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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR VETERINARY MEDICINE

VETERINARY MEDICINE ADVISORY COMMITTEE

Monday, January 25, 1999

8:30 a.m.

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Ballroom
Two Montgomery Village

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C O N T E N T S

GUEST SPEAKERS

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C O N T E N T S (Continued)

PUBLIC SPEAKERS

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P R O C E E D I N G S

Introductions

DR. STERNER: If you would take your seats, we have a very long and busy day. I would ask that we convene the meeting of VMAC.

By way of introduction, I am Keith Sterner, a private veterinary practitioner from Ionia, Michigan. I am in a nine-person mixed, large animal practice. I am this year's Veterinary Medicine Advisory Committee Chair. I am going to start by introducing VMAC members. Dr. Angulo, if you would start by introducing yourself, and a bit about where you are from and what you do?

DR. ANGULO: Good morning. My name is Fred Angulo. I am with the Foodborne and Diarrheal Diseases Branch in the Center for Infectious Diseases at CDC.

DR. NORDEN: I am Carl Norden. I am a Professor of Medicine and Head of Infectious Diseases at Cooper Hospital in Camden, New Jersey, and I am on the FDA Anti-Infective Advisory Committee.

DR. BARKER: Steven Barker, Louisiana State University, Department of Physiology, Pharmacology and Toxicology, representing the analytical sciences.

DR. GALBRAITH: Peter Galbraith. I am the State

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Epidemiologist for the Vermont Health Department, and I have done environmental risk assessment and infectious disease epidemiology.

DR. FLETCHER: Oscar Fletcher, Dean of the College of Veterinary Medicine in NC State University, representing poultry.

DR. HASCHEK-HOCK: Wanda Haschek-Hock, University of Illinois. I am Professor and Head of the Department of Veterinary Pathobiology, and I am representing pathology.

DR. HOLLAND: I am Robert Holland, Michigan State University, representing Minor Animal Program.

DR. DIANE GERKEN: I am Diane Gerken, College of Veterinary Medicine, Ohio State University, representing toxicology.

DR. LANGSTON: Corey Langston, clinical pharmacologist in Mississippi State University, representing pharmacology.

DR. LEIN: Don Lein, past chair of this group and a consultant, Chair of Cornell University Department of Population Medicine and Diagnostic Science, and Director of the Diagnostic Lab for the State of New York.

MR. WOOD: I am Richard Wood, Executive Director of Food Animal Concerns Trust, and I am the consumer representative on the committee.

DR. O'BRIEN: I am Tom O'Brien from Brigham and Women's

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Hospital and Harvard Medical School in Boston, and a consultant to the committee.

DR. STERNER: We have two members of VMAC who will not be here. One is George Cooper and the other is Calvin Koong. I don't believe that Calvin will be here for the entire meeting due to other commitments.

DR. GEYER: I am Dick Geyer. I am the Executive Secretary of VMAC. And Dr. Cooper will be with us tomorrow.

I have just two brief announcements before we move into our scheduled program. First, you will notice on the agenda that we are going to begin with the public speakers at five o'clock today. That is a change from the announcement in the Federal Register. We wanted to make sure that everyone knows this up front. We plan to have most of the speakers in the public session speak this afternoon or this evening. There will be a few who will be speaking in the morning. If any of you who are public speakers have a difficulty with the time that you are scheduled for, please see me sometime today.

There is just one other thing. I would like to ask that everyone who speaks today be sure to speak into the microphone and, if you have not been introduced or if your name has not been mentioned, as you start to talk please

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state your name so that our reporter will be able to get your name correctly. Keith?

DR. STERNER: I think that the turnout at this meeting says it all with regard to the issue of antimicrobial resistance. Just to set the tenor a bit, Veterinary Medicine Advisory Committee is just that, an advisory committee to the Food and Drug Administration's Center of Veterinary Medicine. And, they have prepared a framework document that deals with the issue of antimicrobial resistance as it involves approval and usage of antimicrobial agents in veterinary medicine. To that end, this document deals with an increasing level of both public and professional concern over the issue of emerging antibiotic resistance.

With that said, I need to tell you that VMAC is not here today and tomorrow to debate the issue of antibiotic resistance but, rather, to pass judgment on the framework document that deals with this issue, and to answer those five questions. So, those of you who are here to hear a definitive answer to antimicrobial resistance, I am afraid that VMAC will disappoint you in its deliberations.

I also would point out to you that people coming to this discussion all hold very strong views, many times from polar opposites on a very contentious issue. I think that the

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great thinking that you are going to hear in the presentations today will point out just how dramatically opposed some of those views happen to be.

But with that in mind, we will introduce our first speaker, Dr. Michael Friedman, who is the Deputy Commissioner for our Operations from the Food and Drug Administration.

Introductory Remarks

DR. FRIEDMAN: I appreciate the chance to make a few introductory remarks. Let me reinforce a couple of themes that you have mentioned and that will again be mentioned after me.

This is a very important meeting. It deals with the sort of exemplary, complex subject that affects many different communities in very important ways.

The mission of the Food and Drug Administration is to both promote and protect the public health. As an integral part of FDA, the Center for Veterinary Medicine is charged with these tasks: It protects, it promotes the public health through every decision that it makes whether that is in respect to food safety or whether it is in respect to animal health issues that are very important.

Today's issues represent, I think, a competition between a variety of different areas where there are competing needs

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and competing expectations. There are very legitimate, important veterinarian and animal owner needs.

Antimicrobials are important drugs for veterinary use as well as for human use, obviously.

FDA recognizes the critical need for antimicrobials in veterinary medicine to treat animal diseases; to improve the health of animals and prevent suffering; to help ensure that animals raised for food production are health.

In addition though, concerns have to do with attempts to minimize the transmission of zoonotic pathogens. This is a highly dynamic situation. It is a situation in which we have incomplete scientific data, and I feel that at the end of the day, no matter how clever or how appropriate an overall scheme is devised, we will not have all the scientific information necessary to make a perfect decision, nonetheless, we must at some point make a decision.

There is a balance that is necessary. FDA's goal is to find the balance that protects human health and gives veterinarians the tools they need to treat animals.

The framework document that you have for your consideration and which will be discussed today represents a proposal for a conceptual regulatory framework, an approach toward balancing the needs for safe and effective animal health

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products against the potential impact on human health that would result if pathogens acquire resistance to important antimicrobials.

This is a document for your discussion and consideration. This is a framework document. It represents FDA's current thinking. It represents a synthesis of different opinions from within the agency, but please let me reinforce the idea that none of this document is etched in stone. The discussion here is no mere empty exercise but a serious, thoughtful debate that will be considered very carefully by the agency. We honestly desire input from stakeholders as we move forward to implement the concepts embodied in the document. We will take very seriously this input. We will use it to help guide us in developing a rational science-based process for regulating antimicrobial drugs intended for use in food producing animals.

I want to appreciate the participation of the panel members, of the others who are represented here, of the people who will speak later, of all who participate in this very important exercise. This is not an easy issue but it is a very important issue.

Our goal is to articulate a public policy based on the best science that positions us well for today and positions us

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well for the future. And, as we search for a formulation that is both practical and one supported by the optimal public health position, we deeply appreciate all of your contributions and help. Thank you.

DR. STERNER: Thank you, Dr. Friedman and, in particular, I will personally thank you for keeping us on time.

Our next speaker this morning is Dr. Nicole Lurie, who is the Principal Deputy Assistant Secretary for Health at the U.S. Department of Health and Human Services. Her background includes her degree from the Minnesota School of Medicine where she held the post of Director of Primary Care Research and Education, Director of the Division of General Internal Medicine. She has taught within the University of Minnesota system since 1985, and serves currently in her capacity as Deputy Assistant Secretary since September of 1998. Dr. Lurie?

Introductory Remarks

DR. LURIE: Thank you. I can only observe that the room is so cold because the seats are already so hot.

[Laughter]

I am pleased to be here today on behalf of the Surgeon General and Assistant Secretary for Health to welcome you here, and pleased -- very pleased that you are meeting

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together to address this very important and timely public health concern about antibiotic resistance, treating sick animals and its relationship to veterinary use.

I am going to take you back a step from what our introduction told us, and make a couple of comments about antibiotic resistance since you will spend the rest of the day working on this framework document.

As you may know, not only has antibiotic resistance been designated by the CDC as a high priority in its emerging health concern, but the World Health Organization has also designated it as a very high priority, and in its focus on emerging and re-emerging infections it is right up there with our concerns about multi-drug resistant tuberculosis.

In addition, Dr. Satcher has identified five priorities for his term as Surgeon General and Assistant Secretary for Health, one of which is global health. Again, antibiotic resistance is identified squarely as a global health concern in that framework. It is not only a concern in this country, as most of you know.

Everywhere I go I hear now about this issue. I hear about it from health plans and insurers, including people in the healthcare financing organizations and managed care organizations, who are concerned not only about antibiotic

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costs and provider prescribing behavior but about the morbidity and mortality of antibiotic resistance. Among doctors the concerns span the range from pediatricians to geriatricians.

I hear constantly now from state and local public health officials. I hear also from ordinary citizens with considerable frequency. Interestingly, their questions are not limited to the ones of human use. They are quick to recognize the many links between human and animal uses of antibiotics.

I am also pretty fascinated by the sophistication out there. The distinction between antibiotic use to ensure growth versus the distinctions between antibiotic use to treat sick animals are the ones that the public is increasingly able to make. Just last week, in fact, the public health officer in a large Midwestern city -- and not Minnesota -- asked me about antibiotics in groundwater for example, and asked again what we are going to do about it.

The questions I get asked are the questions you are going to help address today: What is the government going to do about this problem? What is the right mix of regulation and voluntary effort? What kinds of partnerships, both between government entities and between government and private

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sector organizations and businesses, can produce the best public health outcome?

I want to stress, as Mike did, the term "public health outcome" because our job here is to protect the health of the public. One of our overriding principles is that prevention is the best alternative. Another is that, to the extent possible, we use the best possible science to do so. Often the emotion surrounding an issue and the scientific evidence leads us to alternative conclusions, and I am sure there will be a long period today where that will appear to be the case. But we also understand that science does not yet have all the answers. So, we need to consider in this equation not only the potential risks and benefits but also public confidence in our public health decision-making.

We also have here an obligation to define where scientific work remains to be done, and to get it going. In this case, we recognize full well that risk assessment is an imperfect science and we must strive to improve it.

We also recognize that for uncommon events surveillance systems alert us to problems often later than we wish they would. We must strive to improve those too. In both cases we hold ourselves to a commitment that when the science improves, or when the evidence changes, we may need to make

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different public health decisions than we might today. But we certainly don't want to wake up five or ten years from now with a massive problem of resistance and ask where were we; where was the FDA; where was the CDC where was agribusiness; where was the pharmaceutical industry; where was the Public Health Service to allow this to happen? This is why prevention is so absolutely critical.

We recognize, as you have been reminded twice already this morning, that we are dealing with a difficult issue. The science will get us a good part of the way there but not all the way. There are competing views of risk and sometimes competing goals for government, business and the public.

Yet, I believe that it is not only possible but that we must find a common ground here, and I think it will be easier to find a common ground if we remember our common overriding goal -- protecting the public's health.

I wish you the best in your deliberations and debate today, and I certainly look forward to the outcome and to hearing your best advice about dealing with this challenging issue.

I only want to comment in closing that I have had a very interesting discussion with my three boys over the past week about the availability of antidepressants now for dogs.

[Laughter]

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And, one of the things I started wondering as I started thinking about antibiotics in groundwater is when we will see the mood of the public improve.

[Laughter]

So, let me wish you all a good day and the best of luck!

DR. STERNER: Thank you, Dr. Lurie. Our next speaker I think is known to each and every one of us in the room. I consider him a personal friend, and in my comments to him yesterday I said he must be doing a particularly good job as director of the CVM because he has made lots of enemies and usually that is a sign that, if you have made enough, you are doing something right.

Dr. Sundlof is Director of the Center of Veterinary Medicine, and he is going to set the ground rules for VMAC and give us additional background. Steve?

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

DR. SUNDLOF: Well, thank you very much, Mr. Chairman. I always said that you stay in this job until you make a critical mass of enemies and then it is goodbye. So, I am not sure that those remarks last night were too comforting. This is, as most of you are aware, a very, very important

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meeting for CVM. It lays out a plan for a regulatory framework dealing with some of the very complex issues of antimicrobials. A number of people inside the agency worked very, very hard, through long, arduous, contentious meetings but it never got personal. It was always very much a collegial effort although people held very different views. The resulting framework document, as Dr. Friedman indicated, is more or less the synthesis of many diverse views.

I would also like to reiterate what Dr. Friedman said in that this document represents the best thinking to date out of FDA. It is not a document that is etched in stone. It is out there for broad discussion and broad consideration. It is our first attempt to try and lay out a total package, a framework for dealing with these issues.

The development of resistance of zoonotic enteric organisms, pathogens, is the main subject of concern. We all know that the science clearly supports that exposure of microbes to antimicrobials will select from those populations organisms that have genetically encoded resistance. So, the use of antimicrobials does promote the emergence of resistant organisms. In many of the organisms that we are concerned about from a foodborne pathogen standpoint are normal

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commensal organisms in food animals. So Salmonella and Campylobacter are normal gut flora of food animals. They don't produce clinical disease most often in those animals but those diseases do occur in humans as foodborne problems.

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So, we are going to talk a little bit about that. We will talk about the public health concern. Basically, in the framework document we are concerned about two different types of resistance transfer. One of them is direct transfer, and that would be direct transfer of pathogens from animals to humans, zoonotic transmission.

The second is indirect. That is, the transfer of genetic material from one organism to another organism, which is even a more complex issue. I will say that the issues that we are going to be dealing with are very complex, and we have tried simple answers; simple answers just don't seem to get us very far. So, that is why the framework document looks as complex as it does.

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Let's talk about our current regulatory approach. We have fairly stringent pre-approval standards. As everybody I think in this room understands, there is strict evaluation of the toxicologic data. We don't want residues in food

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which are harmful to the public. But until recently, we have only required microbial safety studies for subtherapeutic antimicrobials used in food for more than 14 days. In those cases we did require some safety studies to look at the issues of resistance and pathogen load.

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But it wasn't until a few years ago, when we first approved the fluoroquinolone antimicrobial for use in food animals, that it became very apparent that resistance was not just an issue associated with subtherapeutic use of antimicrobials, and we recognized at that point that we would need additional information to be able to evaluate the resistance development to fluoroquinolone and take the appropriate actions.

So, there are approvals now for cattle and poultry. We made sure that those products were available only through veterinary prescription; that it would be illegal to use them in any way that was extra-label or off-label. We asked the firms to engage in post-approval monitoring programs, and we initiated a national antimicrobial resistance monitoring system.

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So, FDA's goal then is to protect the public health by

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preserving long-term effectiveness of human antimicrobial drugs while, at the same time, providing for the safe use of antimicrobials in food-producing animals.

The purpose of this complex framework is to make sure that we do have a mechanism by which we can still approve these products because they are extremely important in animal agriculture. They are extremely important to the health and welfare of animals, and we just have to make sure that we do it in a way that is protective of the public health.

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We have determined that the current regulatory structure for dealing with the approval process doesn't really adequately take into account the issue of antimicrobial resistance. Again, we have strict regulations and requirements for looking at the toxicologic impact of drug residues but, in terms of dealing with the antimicrobial resistance issues, we haven't had a good system for dealing with that.

Earlier this year or late last year, we published a notification of a draft guidance, number 78, and it is in the book that participants have. Basically, it establishes the regulatory authority for FDA to deal with the issue of antimicrobial resistance. That was the first step in going forward with the program, total program, to deal with the

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antimicrobial resistance issue. From there, the framework document was published last month, in December, and you have that in your package. That is the second part.

Furthermore, we plan to hold workshops to look specifically in detail at what kind of studies would best give us the kind of information that will be necessary to allow decisions of whether or not to approve these products.

Throughout this process, we have asked for a lot of input from the public, and we will continue to do so.

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The draft guidance for industry, number 78, says FDA now believes that it is necessary to evaluate the human impact of microbial effects associated with all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals.

The two issues that have to be addressed are resistance -- what is the potential for the products to cause resistance, and in what organisms? And, what effect does the drug have on the pathogen load that the animal may be carrying at the time it is used for human food?

