing the data are available on the Internet (http://www.fda.gov/cvm/mappgs/narms.htm and www.cdc.gov/ncidod/dbmd/narms).

FDA recognized the need to enhance NARMS and actively solicited funding for this purpose under the National Food Safety Initiative. As a result, NARMS was substantially expanded during 1998 and 1999. Several veterinary diagnostic laboratory sentinel sites were enrolled and the number of *Salmonella* isolates collected from slaughter plants was greatly increased. Case-control follow-up investigations of human cases of salmonellosis and campylobacteriosis with losses in susceptibility to quinolones were begun. Projects on prudent drug use activities were initiated in California and Michigan. FDA recognizes the importance of the American Veterinary Medical Association's judicious use efforts. FDA believes that the development of judicious use species programs is key to the overall management of antimicrobial resistance in animals. On-farm poultry studies, designed to elaborate management, production, and drug use practices that influence the development of resistant zoonotic pathogens, were initiated under collaboration with the National Center for Toxicological Research.

The agency believes, as stated in the Framework Document, that it needs additional information to adequately assess the safety of specific food animal antimicrobials after approval. The monitoring program is only a sentinel system and has a number of inherent limitations. Although it is possible to identify that a problem exists, the magnitude of the problem is difficult to assess with the monitoring system data alone. NARMS is not capable of identifying how or why the resistance occurred. Data related to the resistance findings, such as demographic information and history of drug use, is not collected in the animal populations and NARMS can not be modified to obtain that information. It is important to some stakeholders that the agency not be able to trace back the findings from the animal isolates. Due to these limitations, the data can not be linked to particular practices of concern. Moreover, it is important to point out that further expansion or enhancement of NARMS will not solve the problem or minimize the limitations. The agency has already implemented the recommendation of the FDA Veterinary Medicine Advisory Committee to add diagnostic laboratories to NARMS and use a central laboratory (NARMS uses two central laboratories, one for animal isolate testing and one for human isolate testing).

To address these limitations with NARMS, FDA proposed in the Framework Document that on-farm, drug-specific, post-approval monitoring programs are undertaken by the drug sponsors for drugs of importance in human medical therapy. These programs would be designed to fill data gaps identified in NARMS. On-farm surveys could provide an estimate of the true prevalence of resistance or decreased susceptibility to specific drugs or drug classes in a food animal production setting under actual use conditions. These surveys could also collect risk factor information such as drug exposure associated with the isolates undergoing susceptibility testing. Because the resistance outcome could be linked to contextual information surrounding the isolate, on-farm data would provide a strong body of scientific evidence that specific factors, drug related or non-related, are leading to resistance outcomes. The monitoring programs would need to be species-specific only, since many drug classes could be tested on the same isolates and many pathogens could potentially be isolated from the same sample.

FDA continues to believe that on-farm information is crucial to assist the agency and drug sponsor in the investigation of appropriate mitigation strategies. On-farm surveys provide the testing ground for the effectiveness of these strategies. Identification of effective mitigation actions provides sponsors with options and alternatives to address the development of resistance

before a resistance threshold is reached. These mitigation actions may prevent product withdrawals.

FDA considered that on-farm studies would provide very useful information if resistance should reach a pre-determined monitoring threshold based on NARMS data. On-farm studies could conceivably identify a more precise location where resistance was developing, for example among a certain animal species or in response to use of a particular dosage form. Then, mitigation or regulatory action would have to be taken only on the particular use that was causing the resistance to develop. Without the information these studies can provide, when resistance reached a threshold, action would need to be taken against all drugs and/or dosage forms.

FDA intended that much more discussion and public input take place before making decisions on the appropriate organization responsible for sample collecting and isolate testing, what protocol would be used, and what actions would be taken in response to findings. FDA has the authority to enter the premises where food animals are raised.

Although FDA has on-farm inspection authority, the agency did not intend that FDA would perform the on-farm studies. Since these studies would primarily benefit the drug sponsor, it was anticipated that the animal health industry would voluntarily perform the studies. Due to the number of comments objecting to the studies, FDA has decided not to propose that on-farm monitoring be a post-approval requirement and instead rely on the NARMS program to track loss of susceptibility or development of resistance. However, the agency would request on-farm studies if NARMS data indicates that resistance or loss of susceptibility has reached a monitoring threshold that was set prior to approval of the drug.