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So, those are the two issues. Now, the draft guidance has been out there since November 18, and the comment period

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ended on December 18. We only received a few comments on the guidance, and the comments that we did receive did not materially affect the guidance as it stands. So, we will continue to accept comments, and anybody can comment anytime on the guidance. Pretty much, we think we have put the guidance out there; we have listened and received comments, and the comments have not caused us to revise that document.

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So, the focus of this meeting will be to determine how the agency should change its requirement for data and information. It is not on whether changes should be made. We have come to the conclusion, and that guidance document, number 78, basically is the position of the FDA that we think this is an issue that must be dealt with. So, it is going to be important to make changes. We want to make the right changes, and that is what we want a lot of input during this meeting for.

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The framework document was issued in December, and we will be accepting comments on it until April 6. We are now in the comment period, and we will take all of the information that comes out of this meeting -- all the transcripts, go through those, try and sort out the comments, but in

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addition, if there are additional comments, they can be accepted up until April 6, and we encourage a lot of comments.

The VMAC meeting was called to provide input and to address the specific questions related to the framework document, and the focus of this meeting is the framework document, as was mentioned, and the questions provided to the committee.

There are a lot of peripheral issues associated with antimicrobial resistance but we want to keep the focus of this meeting squarely on the framework document.

It articulates FDA's current thinking on how the agency should respond to contemporary information related to the human health impact of the use of antimicrobials in food-producing animals.

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Now, the framework document lays out a conceptual regulatory construct for addressing the microbiological safety of antimicrobial drugs intended for use in food-producing animals. The elements of the document include adequate and well-controlled studies in the pre-approval phase to provide predictive value on the likelihood and extent to which antimicrobial resistance may develop when the drug is marketed for its intended use.

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It also includes monitoring or surveillance in the post-approval phase to identify the emergence of resistance if, and when it does, occur.

Finally, it includes regulatory endpoints or thresholds which will trigger specific actions designed to mitigate the continued development of resistance.

These principles will be applied to all antimicrobial drugs intended for use in food-producing animals regardless of their intended use. Whether it is therapeutic or subtherapeutic, the same scientific principles apply.

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Some of the concepts within the framework -- basically there are five components. The first is assessing whether the proposed use will result in increased exposure to pathogenic bacteria. This is referred to as pathogen load. If you use the drug in the animals, will the number of pathogens within the intestinal tract of animals increase? If so, how can this be mitigated?

Secondly, it will assess the safety of the proposed animal uses of drugs according to their importance in human medicine. That is, if you are talking in terms of a risk analysis, this is the hazard analysis. The hazard that we are referring to is the impact on public health that would

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result if the antimicrobial in question was no longer effective in the treatment of diseases transmitted directly or indirectly through animal-derived foods. That is the hazard.

Then, the second part of a risk assessment is the exposure assessment. How likely is it that people will be exposed, that the public will be exposed to resistant organisms that are produced as a result of drug use in animals? So, those are the two components to how we intend to evaluate these. We also intend to assess pre-approval data showing that the level of resistance transfer from proposed uses will be safe. We want some pre-approval studies that will give us a predictive value that once the drug is approved the likelihood of resistance development will be manageable. Then, we also will be talking about establishing resistance and monitoring thresholds. That gives us a target against which to regulate. Without those kinds of targets out there it becomes a very difficult regulatory process to say at some point in time, "well, I think now is the time when it is not safe anymore." So, we want to have a target out there from a regulatory standpoint where we can all declare that actions need to be taken, and those actions may not necessarily mean removal of the product from the market, but

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to take intervention steps that will mitigate the continued emergence of resistance. Then, establishing pre-approval studies and post-approval monitoring will be necessary.

The framework document discusses how we intend to categorize these various drugs. There is a two-tiered system. The first system looks specifically at the risk to public health -- how important are these drugs in human medicine? What would be the impact if they were lost from use? So, we have established a category of 1, 2 and 3. Those will be discussed in much greater detail by others. But it is crucial that the importance of an antimicrobial in human medicine be the first determinant before FDA can assess what effect the development of resistance that drug from food animal use will have on human health. We need to know how important it is in human medicine.

The second part is the human exposure to resistant bacteria. This will include looking at the number of animals that will potentially be exposed or treated by the antimicrobial; the ability of drugs to induce resistance in bacteria of public health significance; and the likelihood that use of the drug in animals will promote resistance.

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The pre-approval and post-approval requirements will vary

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depending on the evaluation of these two factors: the impact of the drug on human therapy and the potential exposure of humans to pathogenic organisms.

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So, establishing the requirements will depend on the category; will depend on the ranking system. The number and type of studies that will be required, and the type of post-approval monitoring studies will be determined based on the ranking system that we have proposed in the framework document.

Resistance and monitoring thresholds would be established prior to approval to ensure that resistance does not develop established threshold levels. Resistance thresholds would be set to a defined level of resistance in animals that would result in no or insignificant transfer of resistance to human pathogens.

Monitoring thresholds, on the other hand, would be established so that they can serve as an early warning system, signalling when the loss of susceptibility of resistance prevalence approaches the level of concern.

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So, depending upon the category, pre-approval studies may be needed. Post-approval studies and monitoring, and possibly

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on-farm monitoring studies may be required. We will rely increasingly on the national antimicrobial resistance monitoring system to give us the kind of surveillance information that will be necessary for us to make the right regulatory decisions.

Now, in the presentations to follow, they will provide more of an explanation of the framework document, and presentations will follow on the categorization of antimicrobials by importance in human therapy, the pre-approval studies on microbial safety, post-approval surveillance issues and the need to set thresholds.

[Slide]

So, I would like to start talking about the framework document and the questions on the framework document to the committee. The framework document sets out, again, a conceptual framework for how we intend to regulate antimicrobial drugs in food animals, and the main focus is on resistance although there are some parts of it that refer to pathogen load.

But we are seeking comments on whether the framework will, indeed, accomplish the goals. Is this conceptual framework that we have laid out going to accomplish the goals of protecting public health, while giving us an avenue for

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allowing the approval of drugs when they meet the standards that we have set out, and whether it will provide for the safety of these drugs in food animals. So, we are seeking comments.

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I will go through the questions. Question one that the committee will be asked to address is FDA's goal is to protect the public health by ensuring that the efficacy of human antimicrobial therapies is not compromised due to use of antimicrobials in food animals, while providing for the safe use of antimicrobials in food animals. Does the framework document, indeed, provide a sound scientific basis for achieving this goal, if implemented?

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Question two, categorization of antimicrobials -- the agency is proposing that the categorization of antimicrobial drugs for human medicine take into account the usefulness of the drugs in treating both foodborne diseases and non foodborne infectious diseases. What evidence exists that the use of the drug may result in induction of resistant pathogens or the transfer of resistance elements to human pathogens? This approach recognizes not only the well-known risk of resistance transfer through classical foodborne pathogens,

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but also the threat of transfer of resistant bacteria or resistance genes from other intestinal bacteria of food animals resulting in resistant infections of humans with other types of pathogens, for instance, E. coli or Enterococcus. The question to the committee is do you agree with this concept?

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Question number three, monitoring thresholds -- should multiple monitoring threshold levels be established and should they be based on animal data, human data or both? Should the levels be tied to specific actions, for example, the need for further investigation, the need for mitigation strategies, the need for withdrawal of product from the market, or others?

Secondly, what organisms should be the basis for monitoring thresholds? In the interest of cost containment, should sentinel organisms, and not the pathogens themselves, be designated or should only the foodborne pathogens be used?

[Slide]

The fourth question deals with resistance threshold levels. The agency has proposed the creation of different levels of resistance transfer to humans that would be acceptable based on the importance of the drug or drug class in human

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medicine. Category I antimicrobial drugs would require that the use in food-producing animals results in none or little resistance transfer to humans. Category II antimicrobial drugs would require that a predefined level of maximum resistance transfer be established prior to the approval that would depend on several factors, such as the existence of alternatives to the drug, the human pathogens of concern, etc. The level of resistance transfer must be low enough that there is a reasonable certainty of no harm to humans associated with the use of the product in food animals. What criteria should the agency use to safely define the acceptable level of resistance transfer, if any, for antimicrobial drugs that fall into Categories I and II?

[Slide]

Finally question five, on-farm post-approval monitoring programs will be necessary for certain antimicrobials in Category II and Category II/high exposure, and some Category II/medium exposures. The question is should those on-farm studies be implemented immediately or should they be implemented after there is a for-cause concern, once we see resistance starting to develop?

So, those are the five questions that we hope to have answered by the end of tomorrow, and we will have to have

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answers by the end of tomorrow because most people have flights that are leaving tomorrow afternoon.

So, I commend the advisory committee in advance for what I know is going to be a very lively discussion that is going to occur during the next two days but is of extreme importance to the public and to the Center for Veterinary Medicine. Thank you, Mr. Chairman.

DR. STERNER: Thank you, Dr. Sundlof. Do any members of the VMAC have any questions of Dr. Sundlof at this time?

[No response]

I would like to set the ground rules just a bit. After the break we will begin with our invited speakers, and those are the people seated in the front row, in the reserved seats. We have some housekeeping details that we need to take care of. I understand we are ahead of schedule. The die has been cast for the rest of the speakers and I will hold you scrupulously to the time commitments. You didn't see the trap door over there but it is there!

Setting the ground rules with regard to questions of invited speakers, VMAC members and agency personnel will be extended the opportunity to ask questions. During the public comment period the same applies. If at the end of the public comment period we progress as we have so far, questions from

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the audience will be entertained of any public speakers that remain.

Along the front table, as I indicated, we have invited speakers. There are three people who are there from USDA who do not have prepared remarks to give, Dr. Kaye Wachsmuth, Deputy Administrator, Office of Public Health and Science at FSIS; Dr. Kenneth Peterson, from the Office of Public Health and Science of Emerging Pathogens; and Dr. William James.

Dick, do you have some additional housekeeping details?

MR. GEYER: Yes, I do. Thank you, Keith. We will handle these administrative announcements now and then take a 20-minute break. We need to do some setup before our first speaker. Keith mentioned the need to stay on schedule because we do have a full day, and to help facilitate that we have a little traffic light. In fact, we have two traffic lights for our speakers. There is one right down in front here and then, in case the speaker is unable to see this one, there is one on the lectern, over there. It will go from green to yellow. The yellow is a two-minute warning.

DR. STERNER: And there are no time outs, by the way.

MR. GEYER: No time outs. Then to red. We will set that

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according to the time that we have agree with all of the speakers that they will actually use for speaking. There will be time beyond that set aside for questions as well, except I think, Keith, as we get into the public speakers this evening we are just going to go right on with one presentation after another and, as Keith said, hold questions until the end.

One of things that I need to do as Executive Secretary is to read a conflict of interest statement. Please bear with me as I do that.

Federal conflict of interest laws preclude the participation of committee members and consultants in advisory committee meetings if they have a conflict of interest unless a waiver of exclusion is granted by the agency.

Based on the submitted agenda for this meeting and the review of all financial interests reported by the committee participants, it has been determined that all interests in the firms regulated by the Center for Veterinary Medicine which have been reported by the participants present no potential for a conflict of interest at this meeting, with the following exceptions:

In accordance with 18 USC 208(b)(3), waivers have been granted to Dr. Steven Barker, Dr. Wanda Haschek-Hock, Dr.

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Robert Holland, Dr. Carl Norden and Dr. Keith Sterner.

Under the terms of the waiver Drs. Barker, Haschek-Hock, Holland, Norden and Sterner will be permitted to participate fully in discussions and deliberations which will involve human and veterinary medical issues related to antimicrobial resistance associated with drug use in animals.

In regard to FDA's invited guest speakers, Dr. David Bell, Dr. Sherwood Gorbach, Dr. Patricia Lieberman, Dr. Scott McEwen, Dr. J. Michael Rutter, Dr. Abigail Salyers and Dr. Lyle Vogel, the issues to be addressed at the advisory committee meeting will not constitute a conflict of interest for the above-names guest speakers.

With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they wish to comment upon. This refers to the speakers in our public speaker session, and we will remind the speakers of that when we begin that session.

Copies of all of the waivers are available through the Freedom of Information Act procedures.

I would like to introduce a couple of staff members for VMAC who are here helping today and who will be able to help out with questions that you all might have: Jackie Pace -- if

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you would stand up, Jackie; John Sheid -- John, are you in the back of the room somewhere? I think he is coming in. Michelle Talley. Michelle is back there. Hold your hand up, Michelle. And, is Susan Simmons in the room? She may be outside. Those are the staff members and they and I can answer questions that any of you might have.

Keith, I think those are the only announcements that I have at this point.

DR. STERNER: We are ahead of schedule. We will break for 20 minutes. I have about 9:20 right now. We will meet at 9:40.

[Brief recess]

DR. STERNER: We will start with Dr. Mark Goldberger, from the Center for Drug Evaluation and Research. His subject matter is the importance of antimicrobial drugs for use in human medicine. Dr. Goldberger?

The Importance of Antimicrobial Drugs for Human Medicine

DR. GOLDBERGER: Thank you.

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Just by way of introduction, I am Director of the Division of Special Pathogens within the Center for Drug Evaluation and Research, and we have the responsibility for a substantial number of anti-infective products, including the

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fluoroquinolones, drugs for anti-parasitic disease, drugs for systemic antifungal disease, drugs for microbacterial disease, and some assorted other products. It is a pleasure, obviously, to be here today.

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This exercise of looking at the importance of antimicrobial drugs for human medicine was taken at the request of the Center for Veterinary Medicine. I should point out that under current CBER regulations a product must be safe and effective in order to be approved, however, demonstrating a specific level of importance in human medicine is not required.

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However, many of our regulatory initiatives recognize that some products may be of greater importance in human medicine, and subparts E and H, which I will talk about in slightly more detail in a couple of minutes, deal, for instance, with serious and life-threatening disease, as well as the recently approved FDA Modernization Act which includes what is called the "fast track" designation for certain products.

For those individuals who are interested in a more detailed discussion of issues related, for instance, to definitions

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of serious and life-threatening diseases, one useful resource is the Federal Register, and the citation is 52:19466-19477, May 22, 1987. This was a section that dealt with the IND regulations, and there is a substantial discussion of the topic of serious and life-threatening disease.

[Slide]

Let me also say that our approach was constructed without regard to risks that veterinary use might or might not hold. It is intended to represent the importance of antimicrobials in human medicine. Obviously, our approach is then to be placed in a larger document.

After discussion with the Center for Veterinary Medicine, we did include specific language regarding treatment of foodborne infections. However, I did want to say that we do not regard the issue of importance of the antimicrobial drugs by any means to be limited to that type of infection.

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We put together our approach by utilizing some of the resources within the Center. A number of medical officers from my Division and the Division of Anti-Infective Drug Products as well as microbiologists from those two divisions met weekly for a period of several months. After we put

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together an approach we had it reviewed internally, a little bit within our Center at the level of the Office of the Commissioner, including the new coordinator of antimicrobial resistance activities for the agency, Dr. Jesse Goodman. Then externally, we shared our approach with our colleagues at the Center for Disease Control.

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I did want to make, however, some caveats and a comment about this. First of all, and I think that this will come as no surprise, the importance of a product in human medicine will sometimes change over time and whatever approach is going to be used will need to recognize that. Our system is currently qualitative rather than quantitative. I think that this is an issue that may need to be revisited over time, depending on the construction of the ultimate approach to these issues.

There is a component of subjectivity in determinations of the importance of drugs in human medicine. I had originally thought about titling this "there is an unavoidable component of subjectivity" because that, in fact, reflects some of the issues with medical practice.

Finally, we expect and invite comments. We do not regard this as a completed work. I mean, this is now being

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presented publicly as part of the larger framework document and we would expect that there will be some modifications over time that will need to be made, as well as discussion at different points on how the actual implementation of this approach will need to be done.

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In doing this, we tried to look at several different categories. That is, the disease, drug or drug class, and the availability of alternative therapy.

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Well, as far as the disease, we were thinking primarily in terms, not surprisingly, of severe or life-threatening disease. Again, as I indicated earlier, these definitions have been previously recognized in existing regulatory initiatives. In particular, the subpart E regulations dealing with serious and life-threatening infections, 21 CFR 312.80 and our accelerated approval regulations for products, again, for serious and life-threatening disease, 21 CFR 314.500, as well as in the recent FDA Modernization Act.

As I indicated earlier, we also included some specific language about foodborne disease. I think this is important given some of the data that exists about transfer of

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pathogens from animals to human beings. Nonetheless, I do want to emphasize as we think about the importance of drugs in human medicine we are not certainly, from our approach, limiting this to importance in foodborne disease.

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As far as the drug or drug class, again, I think our emphasis as we thought about this was on serious diseases, drugs that were effective in serious diseases and also drugs that were active against resistant pathogens. I think that is, obviously, an important aspect of this.

There is also, I think, an interest in looking at drugs that may have a unique mechanism of action, recognizing that products like this over time may occupy a very important role in human medicine.

Finally, certainly we looked at issues related to mechanisms of resistance and cross-resistance. In terms of issues like that, let me just say a couple of things. One is that there is certainly a recognition that a product in a class may often, when it produces resistance, produce resistance to all the drugs in the class. That is by no means invariable but it tends to be more common than not, and I think that this is an important issue as we think about a product, for instance, that might have veterinary use, might not be the

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identical product that is used in humans, but we must recognize that if resistance develops to one product it is likely to develop to many others.

We also had some discussion about whether or not we could make definitive comments about mechanisms of resistance or resistance transfer, i.e., chromosomal versus plasmid-mediated resistance. I think that this may be possible now but, as we talked about it, we could see different approaches to that and, at the moment, we believe that rating the comparative importance of any system like this is not easy. Again, this is something that may need to be revisited at a later point.

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I think, therefore, a crucial issue that came up, not surprisingly again, reflecting the way physicians approach the management of patients with serious illness is the availability of alternatives in treatment. And, I think one way we thought about this was that there are essential agents, that is, these are drugs for which really currently there are no adequate substitutes or replacements. There are also drugs of choice for infections or important therapy by alternatives exist. Finally, there are drugs that realistically appear to be of lesser importance, that may no

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longer have major use in human medicine. There may be really little therapy of serious infections with them, or they may have basically essentially been replaced for almost all infections. We think that these categories are extremely important in looking at the overall issue.

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Using the above, drugs were placed into one of three categories. Again, I think practically speaking, at present time most of our emphasis probably is in looking at issues related to serious disease and alternative therapy, however, over time issues of resistance, cross-resistance and unique mechanism will probably grow in importance.

We had originally used a more quantitative approach. When we first thought about this, we thought in terms of potentially using a point system, looking at different issues about drugs resistance, etc. And, I think the advantage of this is that there is a possibility of better discrimination between products and this may turn out to be fairly important.

The drawback, however, is that there is a difficulty in determining what the appropriate points and weights for different categories ought to be. So, this is an issue that we may very well need to revisit, but we must keep in mind

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that although on the surface it would seem as though using a point system would provide greater discrimination, and it may, we must recognize that it also carries the potential for a lot of subjectivity and we would have to be careful how we did this.

In particular, we may need to revisit this issue ultimately because in the ranking as proposed in the framework document one can note very easily that Category II is the largest and the most heterogeneous and, depending on what types of studies, etc., are going to be needed among products in that category, it may be necessary to revisit the system and see if we could provide a little better definition.

[Slide]

Category I -- and I have titled it "essential agents" because I think that is one of the most important aspects of it, although not the only one -- are drugs really for serious and life-threatening disease, essential agents where there are no substitutes, or important for treatment of foodborne infections where, due to resistance or other reasons, there are really limited alternatives, and finally, the mechanism of action or the nature of resistance induction is unique. Keep in mind that these by no means are necessarily mutually exclusive. The fluoroquinolones,

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for instance, which are one of the examples I have for multi-drug resistant Salmonella, although they are very important in serious Gram-negative infections and increasingly important for Gram-positive infections both are useful in serious or life-threatening disease, important for the treatment of foodborne infections and, ultimately have a mechanism of action and nature of resistance induction that are somewhat unique.

So, drugs may be in more than one category here. And, as I mentioned, examples that we have and, again, these are not meant to be comprehensive are vancomycin for methicillin-resistant Staph. aureus and serious Group D strep infections, and the fluoroquinolones for multi-drug resistant Salmonella.

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Category II, drugs of choice, important therapy but alternatives exist. A couple of examples we thought of are ampicillin for the treatment of Listeria infections. Again, ampicillin is the clearly I think the preferred therapy, however, timethoprin sulfa is an important and useful alternative. Erythromycin for Campylobacter infections -- again, at least one alterative currently are the fluoroquinolones.

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We recognize here that, again, there will be a number of diseases, a number of drugs in this category, some which are stronger choices than others; some for which there will be multiple diseases, others there may be only one. So, it may be necessary over time to revisit Category II a little bit to get a little better definition.

[Slide]

Finally Category III, the drugs of lesser importance. Again, little or no use in human medicine, neither the first choice nor an important alternative for human infections. Examples that come up, for instance, are ionophores and polymixins, and there are certainly others as well.

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As far as unresolved issues, I think clearly, as I indicated before, are issues related to refining this approach. Do we need to get better discrimination between products? How exactly in the future will we deal with new products? I think these are certainly important issues.

We need to make sure that our integration into the complete document is satisfactory so that it is clear enough and is understood by the various constituencies that will be involved.

Finally, obviously, and this goes beyond simply the CDER

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component, is addressing the implications of what we have here. Obviously, this is an important aspect for human medicine. It now needs to be fit into a more complete document and, in fact, we now need to understand how we are going to successfully utilize this. Thank you.

DR. STERNER: Does anybody from the panel or invited speakers have questions for Dr. Goldberger? Yes? If you will state who you are and where you are from also?

DR. SALYERS: Abigail Salyers, University of Illinois. First a comment and then a question. The comment is I don't think you should make a difference between chromosomal and plasmid location because there are integrated elements called conjugate transposons that are widely distributed, or found very often in the Gram-positive bacteria and some enteric bacteria which are in the chromosome but they are very transmissible, having a broader host range than a lot of plasmids. So, I think you are right not to try to make that kind of a distinction.

Mu question is that people keep talking about antibiotics that are of importance in human medicine, and they use that in the present tense. Is any thought being given to taking into account the drugs that are coming through the pipeline at the present time that may be important in the future?

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DR. GOLDBERGER: Yes, I think that one of our goals is to attempt to do this at a relatively early stage, and I think obviously we need to have some discussion about when is the most appropriate time in terms of how much information might be needed, for instance, from clinical trials to be able to begin to make such a determination.

But the basic answer to your question is, yes, we think this is important and, in fact, it is products like that which make me think that over time the category of unique mechanism of action or unique mechanisms of development of resistance may become more important as we see genuinely new classes of antimicrobial therapy.

DR. SALYERS: Not to hog the floor here, but just one more thing. There is another aspect of this that maybe should be considered also. Right now there is a large clinical trial of erythromycin treatment to see if this intervention is going to help with heart disease. If that pans out, then all of a sudden the macrolides are going to be a lot more important than they have been in the past. So, there are also new uses of antibiotics in medicine.

DR. GOLDBERGER: Well, if you recall, that was under my caveats, that the importance of antimicrobial therapy will change over time and we can think about examples of that, I

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mean, if you think about the role of vancomycin today and the role of vancomycin twenty years ago, as an example; if you think about the potential role of erythromycin not only in terms of Campylobacter which was the example that we used but also in terms of the role that it has had for many years, perhaps being supplanted recently in terms of the management of a typical pneumonia which became more and more of an issue starting in the later 1970's.

So, we recognize that as changes occur in medical practice, changes occur with emerging infections, there will need to be these alterations. We also need to recognize that it may be that some products that occupy a relatively important position now will be supplanted by newer drugs, either because the newer drugs are better, less toxic, or because resistance issues have rendered some products less useful than they seemed to be. But I certainly agree with you that these are issues that are important, and in the ultimate implementation of this approach will need to be taken into account.

DR. STERNER: Dr. Angulo?

DR. ANGULO: Mark, of the parameters that you list, the one that you did not list is the likelihood of genetic transfer.

On page 14 of the framework document it discusses the

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possibility of taking the categories that you have placed and treating a Category I or II drug as a Category III drug if the likelihood of genetic transfer is deemed to be low. For instance, it points out that if a drug is an essential drug for the treatment of respiratory disease in humans and the likelihood of transfer of genetic resistance from an enteric organism in animals to the respiratory pathogen in human is thought to be low there would be this treatment of Category I or II into Category III.

My question is in your consideration of the parameters, did you consider this concept of likelihood of genetic transfer as a parameter for categorizing importance of human drugs?

DR. GOLDBERGER: Actually not. It is not that we didn't consider it. This was considered as part of the overall of the overall framework document and, as you pointed out, is included in it. Our goal was, as an initial step, to try to focus primarily on how we would prioritize drugs in their importance in human medicine based on information and issues related, I think, to medical practice, the products themselves.

Subsequently, as this approach is integrated into the entire framework document, alterations in categorization, etc., may be made based upon other data. But our first goal was

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simply to get some sort of approach to how we thought of the drugs themselves. Whether drugs get moved up or down by other factors is an issue that I think needs to be addressed in the totality of the document rather than just in our approach.

But, certainly, this is an important issue and I think it is an important issue in terms of the concept, and it is an important issue in terms of how we would actually go about demonstrating that aspect about the level of transmission, and I think that is going to be one of the more challenging aspects to this whole exercise.

DR. STERNER: Thank you, Dr. Goldberger. The next speaker is Dr. Peggy Miller, from the Center for Veterinary Medicine, explaining the animal drug approval process for antimicrobial agents.

The Animal Drug Approval Process for Antimicrobial Agents

DR. MILLER: Good morning. I am Dr. Margaret Miller. I go by "Peggy." I am Deputy Director for Human Food Safety and Consultative Services in the Office of New Animal Drug Evaluation at CVM.

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What I want to do today is talk a little bit about the studies that we require in the approval of a new animal

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drug, new antimicrobial drug; how we evaluate these studies; and how we use these studies to make a prediction of whether or not the product is safe; and then talk a little bit about how we could apply these techniques or similar techniques to making a determination about the safety in the microbiological area.

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Before any new animal drug is approved for use in the United States, the drug sponsor must have an approved new animal drug application. In the new animal drug application the drug sponsor provides data to show that the drug is efficacious, that it is safe for the target animal, that it is safe for the environment, and that it can be manufactured to uniform standards of purity, strength and identity. If the drug is going to be used in a food-producing animal, the drug sponsor must also provide data to show that the drug is safe for humans.

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In the area of environmental safety the agency uses an exposure threshold approach to determine when environmental fate and effect testing are needed. Environmental studies are not needed for compounds that have limited environmental introductions. When an environmental assessment is needed

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the drug sponsor conducts laboratory toxicity studies and in vertebrates, plants and microbes representative of the environmental compartment of concern. The no observed effect level, or MIC in the case of the microbes, is divided by a safety factor to arrive at a predicted environmental no-effect level.

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The predicted environmental concentration of the drug is then calculated, and we compare the predicted environmental concentration, which is referred to as PEC, with the predicted environmental no-effect level to come up with a PEC/PNEC ratio. If this ratio is less than 1 the agency concludes that the compound is safe for the environment or that there will be no significant environmental effects from the use of the drug.

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To determine the human food safety of residues of an antimicrobial product the drug sponsor conducts a standard battery of toxicology tests. The standard battery of toxicology tests looks at systemic toxicity, genotoxicity, mutagenicity, reproductive toxicity and developmental toxicity. Information on these endpoints is required for all drugs which require an acceptable daily intake or a food

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safety assessment.

Additional food safety studies may be required if we have additional human health concerns. For example, if a product tends to bioaccumulate the agency might ask for chronic feeding study in order to establish a no-effect level for that compound.

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The toxicology studies are designed to show a dose that causes a toxic effect and a dose that causes no effect. The no observed effect level is not always a classical tox endpoint. CVM considers the development of diarrhea following treatment with an antibiotic as an adverse effect although clinically this is generally considered a side effect of the drug. The Center views the results of toxicity tests conservatively because we believe that consumers should experience no effects from drug residues in their food.

Once we have established the no-effect level for all endpoints, the most sensitive effect in the most predictive species -- and by that we mean predictive of man -- is established. This no-effect level is divided by a safety factor, and the safety factor takes into account uncertainty, that is, the extrapolation between the animal

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model and the human as well as variability, which is the difference among individuals. After dividing by the safety factor we calculate an acceptable daily intake, and the acceptable daily intake is defined as the level of drug residue that can be safely consumed daily for a lifetime.

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There are special food safety concerns for residues of antimicrobial drugs. It is well-known that therapeutic doses of antimicrobials can cause adverse effects on the human intestinal microflora. The agency has identified the selection of resistance, perturbation of the barrier effect, changes in enzyme activity and alteration in bacterial counts as potential impacts of antimicrobial drug residues on the human intestinal microflora that are a public health concern.

The perturbation of barrier effect is of concern because normally the gut flora prevent the overgrowth and invasion of pathogenic bacteria. When the normal flora is disturbed by an antibiotic, for example, overgrowth of pathogens can occur and infections.

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While the adverse effects of therapeutic doses of antimicrobials on the human intestinal microflora have been

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well documented, in most cases the lowest dose at which these effects occur have not been established. Based on the literature available at the time and the advice of experts in the field, CVM established an exposure threshold for concern of 25 mcg/person/day. For antimicrobial products meeting an acceptable daily intake of greater than 25 mcg/person today the food safety evaluation must include an examination of the effect of the drug on the human intestinal microflora in addition to the standard battery of toxicology tests.

Recognizing that model systems used to evaluate the effects of antimicrobials on the human intestinal microflora were only research methods, CVM funded research to validate an in vitro human fecal culture system and a human flora-associated mouse model. Many of the techniques developed for validating these model systems, especially those to look at the development of resistance and the disruption of the barrier effect, can be applied to assess the development of resistance and changes in pathogen load in the target animals following antimicrobial treatment.

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Now, as was mentioned by Dr. Sundlof, we have asked for microbial safety studies in the past for antibiotics that

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were administered in feed for more than 14 days. These studies, which are often referred to as 558.15 studies, were performed to look at the level of drug resistant bacteria and the level of pathogenic bacteria.

There were two studies generally performed in this battery. The first study looked at the effect of the drug on excretion of Salmonella in the feces of animals artificially infected with a laboratory strain of Salmonella. This study is referred to as the Salmonella shedding study. The other study was a coliform resistance study. This monitored the effect of the drug on the resistance pattern of E. coli present in the endogenous flora.

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In the Salmonella shedding study between 7-12 animals were infected with a laboratory strain of Salmonella typhimurium which was known to accept plasmids. The animals were treated with drug for eight weeks and fecal samples were collected weekly. The laboratory strain of Salmonella was isolated from the fecal samples and examined for resistance patterns, as well as shedding quantity, duration and prevalence.

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The design of the coliform study was similar to that of the

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Salmonella shedding study, except that the animals were not inoculated with bacteria. Rather, the effect of the drug on the endogenous E. coli was evaluated.

Now, because it is difficult to measure a change in resistance against a high background, it was necessary to use animals with less than 20 percent resistance in their endogenous E. coli. A change in coliform susceptibility between the drug-treated and control groups indicated a drug effect.

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I want to say that we do not have standardized protocols developed for the microbial safety studies mentioned in the framework document. However, the techniques that have been used to measure the effect of antimicrobial drugs and residues on the human intestinal microflora, together with a modification of the traditional 558.15 studies, could serve as a basis for developing protocols for these studies, and we are seeking scientific input on both the design and interpretation of these studies and feel that the protocols will be improved if we have significant public input into the process.

As discussed in the framework document, we intend to look at pathogen load issues on an exposure based threshold. Then

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we will determine, based on the amount of the exposure, when a drug sponsor will need to determine if their product alters the level of pathogenic bacteria.

Now, the design of the colonization resistance studies that we did in the human gut flora was similar to the design of the Salmonella shedding study, and it could serve as a prototype for how these studies would be designed to look at pathogen load in the target animal.

Basically, what we are doing in the gut flora studies is that animals are inoculated with a bacterial strain that is resistant to the antibiotic being tested. Also, inoculated bacteria has a propensity to proliferate when the barrier is perturbed. The animals are then treated with increasing doses of antibiotics and the number of indicator bacteria are measured.