Miscellaneous

1. Impact on Product Development

Several comments expressed concern about the impact of the Framework Document on product development. The common theme of comments stated that it would not be cost-effective for a company to develop a new drug. The financial requirements of being placed in a high human importance category represent an additional cost to industry. One comment stated that the potential for resistance would disallow the approval of some antimicrobials.

Another comment stated that it is unrealistic to expect a pharmaceutical company to develop a class of antimicrobial agents, which is not or will not be used for human need, use or medicine. It was stated further that it is unrealistic to expect any producer group to produce the quantity of meat needed to feed our growing population without the use of anti-infective drugs.

2. Impact on Animal Health

Several comments stated that the decreased availability of antimicrobials would not diminish resistance. The adverse cost to food and food animals will bring higher costs to consumers and contribute to a "black market." Another comment stated that this would contribute to impairing the health of animals (diminished animal welfare, increased suffering), provide for a less healthy environment and potentially increase the risk to humans because of the inability to treat animal disease (increased pathogen loads). However, another comment disagreed with the statements connecting drug use with affordable food. That comment cited a 1998 National Research Council study that estimated a ban on subtherapeutic drug use in livestock in the United States would increase per capita food costs $5 to $10 per year.

Other comments disagreed with statements that more stringently regulating food animal antimicrobials would result in diminished animal health and welfare. The comments cited statistics that approximately 80% of antibiotics used in agriculture, or about 1/3 of all antibiotics used in the United States, were for promoting growth of animals rather than for treating sick animals. Another comment stated that the costs of the drugs to the user should be factored into the equation.

Comments also stated that the FDA's statement connecting drug use with affordable food does not take into account the costs associated with large-scale production facilities such as environmental pollution, worker and public health problems, and destruction of rural communities.

Another comment suggested that it was misleading to state that addressing the antimicrobial resistance would result in decreased availability of drugs for animals. On the contrary, another comment stated that it is in the best interest of animals to preserve effective drugs so that they are available when needed to treat animal disease.

3. Request for Public Input

Some of the comments encouraged the agency to seek comment from other sources because FDA has not received adequate input from commodity groups and the veterinarian profession, while receiving misleading input from the public health establishment. FDA also needs to involve stakeholders such as food animal producers, academia, microbiologists and the animal health industry before the Framework Document is presented to the public and should involve all stakeholders in future proposals. Other comments recommended assembling experts with detailed knowledge about animal and human health to address the complex issues in the Framework Document and revise it. Small groups should be convened to assess specific regulatory approaches and make recommendations on how to implement the concepts laid out in the Framework Document. A team approach with other interested parties is needed to address industry and FDA concerns such as having an action plan that allows food animal veterinarians to make judicious use choices, judicious use in companion animals and humans, and the development of scientifically-based post-approval monitoring programs.

A few of the strategies involved establishment of an advisory panel for the evaluation of mitigation, and that experts should monitor information collected for correlating antibiotic use and resistance. Another comment recommended that a blue ribbon committee should be established representing veterinary and human medicine, epidemiology, biostatistics, economics and microbiology. The committee's purpose would be to define endpoints, conceptualize appropriate monitoring systems, evaluate the impact of regulations on endpoints and recommend changes to monitoring systems. The regulatory and scientific process should be flexible to change until measures of safety can be validated using human health as the gold standard.

One comment suggested that FDA propose a process involving outside parties to come to a consensus on the contentious issues in the Framework Document. Another comment recommended having an interdisciplinary panel of experts and regulatory agencies oversee the development and use of antibiotics in humans and animals.

FDA Response:

FDA intends for the requirements to be no more burdensome in terms of time and cost to industry than is necessary to allow the agency to obtain sufficient information to assess the safety associated with antimicrobial resistance.

Comments on the impact of the Framework Document to animal health and welfare were contradictory. Comments warning of an increased cost of food provided no data to support the statements. Contrary to this prediction, the National Research Council found that the increased costs from the elimination of growth promoting uses of antimicrobials would be minimal.

FDA agrees that stakeholder involvement and input is essential in this process. In this document, FDA is making public its analysis of all comments received on the Framework Document. FDA plans to actively solicit stakeholder involvement and expert advice at many

stages of the implementation process. FDA envisions seeking input from the public through three primary mechanisms: guidance, notice and comment regulation development, and workshop-type meetings to gather more expert involvement. FDA is planning to hold workshops on the following topics:

- Risk assessment (scheduled for December 9 and 10, 1999),
- Design of pre approval studies on resistance and pathogen load (scheduled for February 22 and 23, 2000).

The agency may hold additional workshops.

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