One could propose that if there is a margin of safety between the dose intended for use in animals and the dose that causes a proliferation of the indicator bacteria that the product may be considered safe. Alternatively, if the indicator organism or the pathogen proliferates at the intended dose the study could be continued for a recovery period to determine the amount of time required for the endogenous flora to recover from the antibiotic

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perturbation.

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The framework document discusses that we intend to use human health concern to determine when studies will be needed to determine resistance. The objective of these studies is to characterize the development of resistance so that we can make some prediction about the product's safety. To accomplish this, we will need to make several modifications to the traditional 558.15 studies. For example, the traditional 558.15 studies were designed like a bioequivalence study. They were designed to show no difference between the treated and control groups. In order to characterize the development of resistance it will be necessary to design the studies such that the null hypothesis states that there is no difference, and the alternative hypothesis states that there is a drug effect. This type of design will facilitate statistical analysis and improve our ability to make a prediction from the study. The traditional 558.15 studies were done in the target species, and we suggest that the new pre-approval studies should continue to use the target species. However, we believe that there need to be more numbers in order to improve the power of the test and to actually show the

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development of resistance, how that is going to occur.

In the past we extrapolated data from chickens to pigs to cattle. I think this approach is still acceptable provided that the first study provides a more protective standard than the subsequent species.

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In the traditional 558.15 studies all the studies lasted eight weeks. It seems that in the future the treatment period may need to be extended. Basically, the study duration should be sufficient to establish a baseline level of resistance, allow for resistance development and to look at the persistence of the resistant bacteria.

In the traditional 558.15 studies animals were housed individually in separate treatment facilities. This requirement severely limits the number of animals that can be used in the study. The new study will need to look at different approaches for separating treatment and control animals, and for dealing with the problem of cross-contamination.

As far as dosing, in the traditional 558.15 studies animals were dosed continuously throughout the eight-week treatment period, and this is because it was assumed that for feed administration the animal would be continuously exposed to

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the antibiotic. For products that are intended for food-producing animals by therapeutic routes the continuous administration is not appropriate. Perhaps some type of short-term repeat dosing regime, using the dose and route of administration intended in the target animal, would be more appropriate. One could assume that we would do repeat dosing to cover the maximum amount of doses that an animal is likely to encounter under field conditions.

Also, in the traditional 558.15 studies fecal samples were collected weekly. In the new pre-approval studies it seems that the sampling times would need to be tailored based upon the target animal species, the dosing regime and the study duration.

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Finally, we come to indicator organisms. In the traditional 558.15 studies we looked at the development of resistance in Salmonella, E. coli and, in some cases, enterococci. It seems to me that having one set of indicator organisms for all antibiotics may not be appropriate. We may need to change what indicator organism we are looking at depending on the antibiotic. We might have to have drug sponsors provide a justification for what indicator organism they are choosing. Alternatively, we could look at a panel of

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indicator organisms as we are in the gut flora studies. In those studies the indicator organisms cover both anaerobes and aerobic bacteria.

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Bacterial load issues -- in order to look at a susceptibility change in an indicator organism you need to have sufficient quantities of the bacteria there to make an accurate measurement. In the 558.15 studies animals were inoculated with a laboratory strain of Salmonella to ensure that they had sufficient quantities of the pathogen present to measure the drug effect.

Ideally, the study should be conducted with a more normal bacterial load. However, to ensure that there are sufficient numbers of indicator organisms present we may need to do something like use a CDER animal, or provide some other means for establishing sufficient number of bacterial in the animal.

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As I mentioned before, the 558.15 studies relied on no difference between the treated and control groups to predict that the use of the antimicrobial would not affect antimicrobial resistance or pathogen load. The new studies really should be designed to characterize the differences

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between the treated and control groups using standard statistical procedures. In this way, we will have information that we can use to make some prediction about the likelihood of resistance development and transfer to humans.

I want to reemphasize that there will be numerous opportunities for comment on how these studies should be designed and interpreted but, conceivably, we could develop a safety assessment, a risk assessment process similar to that used to do safety assessments in the area of environmental and residue. For example, we could look at the level of resistance development seen in the pre-approval study and compare that to a threshold level in order to make a prediction of safety. The threshold level then would represent the level of resistance that causes an adverse public health outcome.

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So, to summarize then, we have seen that the use of antimicrobial drugs in food-producing animals represents a public health concern, both in terms of the development of resistant bacteria and in pathogen load.

The framework document lays out an approach for when we would look at the studies to address these different areas

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and, as I have just talked about, one way of trying to do predictions in this area would be to apply the safety assessment procedures used in other areas, to make a modification of that to look at the public health and help ensure product safety.

DR. STERNER: Do any of the panel members have questions of Dr. Miller? Dr. O'Brien?

DR. O'BRIEN: I would just make one comment. One difficulty with this general type of study is that if one looks back at the antimicrobial agents that did cause selective overgrowth of resistant bacteria that came over the years to cause this problem, for almost none of them would it have been detected at the time when the drugs were new.

The problem is that the antibiotic resistance genes development is a considered effort of the world's total bacterial populations apparently, and it sometimes takes years or decades for the resistance gene to emerge. Then, after that does happen the selection process by the agent is quite different than it was before.

So, the general problem -- and I don't know how one could approach it in testing a new agent -- is that in any experimental model when the agent is new the resistance gene is unlikely to exist and, therefore, the new agent will have

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no selection for resistance strains. There is nothing to select. Again, I think this has to be at least recognized as a general problem for new agents. And, the general issue that runs throughout this is that it is hard for us to know what the bacteria are going to do.

DR. MILLER: Yes, I don't think that pre-approval studies can supplant the need for continuing monitoring, and Dr. Tollefson will talk about monitoring in a minute. But I do think that they can provide us some information about what we should be monitoring; what indicator organisms we should be looking at. And, I do think that if resistance develops in a very short or relatively short time frame, I would have some real concerns about recommending approval of that product. So, without this type of information I can't make any predictions that can help even in following this along.

DR. STERNER: Other questions? Steve?

DR. BARKER: I would like to agree with Dr. O'Brien's comments that, indeed, it is the entire population of bacteria globally that has to be considered as well, and I am sure at some point we will address imports.

The environmental aspects of the approval for antibiotics, the environmental safety studies that are done for microbes currently address the MIC picture. Given that the soil and

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environmental bacteria that become a component of normal gut flora are exposed to a range of antibiotics through urine and feces dilution in the environment, what contribution to the development of drug resistance might environmental bacteria be adding to the picture, and is anyone examining that?

DR. MILLER: I think the way we are looking at that, and I just briefly alluded to it on the slide, is cross-contamination issues. If we bring clean animals into a dirty facility for subsequent dosing, you know, are they then picking up resistant organisms from the environment? I mean, I am open to suggestions as to how to address all of these issues, but we thought that might be the most convenient way.

The traditional environmental fate and effect studies look at the actual drug entity. So, we haven't gotten into environmental effects of the organisms. That would be handled under these pre-approval studies in the microbiological area. I am looking at it as an environmental cross-contamination issue.

DR. BARKER: Just to follow up, that certainly is a component of controlling your studies but I think my question goes a little bit further than that about what

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contribution this might have just to the general production of resistant bacteria in the environment.

DR. MILLER: So, you are suggesting that as part of the environmental safety studies that we not just look at MIC values but we look to see whether we are selecting for resistant organisms, resistant soil microorganisms?

DR. BARKER: It is just another question of what the use of antibiotics and their effect in the environment generation of resistance, not only in the animals that are actually treated with the drugs but the bacteria that are in the environment that eventually become part of the normal gut microflora of these animals, what effects these drugs may be having there, and how that might be assessed as part of the overall picture.

DR. STERNER: Thank you. We have to draw this to a close. Dr. Linda Tollefson, from the Center of Veterinary Medicine, is going to discuss national monitoring surveillance issues.

Post-Approval Surveillance Issues

DR. TOLLEFSON: Good morning. I am Linda Tollefson. I am Director of the Office of Surveillance and Compliance in the Center for Veterinary Medicine, dealing with all the post-marketing issues.

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What I want to discuss this morning are the post-marketing surveillance issues that are outlined in the framework document.

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Because of the human health concerns related to the use of antimicrobials in food animals, FDA developed an antimicrobial resistance surveillance system as a post-marketing tool to prospectively monitor the emergence and spread of resistance in enteric pathogens. This system is a collaborative effort among FDA, CDC and USDA, and it became operational in January of 1996, and we have expanded it every year since then.

I will describe this national antimicrobial resistance monitoring system, including its strengths and limitations, and then discuss why the agency is considering on-farm studies to monitor antibiotic resistance for Category I and some Category II drugs.

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The program monitors changes in susceptibilities to a number of antimicrobials of zoonotic enteric pathogens from human and animal clinical specimens, from healthy farm animals and carcasses of food-producing animals at slaughter. We are currently monitoring susceptibilities to 17 antimicrobials

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among Salmonella, E. coli 057 and Campylobacter. The antimicrobials are either broad-spectrum or have a Gram-negative spectrum. We have recently begun a pilot study of human Enterococcus isolates using a group of Gram-positive drugs but have not done this for the animal isolates.

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What we have done is set up a system as two nearly identical parts. The veterinary testing is conducted at USDA Agricultural Research Services, Russell Research Center in Athens, Georgia. Human testing is conducted at the National Center for Infectious Diseases at CDC. Both CDC and USDA use a semi-automated system by Sensi-Titer for Salmonella and E. coli testing, and the E test for Campylobacter. The labs have comparable methods of isolate handling too.

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The goals and objectives of the monitoring program are to provide descriptive data on the extent and temporal trends of antimicrobial susceptibility and enteric organisms from both human and animal populations; facilitate the identification of resistance in humans and animals as it arises because we are interested in the emergence of resistance rather than looking at the absolute prevalence of

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resistance; provide timely information to all practitioners; prolong the life span of approved drugs by promoting prudent use; identify areas from our detail investigation; and guide research on antibiotic resistance.

Unfortunately, this monitoring system does not provide sufficient information to ensure continued safety of specific food animal antimicrobials after their approval and marketing.

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The reason for this -- the system has a number of inherent limitations. The national antimicrobial resistance monitoring program is only a sentinel system. We can't estimate the magnitude of problems; we can only identify if resistance is emerging. The system cannot tell us how or why the resistance occurred. We do not, and actually are unable on the animal side to collect data related to the resistance findings, such as demographic information and history of drug use. Therefore, we are unable to link the data to particular practices of concern.

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Findings from the system then will often require complementary sources of information or more focused analytical studies to be validated. Also, selection biases

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arise in both the human and animal populations that we are testing and this can severely limit the statistical inferences that can be derived from the data. For example, only a percentage of humans may visit a physician when they do have a foodborne disease. There are questions concerning accurate diagnoses. Samples are not always taken and submitted or reported. Similar problems occur with ill animals.

Now, the program has been expanded as resources permit, as I mentioned previously. For example, with the cooperation of the Food Safety and Inspection Service we have been able to increase the number of Salmonella isolates that are taken at slaughter. However, we are still limited by the cost of supplies and personnel in the number that we can conduct and, of course, we are dealing with Salmonella in this case only.

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Post-approval monitoring programs would fill many of these gaps for critical drugs. FDA has proposed that these studies be conducted for all Category I drugs and some Category II drugs. They may be necessary for other drugs if the national program, for example, or another source of information found unexpected or unacceptable resistance.

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What we are thinking about here is that on-farm surveys could be designed to obtain a true prevalence of resistance or decreased susceptibility to specific drugs or drug classes in a food animal production setting. Because we could link the resistance outcome to contextual information surrounding the sample collection, on-farm data would provide a strong body of scientific evidence that specific factors, drug related or not related, are leading to resistance outcomes.

We anticipate that these objectives could be accomplished from a broad national on-farm program rather than a drug specific study undertaken by each sponsor. Also, they 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 a single sample.

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In addition to other scientific data, the post-approval monitoring programs could provide a critical early warning system for detecting and evaluating the emergence of resistance under actual use conditions. On-farm studies would allow the agency and the drug sponsor to monitor for established resistance and monitoring thresholds as are described in the framework document.

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If, on the other hand, we relied only on the national antimicrobial resistance monitoring system to monitor for established thresholds among the animal data we would have to either greatly expand the veterinary portion of the national system, or lower the threshold to a more conservative value to allow for the uncertainty in the estimates. The national program is not really robust enough in its current form to either establish or monitor thresholds with any kind of confidence.

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The on-farm studies would be used to collect risk factor information such as drug exposure associated with the collected samples; identify areas to implement mitigation strategies should resistance emerge; and also test effectiveness of on-farm intervention strategies. Identification of risk factors for resistance development, such as production practices of drug use practices, will allow mitigation of antimicrobial resistance at the farm level, and should give us a great deal of information on how to do that. Probably very importantly, on-farm data would also provide scientifically based evidence for evaluation of effectiveness of intervention or mitigation strategies. That is something that we don't have much information on

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now.

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On-farm studies would provide very useful information also if resistance should reach a predetermined threshold.

On-farm studies could conceivably identify a more precise location where resistance was developing, for example, in a certain geographical location for a specific drug of a class, 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 is causing the resistance to develop.

Without the information these studies can provide, when resistance reached the predetermined threshold action would need to be taken against all drugs and dosage forms in lieu of information showing that some forms were safe. In other words, we are looking to more focus for on-farm studies to provide much more detail about resistance emerging under actual use conditions.

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To summarize -- and I know this is a brief presentation but I will answer questions -- although the national antimicrobial resistance monitoring system can provide a broad overview of resistance trends for both human and

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veterinary enteric pathogens and information on several drug classes, it cannot provide demographic and drug-related and non-related risk factor information on the animal side of the system.

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The post-approval monitoring programs then are expected to provide data on both resistance and risk factors under actual conditions of use; a means to monitor for established resistance and monitoring thresholds after approval; to help ensure they are not exceeded; and, a means to investigate intervention and mitigation strategies, and implement promising strategies in a timely fashion, and then follow what happens once the mitigation strategies are implemented.

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On-farm post-approval monitoring programs are proposed for certain antimicrobials, Category II, Category II agents, some Category II/M products. The question that we are putting to the committee is one of timing. Should on-farm monitoring be instituted by drug sponsors immediately after approval, or be triggered by a change in data generated from other sources, such as the national antimicrobial resistance monitoring system?

The advantages to having these studies instituted

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immediately post-approval are an increased insurance that resistance and monitoring thresholds will not be exceeded; that data from on-farm studies will allow us to more precisely determine why and how resistance is emerging; and that mitigation strategies can be implemented in a timely manner. The disadvantage is the cost associated with the studies, potentially in situations where a problem will never arise.

Are there questions?

DR. BARKER: For the on-farm type of study, what are the advantages of doing those on farm versus doing them at a stockyard or slaughterhouse?

DR. TOLLEFSON: The main advantage -- I would consider a stockyard on-farm -- the major advantage is to try to pick up the contextual information surrounding the sample. In the national program when we collect the slaughter isolates, for example, we get species and the sample. We get a broad geographical location but nothing else. So, we don't have any kind of information on the sample that could rule out drug, non-drug causes to that resistance development. If you have a program in place where you are monitoring on-farm -- actually, the collection of the sample should probably be close to slaughter because we may not be interested in what

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happens earlier, conceivably you would have at least a mechanism to collect the information on the risk factors, to find out if, say, a poultry house or the group of animals was treated with drugs what other husbandry practices could be going on; not cleaning up the farm and the environmental concerns that you had mentioned in response to Dr. Miller's presentation. That is what we are thinking of. We don't have any means of doing that in the national program.

DR. STERNER: Yes, Dr. Lein?

DR. LEIN: My concern really in bringing up this fact of on-farm versus at slaughterhouse is that we have attempted to do those studies. At least fecal-carrying organisms may stay basically pretty stable between leaving the farm and getting to the slaughterhouse. On-hide contamination -- what you brought up, Steve -- is a big problem. We see changes taking place. Hide is a big sponge that works very nicely as a swab. And, just transportation changes. So, we have to be very definitive, as you start to look at Salmonella, as to typing those and that becomes very expensive because they do change. And, we see a lot of environmental effect in this situation. So, bird contamination, trucks and other things begins to accumulate on these hides as they get to the slaughterhouse.

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Also, at slaughterhouse one thing that we have never done that needs to be looked at is what is the environment of the slaughterhouse? What is happening basically as we bring people into this? People become a problem too. So, you have that problem to look at as well.

The on-farm studies, as we start to look at these, I think in veterinary medicine and this is probably also true in human medicine -- we have looked at the individual and as we start to look at herds we certainly can make a diagnosis of the condition. The next thing is how that changes over time is not looked at very easily. And, if you start to look at what is happening with that herd, and that is where it becomes very expensive for the farmer and veterinary medicine -- over time I think it is necessary but who is going to pick that up? Who is going to pick up the price of monitoring as we go on to following a treatment basically? And, even the laboratories to do herd type work -- we have to redesign the ability to look at least at a percent of those samples to know what we are looking at and the environment that they are in.

The environment changes so quickly. I was just at a herd the other day doing testing, and if you look at the amount of bird contamination that comes into that herd -- and I

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know as we work with the poultry industry, and this would be true of any industry, the amount of rodent contamination -- it is quite interesting, how that changes. So, the monitoring is going to be something quite interesting to look at.

DR. TOLLEFSON: But I think those are risk factors that you have identified --

DR. LEIN: Yes.

DR. TOLLEFSON: You know, the environmental contamination, rodents, birds and so on.

DR. STERNER: Dr. Angulo?

DR. ANGULO: I just wanted, Linda, to make sure you are aware of how much we support your concept. I think there is much detail that has to be worked out for exactly what on-farm monitoring might be, but the point is well taken that there are limitations in national surveillance through the NARMS, and if we see increases in resistance, unless there is some work being done on the farm -- and I am not sure who is going to do it and to what extent it gets done, but unless something is being done on the farm it is unclear how to mitigate what we are detecting in the national system. So, the point is well taken. There are clear limitations in the national system, and unless there is

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something being done on the farm we are left with uncertainty on how to mitigate the resistance.

DR. STERNER: We have time for just one last question and, Wanda, I saw your hand first.

DR. HASCHEK-HOCK: I just wanted to follow up on what Dr. Lein said about on-farm surveys versus slaughterhouse surveys because recent studies at the University of Illinois have shown that transportation markedly increases shedding of Salmonella in animals that were not previously shedding. There is also a study showing that food withdrawal can also affect shedding. So, I think that those factors are really important in this discussion.

I also wanted to ask if any other countries have been looking at implementing this type of monitoring and, if they have, if you could give us some details.

DR. TOLLEFSON: In answer to your first point, we are aware of those studies that show transportation effects, but keep in mind that we do have the national program which is heavily weighted towards slaughter samples so we can look at the broad emergence of resistance by species, and we would use the data together. The on-farm data would be really more to refine where and how to implement mitigation strategies before it reached a point of no return, if you

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will, or before resistance would be great enough to impact human public health.

In answer to your other question, there are actually quite a few surveillance programs that are either just beginning to be developed, or in some countries have been in place for a while. One that comes to mind is the Danish system, which is in human and animal and retail food. It is really quite extensive. That does incorporate on-farm data. They have limited information collected with those samples and I am not sure how much. I know they do like thousands, 30,000 samples a year. For a very small country it is quite large.

Then, there are some European-wide ones that are just starting to get into place. Also, the Canadians. Rebecca Irwin is here. They also are starting to do a surveillance program. I don't think, though, that it incorporates an on-farm component but she can talk to you. I am sure she would be willing.

DR. STERNER: Excuse me, as Chair I am charged with keeping us on task, and thank you, Dr. Tollefson.

Next, we have from the Centers for Disease Control, Dr. David Bell addressing the issues and the needs for looking at the benefits for establishing threshold levels. Dr. David Bell?

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Need for Addressing Issue and Benefits of Establishing Threshold Levels

DR. BELL: Thank you. The introduction of antibiotics in the 1940's has led to enormous benefits to mankind, and human medicine has led to dramatic reductions of illness and death due to infectious diseases and, by improving animal health, has led to increases in food production. However, the widespread emergence of drug resistance threatens these benefits.

Antimicrobial resistance develops as a consequence of antibiotic use in hospitals, in the community and on farms. Although there is some overlap, the pathogens that acquire resistance and are transmitted in each of these settings tend to be different so that efforts to prolong the useful life of antibiotics must focus on each of these settings. Our focus today is on farms.

CDC recognizes that the use of antibiotics in agriculture is important to enhance food production. However, antibiotic use on farms can pose a risk to human health due to development of resistant bacteria that can infect humans. Resistant bacteria can be transmitted by food, contact with infected or colonized animals, or resistance to genes that emerge in animal strains can be transferred to human

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pathogens. Judicious use of antibiotics is, therefore, an important preventive and control measure.

I would like to take a minute to pay tribute to the efforts of the American Veterinary Medical Association. I believe that Dr. Vogel is going to speak about their efforts later and I don't want to steal too much of his thunder, but they have really pioneered, over the last year, and have developed an excellent set of general principles to guide the use of therapeutic antibiotics by veterinarians. I am associated with the committee and I can testify to the dedication and commitment of the AVMA and the people who work on this committee, and this is a very impressive contribution.

Much of the difficult work remains to be done as specialty groups take the general principles and develop specific recommendations for their members. This is a pioneering and important effort, but it only applies to the therapeutic use of antibiotics under the control of veterinarians and, as we know, much antibiotic use on the farm is neither therapeutic nor under the control of veterinarians.

Partly to fill these gaps, and partly because compliance with voluntary measures may vary, we very much need a regulatory framework that ensures the availability of safe

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and effective drugs for treatment of human disease and for food production.

Now, there has been a lot of disagreement over the years between human and animal health communities on these issues. Unfortunately, the controversies have progressed beyond disagreement. There have been a lot of bridges burnt over the years between the animal and human health communities. These bridges need to be repaired. I think in the last year we have seen steps in that direction, and I would mention again that AVMA's efforts in inviting representatives of human medicine to serve as liaison members to their committee has been very helpful. We still do have a long way to go.

Now, it has been very difficult to arrive at a consensus between the human and animal health communities. We all pay homage to the scientific data. However, the problem is that people with different perspectives interpret the same body of information differently. Physicians in human medicine who deal everyday with drug resistant infections may not appreciate the difficult problems in food animal production. People who wrestle everyday with how to produce food economically may never have stood at the bedside of a critically ill patient with invasive Salmonella or other

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serious infection, hoping that the antibiotics will work and having to deal with the consequences when they did not work. These differences in professional experience and perception inevitable affect how people interpret available information on the issue. In addition, of course, some people with major economic interests at stake may find it difficult to adopt a position contrary to those interests, no matter how much scientific data may be available and what it may show. So, although more scientific data may help to narrow the gaps, I am starting to wonder if there will ever be a true scientific consensus shared by both the animal and human health communities. I am starting to think that we are reaching the point of diminishing returns from expert committees and scholarly reviews. It seems that if we know the percentage of human versus animal health experts on a particular committee, or writing a particular report, we can often pretty much predict what the report will say. These reports in general have not changed people's minds anyway. They have been basically used by partisans of various positions to wave at each other and selectively quote passages from.

In frustration, some people on both the human and the animal side have given up hopes of truly working together. They

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have sought to impose solutions through legislation or other types of congressional intervention. These strategies may occasionally produce short-term victories. However, these victories just galvanize the opposition to fight harder, and are really not a long-term strategy for the long-term goals of ensuring safe and effective antibiotics for the treatment of human disease and for food production.

Some may find a stalemate acceptable but ultimately history will pass us all by since it will inevitably be difficult to get approvals for new drugs on the farm if public health concerns are not addressed. Countries that do address public health concerns may well seek to erect trade barriers against products from countries that do not.

So, what is the solution? There really is no substitute for folks in human and animal health communities to roll up their sleeves and figure out an approach that meets the needs of both. We are going to need to look outside the box for solutions.

I just want to reiterate that, you know, I have heard people say that we need more research; if we just wait for this upcoming scholarly review, then everything will become clear; if we have one more meeting or blue ribbon commission, that will lead to consensus. I am starting to

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hear talk about waiting for scholarly risk assessments. You know, all of these approaches do have some value, but I am not sure that they are going to produce consensus at all. The risk assessment scholarly reviews inevitably depend upon assumptions and weighting factors, and whatever the results are they are going to be challenged by the other side.

I think that what we have to do is figure out an approach that we can all live with even if we don't totally agree with each other. There has been a lot of progress in the last year. I mentioned the AVMA. There was an interesting initiative during the summer in connection with the approval of the cattle fluoroquinolone product, whereby the FDA and the sponsor, the Bayer Company, arrived at an agreement that permitted the licensure of that product. CDC was happy because the public health needs were met. The FDA and the company was happy; the producers were happy. Hopefully, even the cattle were happy. And, this is the kind of pioneering, outside-the-box thinking that we need.

So, we are now looking at a novel FDA proposal. FDA is really to be congratulated in stepping outside the box to develop this proposal. This is pioneering, innovative thinking. It needs tuning. It will be difficult to implement, but it is a framework offering the hope of the

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way forward. If it really works it could be offered as an alternative to more draconian measures proposed or undertaken in other countries. If we have a framework in the United States that both the FDA and CDC state meets the needs of protecting the public health, that will be a strong argument in any trade dispute where public health is an issue.

Now, the three options in responding to the FDA proposal that I think folks have available. One option is purely negative; just say, "no, this will never work; it's a bad idea; just say no."

The other is to pay lip service to the approach, to proceed to go along but then basically sabotage the implementation in one way or another. I suspect that might not be too hard to do with a determined effort. I think we all know there are a lot of questions about how this proposal will be implemented. There are going to be difficulties, and I think if a major stakeholder were really determined to block its implementation it might be possible.

Well, if this FDA proposal fails I predict we will all be back here in a few years, looking at each other, in the same predicament but with a dramatically increased level of bitterness as people point fingers as to why it failed.

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The third option that people have is to make it work -- just make it work. We know there are going to be issues and difficulties, and it needs to be tuned but just make it work because when we all get down to it, you know, aren't we all basically sick and tired of these endless arguments and disputes? Don't we really basically want the FDA to come up with a proposal that we can all live with?

We are going to have to help them. I guess for some folks the idea of helping a regulatory agency might not be something they think of as part of their daily duties but, in this case, we are really helping each other; we are helping ourselves to help the FDA come out with a proposal that works. So, I want to just reiterate a plea that we help them make it work.

I have also been asked to comment on the issue of preestablished thresholds. Using preestablished thresholds to trigger public health interventions is a well-established concept. Many people are aware that thresholds are used in mitigating chemical hazards, but also in infectious disease this concept is used. For example, in deciding whether to mount a mass vaccination campaign to interrupt transmission of meningococcal disease in a community CDC uses a threshold level of 30 cases per 100,000 population annualized. For

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comparison, the background rate of invasive meningococcal disease in the United States is 1 case per 100,000 people per year. If a population such as a school or a community has an annualized rate of 30 per 100,000 in a specific time period, CDC recommends mass vaccination. Sometimes in a small community or college that can only amount to a few cases but the idea of having this threshold saves a lot of time and effort, and streamlines things and provides guidance, and we have found it to be very effective. Currently, for animal drug approvals the only public health safeguard is the approval process itself. This process can only predict what may happen after a drug is marketed. After approval, if a problem develops the burden is on the FDA to prove that the drug is unsafe. This process can be lengthy and difficult and meanwhile the consequences mount. Therefore, the FDA needs to be cautious in approving new animal antibiotics. If resistance thresholds were established prior to approval in sentinel organisms, for example Salmonella, and if rates exceeding these thresholds more or less automatically resulted in corrective actions, including ultimately withdrawing the approval, CDC would be less concerned about seeing certain antimicrobials approved for food animal use. The AVMA prudent use guidelines would

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be an essential component part of this framework, providing guidance for veterinarians to use the antibiotics in a way to minimize the likelihood of crossing the thresholds. Preestablished thresholds are important to focus preventive efforts and to allow prompt mitigation of hazards if the thresholds are exceeded, that is, without an extended period of discussion while resistance rates continue to rise and the antibiotic becomes progressively less effective. Monitoring thresholds should also be applied to certain currently approved antibiotics, regardless of whether they may be therapeutic or subtherapeutic, with threshold levels requiring corrective action determined by increases in resistance rates for sentinel organisms. The thresholds must be scientifically based and determined on a drug by drug basis.

We are not sure exactly what mechanism the FDA would use to develop these thresholds. They will undoubtedly want outside input, and thresholds would need to be reviewed periodically.

Since CDC is primarily concerned with human disease, we are most concerned about resistance in human isolates. We would advocate that thresholds based on resistance data from human strains derived from animals be a major determinant of

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regulatory action. For example, CDC estimates about 2,500 cases per year of invasive Salmonella infections in the United States. At the present time, fluoroquinolones are often the drug of choice for invasive Salmonella infections. If the rate of fluoroquinolone resistance in invasive Salmonella from humans rises to 1 percent that will place about 25 patients per year at risk. Treatment failures will be expected. A resistance rate at that level would be of great concern, particularly if the trend was upward. These isolates would be from patients who are not travelers, without pets, not taking antibiotics, and there really wasn't much reason that they could have developed this other than from food animal origin in the U.S.

Now, this would be an example of a threshold that should lead to withdrawal of use from the particular species of animal linked to these infections, and a comprehensive system of surveillance in slaughterhouses would not only confirm that a particular species was associated with the increased human rates but would provide early warning because increases resistance rates at slaughter would precede increased human rates.

In closing, I just want to reiterate one more time the importance of taking the framework proposed by the FDA,

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making constructive suggestions to improve it and then really rolling up our sleeves to work together to make it work. Thank you.

DR. STERNER: Thank you, David. I will editorialize for just a moment. I hope that panel members were listening very carefully to a very astute insight into the people and politics of what is really a very divisive issue within the professions. Thank you. That was really remarkable, David. Are there questions for Dr. Bell from the panel?

DR. LANGSTON: I wanted a clarification on that one percent resistance in Salmonella leading to so many human cases. Is that veterinary isolates that you were referring to or human isolates?

DR. BELL: Human isolates.

DR. LANGSTON: Okay. It seems that a key point in this is the fact that there is an association between an increase in the veterinary isolates leading to a human outcome. Do we have a model to do that, and how good is that association? How predictive is it? Do we have any data on that?

DR. BELL: I think my colleague, Dr. Angulo, could speak to the scientific data issues with a greater depth of expertise than I could. We believe that the great majority of Salmonella cases in humans in the United States are

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attributable to Salmonella derived from food animals. Taking a level of resistance in animals and predicting what would be the human level of resistance, and how to model that, I think might be difficult. But if we start -- perhaps not start, if we use as a major determinant the threshold of Salmonella resistance in human cases-- and these human cases would not have pets, or have traveled, or have any other realistic explanation -- we could be confident in attributing that this was resistance resulting from drug use on the farm. I don't know if Fred wants to add to that.

DR. ANGULO: Well, I think one of the important background statements by the FDA in the framework document, at the bottom of page three, the last sentence, says for foodborne pathogens, especially for those such as Salmonella which are rarely transferred from person to person in the United States -- to paraphrase what it says, antimicrobial resistance in those foodborne pathogens, the driving force for that resistance is use of antimicrobials in food animals.

It is true that we cannot say with certainty with a single case where the resistant infection that that person got came from, but when you use epidemiology and look at a population

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basis, we can say with extreme confidence that the dominant factor contributing to antimicrobial resistance in foodborne pathogens is use of antimicrobials in food animals. That is an important background statement. It is actually not one of the discussion points of this committee but it is an important epidemiological certainty.

DR. BELL: I don't know if this would be better reserved for the discussion part of this, but I can see that for a Class I disease where you are not allowing any increase in resistance, but I don't think I buy into it for a Class II disease where you are having to establish a baseline. I would think you would want some sort of strong association or at least an association on a Class II or a Class III if you are trying to make a quantitative assessment.

DR. ANGULO: I just have one clarification. I understand that except that, of course, the categorization of I, II or III is based upon the antimicrobial not the organism. Salmonella, whether it be tetracycline-resistant Salmonella or whether it be fluoroquinolone-resistant Salmonella, that assumption of where the resistance comes from is still clear.

DR. STERNER: Dr. Galbraith?

DR. GALBRAITH: David, given some of the regulatory

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traditions of the federal government, I am curious what you would say about the justification for human indicators and thresholds as opposed to a more conservative approach.

DR. BELL: I am not sure I understand the question. What would be the more conservative approach? I apologize, I just don't -- in the background of regulatory tradition, I am not sure what you mean by that.

DR. GALBRAITH: Well, for example, the regulation on pesticide residues in air, food and water -- we don't wait for human indicators before taking action, and what you were referring to are some human indicators and thresholds that would trigger action.

DR. BELL: Well, I am not knowledgeable about regulation of pesticides. I think one of the problems that we face here is that we need antibiotics in animals. When antibiotics are approved for use in animals we can't really predict what level of resistance will result; how soon it will result. I support Dr. O'Brien's comments in that regard. So, we would be willing to take a chance, if you will, recognizing the legitimate needs of antibiotics on the farm, as long as there was a good surveillance system that picked up the first signs of adverse human consequences and there was a system already in place to mitigate the hazard. Otherwise,

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I don't see any other way out of these endless arguments of what would the risk be from approving a drug to be used on the farm. We can't predict it. There is a fair amount of data based on studies in laboratory animals indicating at what level a chemical in the environment would pose a hazard, and so we don't need the human cases to develop; we can monitor the level of chemical in the environment. But in this kind of situation I think it is different.

DR. STERNER: Thank you. That concludes Dr. Bell's remarks. We will move on to this afternoon's first speaker and we will stay on task. Dr. Scott McEwen, from the University of Guelph, is going to talk about risk assessment. We have all heard many comments alluding to the need for good risk assessment. He is going to explain what happens.

Risk Assessment

DR. MCEWEN: Well, I certainly hope so. While we are getting to the slides, I would just like to echo the Chair's comments. We really have heard a lot of references to risk assessment this morning. Dr. Friedman talked about the need for balance and making decisions in the face of uncertainty; that it is a prescription for formal risk assessment to do that sort of thing. Dr. Lurie talked about risk assessment being an imperfect science. I think that is something we

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have to work on. Dr. Sundlof talked about the complexity of this issue of antimicrobial use in animals, and simple answers don't seem to work anymore, and I think that is a compelling for risk assessment. Dr. Miller talked about the possibility of using a risk assessment approach to achieve the goals of the framework document, and I would like to echo that. Dr. Tollefson referred to some issues that I would fully endorse, and am excited about, in terms of the post-approval monitoring that could provide data to use in risk assessments. Of course, Dr. Bell set the stage up very well in describing some of the problems we have had with risk assessments in other areas where they have been used perhaps to obfuscate problems or issues of delay processes. I think we don't want to see that but there are other aspects of risk assessment that can be quite useful. So, with that kind of introduction, if I could have the first slide, please?

[Slide]

I hope you can read that at the back. As a researcher in the area of epidemiology of food safety issues on the farm, as I teach veterinary students in public health, I have been interested in risk assessment for a number of years. And, I should thank you very much as a Canadian for having me down

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here to talk about this topic. I feel a little bit awkward in a sense engaging in discussions that have to do with U.S. policy, but I hope you will understand, and I will try not to step out of bounds.

[Slide]

This is a little outline of the talk, basically a brief background on risk assessment. I know a lot of people here know a lot more about risk assessment than I do, especially folk on the chemical side of things but I will just touch on a few sort of salient points. I will talk about the needs and possible uses for it on farms. I think that is a very germane issue to today's topic; then a little bit about some general model structures, what is being used on the microbial side in other fields which I think also is relevant. And, I will touch on some data needs.

[Slide]

I guess the purpose of my brief talk today is that I would like to encourage very much the use of a formal risk assessment approach in dealing with this issue, and I think it should be done very explicitly.

The history of this -- the U.S. has made very major contributions to the whole field of risk assessment. As everybody knows, part of the total risk analysis packaging

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includes risk management and risk communication, and I won't touch on those topics today. I like to think of the beginning, starting with the issue of trying to assess, as was just mentioned a few minutes ago, the risks from contaminants in the environment, emissions, pollutants and other things of that nature where, because of the nature of the problems these hazards might cause, we don't have actual counts of human disease. So, there needs to be a surrogate way of looking at it. So, the EOA, as I understand the literature, has provided a lot of background there.

We also know that it has been used to assess risk for food additives, especially veterinary drugs in today's context. It is used in the engineering field to look at safety of public facilities. On the animal health side of things, risk assessment is being embraced more fully in the way of addressing the hazards that may be associated with importation of animals from other countries. Importantly, in the upper right-hand corner is the sort of recent burgeoning of information having to do with microbial food safety and risk assessment, and I will touch on that in greater depth.

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People have referred to the various documents and expert

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groups that have looked at this issue in the past. One that I am especially fond of is this one here. You can't read the title. It is the Institute of Medicine report from 1989 that looked at subtherapeutic use of penicillin and tetracycline. This copy is very ragged because they have had law students borrow it and drag it in their backpacks, and there is a tremendous amount of information there. I would like to compliment the people who worked on it.

[Slide]

The one sort important follow-up and, again, this slide isn't going to show up very well, is that this document used a risk model. A lot of people have referred to that. The point I am trying to make here is that there is a variety of ways of conducting developing risk models. This one was based pretty much on CDC type data where you have information on outbreaks of Salmonella, and that sort of thing, and they used a sort of default approach to try to portion out the number of cases that may happen as a result of drug-resistant salmonellosis that could happen as a result of use of these drugs in food animals.

The type of risk assessment model I would propose is different than this. This would be a vehicle for validation. It would be useful for other purposes. It

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underpins the type of estimates that Dr. Bell referred to a few minutes ago. Estimated 2,500 cases per year would be developed through this type of modeling approach. The type that I would foresee or others have suggested would be quite different.

[Slide]

If this was a group of students, and I know it is not, I would say you should go downtown to the National Academy press and buy all their books on risk assessment. If you really want to learn a lot more about what has been done in other fields in this area and how it could be applied to this difficult issue of drug resistance, there is a tremendous amount of information there and I think it is well worth seeking out.

The book on the far right, and again you can't read the title, is called The Red Book. It laid out for readers like me in other countries, and everybody else, the basics or concepts for risk assessment. The other books sort of grew out of that.

[Slide]

This sort of outlines what I would call the NRC model for risk assessment. There are four basic levels: hazard identification, to which Dr. Sundlof referred, is on the

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left; dose response assessment or hazard characterization; exposure assessment and risk characterization, the sort of classic setup, and that is what I think would be sort of useful here.

[Slide]

Some roles of risk assessment -- I think this is where we start to get into areas that haven't been looked at a lot outside of the chemical area. People are talking a lot more about this in the food micro side. If you have any food micro experts, I would welcome their comments.

One of the issues around the role of risk assessment and food safety, food microbiology is that we have known for a long time that end-product testing is really not the answer to try to solve the problems, and we have to engage more in process control. That is where the HACCP program has come in. One of the problems with developing that sort of program is that we don't really have very good data on which to specify limits for critical control points, and I think a lot of folks would look to risk assessment as a way of modeling the process and quantitating the process, if possible, as a way of specifying those types of criteria for a HACCP or quality assurance program.

Of course, hazard assessment is an important part of it,

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quantifying the probability that hazard will exist, in this case drug-resistant pathogens. The third point is the one that most people sort of refer to a lot, and that is getting the estimate of risk from a given scenario. I think a lot of people in the literature say we put too much emphasis on getting the estimate and not enough emphasis on understanding the process, setting out the process and finding out where the data gaps are.

Mention has already been made about the trade implications. I won't go into that. I think the bottom line is important in this context, and that is that risk assessment's greatest value in a regulatory scene is to try to assist decision-making, no more than that.

[Slide]

We need to identify the outcomes of interest, and in general terms the risk to human health of antibiotic use in animals is well described in the framework document, but I think that most people, when they start putting together the specifics, need a lot more specification. There may be subgroups of the population that need to be especially looked at.

There needs to be discussion about whether it is possible to do quantitative risk assessment or we may just have to do a

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qualitative one. It is useful perhaps to think about what are bounds of acceptable risk, and this has been talked about today. So, the risk assessors can give the estimates in those sorts of terms -- is it risk per million of population? Is it risk of too many drug-resistant bacteria in carcasses? What are the bounds of acceptable risk?

[Slide]

Hazard identification or first stage of risk assessment I won't go into anymore at this point because it has been well laid out in the framework document and we have talked about it already. There is sort of some fine-tuning that we could talk about at some point.

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This is sort of the heart and, again, I apologize for it not showing up too well. There is too much information on one slide. The heart of the risk assessment, the way it is sort of evolving in the microbial food safety area, in my opinion lies within the exposure assessment phase and the dose response modeling phase of the process. Now, the main goal of the exposure assessment phase is to be able to estimate the prevalence of contamination, microbial contamination of the product at the time of consumption. That would be the ideal. And, the concentration of bacteria, or genetic

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determinants or whatever it happens to be, in the food. So, what total dose is a person getting at the point of consumption? Because microbial agents tend not to be cumulative, we usually don't think in terms of prolonged exposure over a period of time. So, in a one-time setting what is the exposure?

The dose-response aspect of it is a very hot topic of research in the food and microbiology area. These are the efforts, a set of efforts that are going into trying to determine what are the expected efforts from a given exposure. That is the prevalence of the organism and, if it is there, what is the concentration. It is a very difficult area to work towards but it is a very important one, and it has implications to this situation as well on the drug resistance side.

[Slide]

This is a very rough outline of a quantitative microbial risk assessment, 0157 in hamburger, that was done by some colleagues at Guelph, Mike Cassin et al., in the International Journal of Food Micro. This year, I know that USDA is working on this in a modular sort of approach in a very big way, and I know there are other researchers working on it as well.

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Again, it is not showing up, unfortunately, and the reason I am showing you this is just to give you a rough outline of the types of exercises that other people are working towards and maybe we can learn some lessons on the drug resistance side. On the upper left of the screen, basically this could be a set of equations or a single figure on estimates of prevalence and concentration of 0157 in feces of cattle. I had a Ph.D. student who did his thesis on trying to model that component of the process itself. So, it can be simple or it can be complex depending on how you do it.

These data from the prevalence and concentration phase feed into processing and grinding module within this risk assessment model, basically looking at the slaughter and processing and handling of ground beef, and trying to determine the various effects of parameters within that system. So, within that little box I have incorporated many different parameters and haven't broken it down for the sake of simplicity.

That provides input for another model on the prevalence and concentration in ground beef. So we go successively down the road to the point of consumption. We try to estimate again prevalence and concentration, feed that into a dose-response model and get estimates of mortality as a

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desired outcome. That is the general outline of the quantitative risk assessment model.

[Slide]

We could apply the same kind of ideas to the antimicrobial resistance area. On this slide, which is a bit complex, I have partitioned out the different animal species and just given examples of subtherapeutic and therapeutic use. You can look at those differently for a drug or a family of drugs, or what-have-you.

We have events that feed from the farm, as we know, to slaughter animals, then through processing, and dose response assessments. We also know that there is added complexity. Reference has been made to birds and transport and rodent vectors, and other things, and we all appreciate that added complexity to the model. But I think it is possible to do these things in a modular sort of format. I don 't know if it is realistic to think about doing food processing modeling for any microbial-resistant pathogens alone. Hopefully, we could borrow a lot of the work that has been done for Salmonella enteritides for poultry drug-related resistance problems, 0157 models in beef perhaps. So we could focus on the on-farm aspects which are most germane to the issue of drug use.

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In the swine area, just for the sake of argument I have sort of boxed out a little bit the subtherapeutic side, and we could look at that in more detail if the issue happened to be approval of a new drug for subtherapeutic use in swine. If you did that, you might want to structure the model the way the industry works or could work. So, we could try to conceptually lay out the process from birth through transportation to slaughter for swine, and identify the various segments in that life of a fat pig, where drugs enter the system; what drugs are used; what is the duration of treatment; what mixing of animals in shipping phenomena do we have; what is the pathogen infection rate at different stages of the industry. All of these things, and there are many different parameters of each of those, might help us if we better understood them or laid them out at least for how the process works.

[Slide]

There is a great deal of interest in the whole area of quantitative risk assessment of using tools, information that is much more complete than we have in the past in the sense that we have in the past too often, I think, used point estimates of various parameters when that loses a lot of information. As new techniques become available and

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computing becomes much more amenable to doing these sorts of things -- there are a lot of people engaging more in Monte Carlo type processes which can handle the very variability that we see in these sorts of parameters.

This is an example of one parameter from the 0157 risk model that looks at within-herd prevalence of the organism in the literature. Based on information from the literature we know that there is a range of prevalences that have been detected, but there is a lot of uncertainty in that prevalence because of the test methods that were used, or the variation that we know exists in the cattle population, and the actual biological variability that exists. We have to capture that variability in some way and that is what the statistical distributions do to assist us. So, to the extent possible, we try to apply this to other parameters that vary in the model, and try to develop the approach that will best use that information in a full and complete way.

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There are other issues around risk assessment that I think are appropriate for today's discussion. The issue of making default assumptions in the process has been made, and I think in general for most public health agencies they would favor public health, whereas many people have commented in

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the literature and elsewhere in the past that when you do that successively you end up with risk estimates that are very conservative, and perhaps overly conservative, which may be justifiable on public health grounds but do pose some difficulties.

We have considerable problems with uncertainty and variability. One of the great things that impedes movement of quantitative risk assessment into this particular issue is the lack of knowledge of how the biological mechanisms really do work in the field at the microbiological level, at the animal production level, and at the slaughter and consumption level. So, we don't even know perhaps how to correct the structure of the model, let alone the problems that we have with respect to not knowing much about how to specify the parameters. We don't have very good data so that creates lots of difficulties.

Validation is always an issue, and when people talk about modeling we always want to know about validation. One of the reasons for doing risk assessment in the first place is because we can't really conduct experiments to look at the whole process. We can't conduct an observational study that would give us all the answers that we are looking for. So, validating with an independent type of experiment is

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problematic. One way that does come to mind to sort of validate this is to use the idea of alternate models which are themselves based on assumptions and distributions, but if you get similar answers that gives you some confidence that you may have the right approach.

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The yellow light is on so I will skip the links. What I think the FDA should consider embracing in its vision of how to deal with this problem is the idea of a tiered approach to risk assessment, that is, that we acknowledge that we have to take action. We can't, as Dr. Bell says, just delay things in order to get the last word on risk assessment. We have to move ahead to protect public health. But we also should recognize, I think, that the techniques that we have are not perfect; we don't have all the information and so we have to go with the best that is available. That would probably be a qualitative approach that is suggested in the framework document.

But, I think down the road, as techniques evolve, as understanding of the way that antibiotic resistance improves, as we get more information, as the techniques for quantitative microbial risk assessment evolve in other fields, and as researchers try to improve things in this

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field we can see, firstly, a better way where there could be a higher sort of level of tiers of risk assessment modeling which could be more expensive -- well, undoubtedly would be more expensive, more demanding of resources but might give more precise estimates. We might have to rely less on these conservative defaults.

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I think an important message that I would like to give as an international sort of visitor and as a scientist working in the area is that the very fact that FDA would use this type of approach would encourage others to do it as well. People in the industry and people in academia, and students will start to learn about it and would approve the process.

Thank you, Mr. Chairman.

DR. STERNER: Thank you, Dr. McEwen. We will keep on task and finish one more talk. We will hold questions until later this afternoon for our panel and invited speakers. So if you will write them down so you remember them correctly. Next, we have Dr. Pattie Lieberman, from the Center for Science in the Public Interest, giving their overview of their report on recommendations relevant to the use of antimicrobials in food animals. Dr. Lieberman?

Overview of CSPI Report on Recommendations Relevant

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to Use of Antimicrobials in Food Animals

DR. LIEBERMAN: Thank you very much.

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CSPI has been working since 1971 on nutrition and food safety issues. We are the largest consumer organization which focuses primarily on food issues, reaching more than a million North Americans with our publication, Nutrition Action Healthletter. While we are best known for our nutrition work, recently we have represented consumer interests in efforts to bring about changes in policy concerning the use of antibiotics in doctors' offices, hospitals, and on the farm. We released a report in May, 1998, that is part of the packet today, Protecting the Crown Jewels of Medicine. And, we work with a coalition of other health groups and scientific experts in antibiotic resistance. We appreciate the opportunity to speak at this important meeting.

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In the past few years, many leading experts have urged reductions in agricultural uses of antibiotics. As you know, in the fall of 1997 a World Health Organization commission stated that any antimicrobial agent for growth promotion in animals should be terminated if it is used in

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human therapeutics, or if it is known to select for cross-resistance to antimicrobials used in human medicine.

In February, 1998, Wolfgang Witte, of the Robert Koch Institute in Germany, stated in a commentary in Science magazine, "In the future, it seems desirable to refrain from using any antimicrobials for the promotion of animal growth. As exemplified by the use of virginiamycin in animal feed and the subsequent emergence of enterococci resistant to antibiotics, the use of any antimicrobial can lead to unexpected consequences that limit medical choices."

In May, 1998, Stuart Levy , of Tufts University, wrote in the New England Journal of Medicine an editorial that recent findings have "made it even clearer that the use of growth promoters affects the drug resistance of environmental reservoirs, with direct consequences for the treatment of disease in humans" and that "such findings led to a ban on avoparcin in the European Union countries and, recently , on virginiamycin in Denmark."

In December, 1998, the European Union voted to ban the use of tylosin, spiramycin, virginiamycin and bacitracin for growth promotion in livestock to come into line with the WHO recommendation.

But in the U.S., instead of reducing uses of antibiotics in

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livestock, we are still expanding into new uses that have the potential to endanger human health. Therefore, we applaud the FDA for at least attempting to slow this trend by including in the new animal drug approvals process new criteria that will consider antibiotic resistance. We strongly agree with the statement in the framework document that "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." That is a standard that must not be undermined by economic concerns.

The FDA framework document has several strengths. The first is that the proposal would require that detailed drug sales information be submitted as part of drug experience reports. In addition to sales data, it is imperative to know how the antibiotics are being, in what species, in what dosage, for what purpose, and for how long. Currently, drug usage information is sorely lacking. Instead, the FDA must rely on rough estimates of how much antibiotics are used. Without detailed information it is difficult to correlate antibiotic use with the emergence of resistance. In order for any post-approval monitoring system to be effective, the FDA needs that piece of the puzzle. Furthermore, that usage

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information should not only be available to FDA but should be made publicly available to consumers and researchers.

In general, CSPI is supportive of a tiered approach to new animal antibiotic approvals, but we disagree on which categories are appropriate for us in food animals. We agree that the categorization should be based on several criteria.

First, it should be based on how important the antibiotic is in treating human infections.

Second, it should be based on how likely that its use in animals will cause resistance.

Third, it should take into account the level of exposure to humans that the use in animals will cause.

Certainly a fluoroquinolone, because of its extreme importance in human medicine, should be subjected to a higher level of scrutiny than would an ionophore. And, antibiotics that are given for a long duration or to an entire flock should receive more scrutiny than a short-term use injectable product.

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It is clear that the use of antibiotics in livestock leads to resistance among commensal bacteria in animals that can make people sick, for example enterococci, or can horizontally transfer their resistance factors to human

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pathogens.

A striking example of horizontal transfer of resistance genes to a human pathogen due to agricultural uses of an antibiotic comes from Germany. In 1983, German farmers introduced a new antibiotic, nourseothricin, for growth promotion n swine. Before nourseothricin was used, nourseothricin resistance had never been observed to nourseothricin in bacteria from animals or humans. In 1985, nourseothricin-resistance genes were found in E. coli in swine and pork products. By 1990, E. coli containing the resistance genes were found in farm workers, farmers' families, citizens in the community in which nourseothricin was used, and patients suffering from urinary tract infections caused by E. coli. No nourseothricin-resistant bacteria were isolated from people or animals in other parts of Germany where the antibiotic was not being used. A few years later, the resistance gene was found in Shigella, a bacterium found in primates but not in swine. The appearance of nourseothricin-resistant Shigella suggested that resistance emerged due to the transfer of a resistance gene from bacteria exposed to antibiotics on the farm to a human pathogen. Therefore, the potential horizontal transfer of antibiotic resistance from commensal bacteria to

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pathogenic bacteria must be considered in ranking the antibiotic's importance. Similar considerations should be paid to antibiotics that select for multi-drug resistance.

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While we agree with the FDA on the basic principles of how antibiotics should be categorized, we disagree on what would be the appropriate way to handle approvals of antibiotics in certain categories. The biggest problem is that Category I drugs should not be approved at all for use in livestock. Drugs that are essential for treating serious or life-threatening diseases in humans, for which there is no satisfactory alternative, or antibiotics that are important for treating foodborne diseases where there are limited therapeutic options, and drugs that are members of classes of drugs that have a unique mechanism of action or a unique resistance mechanism should be preserved to protect human health. As previously stated, the FDA's primary responsibility is to protect the public health by preserving the long-term effectiveness of antimicrobials for treating diseases of humans. Approving any Category I drug for livestock endangers the public health and should only be considered if there are no other effective means, either other available antimicrobials or changes in management

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practices, to reduce a particular livestock disease.

Category II drugs delineated in the framework document should be held to the standards that FDA put forth for Category I drugs. Even though satisfactory alternatives currently exist, we must not allow their use in livestock to compromise their effectiveness in treating human disease.

Drugs deemed Category III in the existing framework document should be subdivided into two categories. Antibiotics that are little used in human medicine should be subjected to pre- and post-approval monitoring, detailed drug sales information should be kept, and resistance should trigger withdrawal of approval, as described in the framework document for Category II drugs.

Drugs that are not used in human medicine, such as ionophores or polymixins, should be held to the pre- and post-approval studies and monitoring laid out for Category III drugs, unless there is new evidence to suggest that their use in animals endangers human health, for example by causing cross-resistance to antibiotics important in human medicine or selecting for multi-drug resistance.

To adequately protect public health, FDA's framework must prevent agricultural drug use from causing human illness. It is not enough to just set guidelines for revoking a drug

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approval once people get sick. For any antibiotic that is the drug of choice or important in treating potentially serious human disease, decreased in vitro susceptibility in animal isolates may be the appropriate threshold instead of waiting to see decreased susceptibility develop in human isolates, or complete clinical resistance.

If after an approval is granted a resistance threshold is reached, the drug should immediately be withdrawn. Our concern is that if the drug is not withdrawn immediately, and a protracted regulatory process is necessary to stop the drug's sale, the public health may be put in danger. For example, if the FDA must rely on section 512(e) that allows for industry to request a hearing if FDA wants to revoke an approval, it may be years before an antibiotic that is causing resistance to develop is removed from the market.

We also are concerned that the industry will endlessly stall the FDA by arguing that no action should be taken because the threshold set was inappropriate or that it was not based on sound science.

After the product is off the market, the drug sponsor could propose mitigation strategies, such as changes in dosage or duration of treatment, education of veterinarians and farmers about proper use, and restrictions on how the drug

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is marketed, that might decrease the development of resistance and increase safety. If the proposed mitigation strategy is acceptable to the FDA then approval could be reinstated.

In the current framework document there is no proposal on how thresholds will be set. In general, and perhaps as expected, we are concerned that they will be too high. For antibiotics used in human medicine, thresholds should be set extremely conservatively to adequately protect the public health. Additionally, any post-approval monitoring system must be sensitive enough to detect even small changes in resistance, and include non-foodborne as well as foodborne pathogens.

A major weakness in the framework document is that, as written, it does not address already approved antimicrobials. Since almost half of all antibiotics used in the U.S. are used in agriculture, and those drugs already are approved by the FDA, the framework must be applied to drugs already on the market in order to protect the effectiveness of the antibiotics for human, as well as veterinary, medicine.

We are particularly concerned about the antibiotics approved for subtherapeutic use in livestock. In FDA's own words,

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prudent use of antimicrobials is use that maximizes therapeutic effect while minimizing the development of resistance. CSPI believes that under that definition of prudent use the subtherapeutic, or non-therapeutic use of antibiotics would not be allowed. Subtherapeutic use for growth promotion is not prudent because it increases the likelihood of antimicrobial resistance and jeopardizes the continued efficacy and availability of antimicrobials for use in livestock and people while providing no therapeutic effect. We urge the FDA to take steps similar to what the World Health Organization has proposed and the European Union has implemented to stop wasting these vital drugs on growth promotion. The minor and often unnecessary benefits of improved feed efficiency are not worth the threat that such uses pose to the continued effectiveness of antimicrobials and to the public health.

We also are concerned about certain therapeutic uses of antibiotics already on the market. For instance, the 1995 fluoroquinolone approval for poultry in the drinking water. Already fluoroquinolone resistance is emerging in poultry in the U.S. Michael Osterholm from the Minnesota Department of Health has reported preliminary findings from a study of poultry. He found that as many as 79 percent of supermarket

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chickens are contaminated with Campylobacter, 20 percent of which were resistant to fluoroquinolones. Among turkeys, 60 percent were contaminated with Campylobacter, 84 percent of which were resistant to fluoroquinolones. Campylobacter causes 2 million to 8 million illnesses and 200 to 800 deaths per year, and is linked to Guillain-Barre syndrome. We also think that the FDA should not have approved Baytril, the injectable fluoroquinolone product for cattle, in 1998. Previously approved antibiotics are just as effective in treating bovine respiratory infections. At a minimum, the FDA should have required automatic withdrawal of Baytril if harmful fluoroquinolone-resistant bacteria reached predetermined levels set by the FDA and CDC. Bayer agreed to voluntarily withdraw the product from the market if the FDA finds significant increases in fluoroquinolone resistance in post-approval monitoring. But that agreement lacks teeth. And, if resistance develops due to Baytril's use it is likely to result in endless stalling and negotiations.

I am encouraged by Dr. Sundlof's recent comments at the FDLI meeting, stating that review of already approved antimicrobials would be possible within the new framework contingent upon available funds. However, the language of

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the framework document should explicitly state that it will be applied to previously approved antimicrobials. Also, a review of the fluoroquinolone approvals, especially in poultry, should be among CVM's highest priorities.

[Slide]

We applaud the FDA for considering adding criteria on antibiotic resistance of the animal drug approval process. let me summarize that if the FDA really wanted to protect the public health and preserve the effectiveness of these miracle drugs, then it would need to fine-tune and strengthen the framework document by applying it to drugs that are already on the market, such as antibiotics for growth promotion and fluoroquinolones for disease treatment in poultry and cattle; by more clearly laying out the process that would occur if thresholds are reached to withdraw a drug from the market; and by not allowing Category I drugs to be approved for livestock other than in the most extreme cases to alleviate animal suffering when no other options exist.

We urge the members of VMAC to take into account these comments in their deliberations of the framework document. Thank you very much.

DR. STERNER: Any questions from the panel members for Dr.

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Lieberman?

[No response]

That will conclude our morning commentary. Dr. Geyer has some housekeeping announcements to make.

DR. GEYER: I have just two announcements. The first one is crucial because it has to do with lunch. All of you who are seated at the tables and wearing one of these name badges, the area behind the salad bar in the restaurant is reserved for you. The restaurant is on your left as you go out of the doors here.

The other announcement is that I would like to remind the guest speakers if you have hard copy of your slides and overheads, we would like to have copies. You should give them to either me or to John Sheid.

What time are we going to resume?

DR. STERNER: We will start promptly here at one o'clock. The gauntlet has been laid by this morning's speakers. Thank you, one and all, for your timely presentations.

[Whereupon, at 11:45 a.m. the proceedings were recessed, to be resumed at 1:00 p.m.]

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A F T E R N O O N P R O C E E D I N G S

[1:00 p.m.]

DR. STERNER: We will proceed with this afternoon's deliberations. Since it has been pointed out to me that the ability of the mind to absorb is directly limited by the ability of the rear end to sustain, and recognizing that we have a very long program to get through this afternoon, we will begin this afternoon's deliberations with our representative from the American Veterinary Medical Association, Dr. Lyle Vogel and the need for safe and effective antimicrobials for food animals and the AVMA's efforts regarding prudent use of antimicrobial drugs.

Dr. Vogel.

Need for Safe and Effective Antimicrobials for Food Animals and AVMA Efforts on Prudent Use

DR. VOGEL: Thank you, Mr. Chairman.

[Slide.]

The American Veterinary Medical Association is a professional association with over 62,000 members, which includes 85 percent of the veterinarians in the United States. The objective of the association is to advance the science and art of veterinary medicine including its relationship to public hearth, biological science, and

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agriculture.

Since its inception in 1863, the AVMA has continuously integrated the objectives of public and animal health. A portion of the veterinarian's oath that is administered to every United States graduate veterinarian reads: "I solemnly swear to use my scientific knowledge and skills for the benefit of society through the protection of animal health, the relief of animal suffering, the conservation of life cycle resources, the promotion of public health, and the advancement of veterinary ethics."

Let me assure that the AVMA takes its responsibility for the protection of public health very seriously.

[Slide.]

The American Veterinary Medical Association shares the concerns of the public, governmental agencies, and public health community regarding the broad issue of antimicrobial resistance and specifically the potential risk of resistance developing in animals with subsequent transfer to humans. We acknowledge that a significant proportion, but not all cases of human Salmonella and Campylobacter infections originate in foods of animal origin. We also acknowledge that the use of antibiotics by veterinarians could possible contribute to antibiotic resistant bacteria developing in

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animals which can then be transferred to humans.

Because of that concern, the veterinarian profession has invested considerable resources of personnel and money into what we believe will be an effective response to the potential problem.

However, we are also concerned that increased regulation of animal drugs that is not commensurate with the actual public health risk may adversely affect animal health and welfare and may have unexpected adverse human health consequences.

The magnitude of the human health impact of the use of antimicrobials for animals is unknown, and inordinate and unmeasured regulatory actions may unduly contribute to the existing animal drug availability problem. This will have consequences that negatively affect animal health and welfare and ultimately could create other public health risks, such as an increase in the transmission of zoonotic pathogens to humans.

Increased regulation of animal drugs may have significant known and unknown impacts on human and animal health that need to be evaluated.

The issue of antimicrobial resistance has already impeded the approval process for, and usage of, animal drugs especially for food animal drugs. Actual label use of

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fluoroquinolones in food animals has been banned. Drug approvals of antibiotics, particularly the fluoroquinolones, have been slowed. The number of fluoroquinolones approved for food animals is extremely limited.

In at least one case, a drug sponsor has halted further development of a good animal antibiotic. Who knows how many other promising antibiotics are not being developed because of the increased regulatory requirements?

[Slide.]

The use of drugs in animals is fundamental to animal health and well-being. Antibiotics are needed for the relief of pain and suffering in animals. For food animals, drugs additionally contribute to the economics of the industry. The gains that have been made in food production capacity will not have been possible were it not for the ability for reliable drugs to contain the threat of disease to animals. The increased capacity of the American livestock producer has kept high-quality protein available for the majority of U.S. consumers and consumers in many other countries.

Other groups also recognize the need for antimicrobials for animals. For example, the report of the 1997 WHO meeting states, "Antimicrobials are vital medicines for the treatment of bacterial infections in both humans and

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animals. Antimicrobials have also proved to be important for sustainable livestock production and for the control of animal infections that could be passed on to humans.

The recent report of the National Research Council and Institute of Medicine's Committee states, "The benefit to human health and the proper use of antibiotics in food animals is related to the ability for those drugs to combat infectious bacteria that can be transferred to humans by either direct contact with the sick animal, consumption of food contaminated with pathogens from animals, or proliferation into the environment.

[Slide.]

We are concerned about the potential human health impact, and we want to maintain the long-term effectiveness of antimicrobials for animal and human use. We seek to increase drug approvals for the treatment of animals. Therefore, the AVMA is committed to ensuring judicious use of antimicrobials by veterinarians for the prevention, control, and treatment of animal diseases.

The AVMA has started a profession-wide initiative, and we have included companion and food animal practitioner groups and public health representatives to develop and implement judicious use principles.

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The approved document which contains the principles is published in the January 15th, 1999 issue of the Journal of the AVMA, and is being distributed in many other ways. I have provided a copy for all of the committee members.

[Slide.]

The document states the position of the AVMA as when the decision is reached to use antimicrobials for therapy, veterinarians should strive to optimize therapeutic efficacy and minimize resistance to antimicrobials to protect public and animal health.

The position statement recognizes that veterinarians consider other therapeutic options before using antimicrobial therapy. The statement encourages veterinarians to balance public and animal health in their considerations.

[Slide.]

Related to this concept, the objectives of the AVMA are to support development of a scientific knowledge base, support educational efforts, preserve therapeutic efficacy of antimicrobials, and ensure current and future availability of veterinary antimicrobials.

Let me share with you a few of the general principles that will serve as a template from which species guidelines will

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be customized.

[Slide.]

The first principle states that preventive strategies, such as appropriate husbandry and hygiene, routine health monitoring, and immunization should be emphasized.

The second strategy says that other therapeutic options should be considered prior to antimicrobial therapy.

[Slide.]

The third point is that antimicrobials considered important in treating refractory infections in human or veterinary medicine should be used in animals only after careful review and reasonable justification. Consider using other antimicrobials for initial therapy.

In this context, the principle takes into account development of resistance or cross-resistance to important antimicrobials. Taken together, these three principles state that encourage preventive actions to avoid disease, if disease occurs, consider using other options before using antibiotics, and if antimicrobial therapy is needed, don't use the important ones first.

[Slide.]

The next step is to work with species practitioner groups to develop more detailed guidelines appropriate to each species

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disease and type of client. This will be addressed at the next meeting of the Steering Committee in March.

The AVMA will also work with these groups to develop and deliver a continuing education program to raise the awareness of the profession to the issue and to encourage utilization of the principles.

The profession intends to reach the practitioners with this message at state and national meetings, as well as through publications.

Additionally, the American Academy of Veterinary Pharmacology and Therapeutics has developed an educational proposal for veterinarians and producers. The proposal includes the development of a coalition of veterinary and producer organizations to implement the program.

Educational programs will be presented at national, regional, state, and smaller continuing education conferences.

A series of articles will be developed for publication in the Journal of the AVMA. Veterinary schools will be encouraged to incorporate the program into the veterinary school curriculum. This proposal will also be considered further by the AVMA Steering Committee at its next meeting.

We also want to maximize the use of good scientific

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information as veterinarians use their professional judgment in the drug selection process. The AVMA and the American Association of Bovine Practitioners, the American Association of Swine Practitioners, the Academy of Veterinary consultants, and the National Cattlemen's Beef Association are partnering to fund a project to develop a therapeutically-based antimicrobial use informational database. The project's objective is to provide veterinarians with a source of easily assessable information on the therapy of specific diseases to help veterinarians make wise therapeutic decisions.

In the past, therapeutic antimicrobial use has focused on clinical efficacy, but now judicious therapeutic use is being redefined to include the optimization of efficacy and the minimization of resistance.

The database will allow veterinary practitioners to utilize current peer-reviewed information when they select treatment regimens. The information will include a full range of therapeutic options including alternatives to antimicrobial therapy.

The pathogen data will included susceptibility profile information. We anticipate that the informational database will be available in book form, but will also be web-based

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and possibly distributed on CD-ROM.

We believe that these efforts by the veterinary profession will reduce the development of resistant zoonotic pathogens and commensals in animals, and will lessen the apparently already small risk of a human health impact related to the therapeutic use of antimicrobials in animals.

[Slide.]

Are judicious use principles and education enough? Possibly so. We find it curious that the introduction to the FDA framework document states, "FDA, along with other agencies and groups, is actively working to find ways to encourage the prudent use of antimicrobials in human medicine to help address the significant contribution of human use to antimicrobial resistance."

What is curious is that nowhere in the framework document is it mentioned that the FDA, along with the CDC, is working with the AVMA and other groups to encourage the judicious use of antimicrobials in veterinary medicine.

The omission gives the impression that the FDA assigns value to the human prudent use campaign, but has judged the veterinary judicious use efforts to be worthless. The impression is further strengthened by FDA's decision to move forward with a complex and expensive new regulatory

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initiative without taking the time to evaluate the effectiveness of the veterinary profession's initiative.

[Slide.]

The real answer to the question of whether judicious use principles are enough or whether there is a real need for increased regulation depends upon determining the true risk to human health from the use of antimicrobials in animals. Risk depends not only on the nature and severity of the hazard, but also on the probability of its occurrence, and the probability of the occurrence of an adverse human health effect depends on more than just the prevalence of resistant zoonotic pathogens or commensals in food animals.

Risk is also dependent upon the degree of exposure of people to the resistant organism, the likelihood of causing a disease, the probability of the disease requiring antimicrobial therapy. Remember most cases of food-borne diseases do not require antimicrobial therapy, and finally, whether the preferred drug is a specific one for which the pathogen is resistant.

What is the risk of a human health impact of the transfer of antibiotic resistant pathogens from animals to humans? My generation calls that the $64,000 question. However, it will cost more than that now to get the answer, but it would

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be advantageous if we did know the magnitude of the problem. Then, we would know whether we needed to attack the problem with a bee-bee gun, a rifle, a cannon, a cruise missile, or whether an atomic bomb is needed.

What constitutes responsible action? Are judicious use principles enough? Judicious use principles combined with an educational program? Judicious use principles plus an educational program that is supported by an easy-to-use informational database to support clinical decisions by veterinarians?

We won't know the answers to those questions without a thorough risk assessment. This is a formidable task requiring a significant financial input, as well as scientific manpower, but to proceed forward with increased regulation without an assessment of the beneficial and detrimental effects of that action is unacceptable. Without that information, we are only acting with the hope of favorable results, and we cannot predict the magnitude of the improvement if it does occur.

There are many challenges to conducting microbial risk assessments as was explained to us this morning by Dr. McEwen, but people and organizations are learning how to do microbial risk assessments.

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The USDA has recently completed a risk assessment on Salmonella enteritidis. They are starting another on E. coli 0157:H7 in beef. Georgetown University is performing a risk assessment on antimicrobial resistance associated with animal use of antimicrobials.

We are aware that the FDA attempted to perform a risk assessment on fluoroquinolones, which apparently was not completed. At least it has not been shared with the public. It is interesting to note that the USDA has published their preliminary E. coli document and actively sought public comment and input. Additionally, a draft risk assessment report is expected to be released by USDA for external review in June of 1999. FDA should follow a similar public process.

[Slide.]

There are a number of indications that the risk to humans from animal origin resistance organisms does not constitute an imminent public health crisis and that we can take a reasonable amount of time to properly evaluate the risk, the proposed actions, the expected results of those projected actions, and the potential for unexpected adverse events. For example, Dr. Angulo recently said, "If the same resistance development on food animals should continue in

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the next 20 years, we would be faced with a major public health problem." This statement implies that we have some time to take responsible action. We do not need to rush forward with experimental regulations.

Let's do a proper analysis to determine the most effective and efficient intervention method or methods, whether it be judicious use principles, alterations in the drug approval process, changed in animal husbandry practices, pathogen reduction activities in slaughter and processing plants, improved transportation and storage of food, and/or improved food handling by food service workers and consumers, or a combination of the above.

The press release resulting from the 1998 WHO meeting states, "To date there has been little documented impact on human health of fluoroquinolones use in livestock, but there is concern over the potential human health consequences if resistance were to increase and spread. Further research and data gathering are thus essential.

[Slide.]

The major food-borne pathogens of concern for the development of antimicrobial resistance are Salmonella species and Campylobacter jejuni. The incidence of food-borne disease caused by those pathogens may actually be

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decreasing.

As reported by the U.S. Department of Health and Human Services in the Healthy People 2010 draft document, the incidence of disease caused by these pathogens has already decreased to levels below the year 2000 targets established by the Department.

For Salmonella species, the year 2000 target was 16 cases per 100,000 people. The preliminary 1997 data demonstrated 13.8 cases per 100,000. For Campylobacter jejuni, the year 2000 target was 25 cases per 100,000, and the 1997 preliminary data demonstrate 23 cases per 100,000, which is more than a 50 percent reduction from the 1987 baseline figures.

The point is that as the number of human cases of Salmonella and Campylobacter decrease, so do the number of potential cases with decreased susceptibility to antimicrobials.

[Slide.]

In addition to a reduction in the number of human cases of salmonellosis, a reduction of Salmonella on animal carcasses has been measured. A preliminary report from the first nine months of Salmonella sampling performed by USDA FSIS on animal carcasses as part of its 1998 pathogen reduction program demonstrates significant reductions in the

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prevalence of Salmonella on chicken and swine carcasses and in ground beef. There was nearly a 50 percent decline in the prevalence on chicken carcasses, a 40 percent decline in ground beef, and a 25 percent decline on swine carcasses. These figures indicate that the exposure potential to Salmonella through the food supply is decreasing along with the potential subset of resistant organisms.

[Slide.]

Let's turn briefly to addressing the questions posed to the committee. The challenge to VMAC today is to advise on a solution that balances a real drug availability problem with an unquantified potential public health risk.

FDA's stated goal is to protect the 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.

The first question that the VMAC is asked to consider is whether the framework document provides a sound scientific basis for achieving FDA's goal of protecting the public health while providing for the safe use of antimicrobials in food animals.

The scientific premise of the framework document is that the

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use of antimicrobials in food animals causes the development of resistance, a hazard, that is or will be a risk to human health; further, that the risk is of the magnitude that justifies the implementation of a complex and expensive drug evaluation and monitoring progress that may have negative animal and human health consequences.

We believe that the agency has demonstrated that a hazard exists, however, the agency has not adequately characterized the risk to humans. We accept the premise that use of antimicrobials, whether in animals or humans, will allow resistance to develop, however, the science has not been presented by the agency that demonstrates the probability of human disease occurrence resulting from that resistance. Without the necessary science and risk assessment to evaluate the management efforts, the agency's framework document can impede the development and approval of antimicrobials for animals and remove previously approved antibiotics without knowing whether the effects will have a positive effect on human health.

[Slide.]

The second question to the committee addresses the categorization of antimicrobial drugs for human medicine. We are concerned because the categories are not well

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defined. The classification is very subjective which will create uncertainty and will allow controversy for each drug that is being classified.

We also propose for the consideration of FDA that another factor should be included in the categorization scheme, and that is the importance of the drug to animal health and welfare.

Category I contains some eclectic criteria. For example, the first criterion is that the drug is essential for treatment of a serious or life-threatening disease in human, but then the second criterion included drugs that are important for treatment of food-borne diseases.

The first criterion addresses essential drugs, but the second concerns a lesser group of important drugs. Also, in the vast majority of cases, food-borne diseases are not life-threatening nor serious, and for some of the few that are, such as E. coli 0157:H7, antimicrobial therapy is contraindicated or at least the need for antimicrobial therapy is controversial.

[Slide.]

The third and fourth questions address threshold levels. For both monitoring and resistant threshold levels, a more basic question that needs to be answered first is how do we

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measure the impact on human health of various threshold levels. The answer can only be determined by risky and costly trial and error or by developing a risk assessment. [Slide.]

The fifth question concerns on-farm monitoring. Again, we need to answer the question what is the degree of relationship between resistant levels measured on the farm and the human health impact, what are the outcome measurements.

Until those questions are answered, resources would be more appropriately applied to improvement of the National Antimicrobial Resistance Monitoring System. Questions identified by NARMS could then be investigated with specific research projects.

This can be likened to Food Net, which, based on the results of active surveillance for food-borne disease, institutes case control studies to answer questions raised by the surveillance program, but the difference is that Food Nets uses the case control studies for the purpose of research, not regulation.

To summarize, the AVMA is dedicated to the protection of public and animal health. We are very concerned that the use of antimicrobials to treat food animals may cause a

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public health risk.

Because of that concern, the veterinary profession has invested considerable resources of personnel and money into what we believe will be effective responses to the potential risk, but we are also very concerned that because the human health risk has not been characterized, increased regulation of animal drugs that is not commensurate with the actual public health risk will adversely affect animal health and welfare, and may have unexpected adverse human health consequences.

We recommend that the agency work with other governmental agencies and the public to perform a risk assessment. We believe that the framework document is too complex, uncertain, and possibly too restrictive in comparison to the actual public health risk.

It appears that much of the framework document is designed to gather the scientific information that is needed to measure the risk. Is it appropriate for a governmental regulatory requirement to be used to gather data that rightfully should be obtained through research? We don't think so.

One final thought. Part of the problem may be that the agency is attempting to regulate microbial safety under the

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rules for food additives instead of as food contaminants. Food additives are those substances deliberately incorporated into foods which includes, for legal purposes, animal drugs.

The second group, food contaminants, includes anything not specifically approved for food use. Food contaminants are those substances which are unavoidably present and whose presence is tolerated.

According to the Food, Drug, and Cosmetic Act, in general, FDA may not consider values other than safety in approving additives. If a substance is judged reasonably certain to produce no harm when used as intended, FDA is supposed to approve its use.

Conversely, for contaminants, FDA must balance several often competing objectives including safety, food costs, and practicality of the regulatory action. These legal requirements imply very different risk assessment needs. For additives, FDA reaches a judgment on an intake level that will be without effect. For contaminants, FDA needs to know of the likelihood of harm.

We suggest that the agency reevaluate its regulatory approach to consider if microbial safety is more appropriately regulated as a food contaminant.

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Thank you.

DR. STERNER: Do any of the Veterinary Medicine Advisory Committee have questions for Dr. Vogel? Dr. Angulo.

DR. ANGULO: Dr. Vogel, I have heard a couple comments about impressions that this new framework might impede new approvals. It is obviously an essential issue, but it might be peripheral to the questions that are asked, but you raised that under the questions about does this framework based upon a sound scientific basis.

So, I am just wrestling with -- I mean I actually have a converse perspective, that I actually think this framework facilitates new approvals. We don't know exactly how it would move forward, the details we don't know essentially, but I see it a way to facilitate new approvals, not to impede new approvals.

How does it impede new approvals if we lay a framework out that shows how to move forward with approvals? The current system obviously isn't working.

DR. VOGEL: I think the answer to that gets back into the drug approval process and the long time it takes a company to develop a new antibiotic and get it through the system. Which company is going to invest 10 years of time, money, and effort in developing an antibiotic for a food animal

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when it cannot predict when it's done with its work whether that will be approved by FDA or not?

It just does not make sense for a drug company to invest millions and millions of dollars into an unpredictable system.

DR. STERNER: Further questions or comments? Dr. Angulo.

DR. ANGULO: The second point then on your discussion about the sound scientific basis of achieving of this framework, you mentioned that we haven't quantified the risk, and although you did acknowledge that there is a risk, that it hasn't been fully quantified, which I fully appreciate that it has not been precisely quantified, but the point that should be understood, that the reason why the risk has not been fully quantified is because we have not yet reached antimicrobial resistance that causes treatment failures. The only way we will fully quantify the risk is if we have treatment failures, and it would reckless for public health to await that point in time. In other words, we should not wait until we have fluoroquinolone resistant Salmonella in this country before we revise the drug approval process in the FDA.

We want to move towards quantified risk assessments, I agree, but we cannot wait until we get those endpoints of

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clinical treatment failures to answer that question that you are asking.

DR. NORDEN: Dr. Vogel, you raised a lot of points, and your concern about the lack of a quantitative risk assessment, it is correct that it is not there, but what I think is clear, and although I commend your group for judicious use principles and education programs, I think it is very clear from medicine at least, "human medicine," quote, unquote, that that doesn't work, and it hasn't worked, and we have major problems in medicine with prescription of antibiotics and all of the education programs, and the data is very clear on this, really don't make any great difference.

So, I think that it's fine to do it, and I think it's a necessary part of any practice of animal or human medicine, but I think to think that it will make a major difference in the way antibiotics are used is unlikely.

DR. VOGEL: Well, I hope veterinary medicine can prove something to the human medical field, that we can make it work.

DR. STERNER: Thank you, Dr. Vogel.

As has been alluded to earlier, we live in an ever shrinking world, and are more and more influenced by our global economy. To that end, we have an invited speaker from over

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the Atlantic, from the UK, Dr. Rutter, who is Dr. Steve Sundlof's counterpart in England.

The Authorization of Antimicrobial Products in the European Union

DR. RUTTER: Thank you very much, Chairman, and thank you also for inviting me to attend this meeting.

[Slide.]

It has been a very interesting morning. I am not sure that I am going to introduce any major new insights into the debate. I suspect I may just be repeating what is happening over the water.

I usually slip over this first slide pretty quickly, but I did want to emphasize that the Veterinary Medicine's Directorate is the UK regulatory authority, and I am the head of the VMD. We are responsible for authorizing veterinary medicines in the UK for residue surveillance in the UK, and for advising ministers on Veterinary Medicine's policy.

I would emphasize that I am not a member of the staff of the European Medicine's Evaluation Agency, which also happens to be based in the UK, in London, although I do sit on the Committee for Veterinary Medicinal Products, which advises the EMEA on the scientific opinions.

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Neither am I a member of the EU Commission as I noted in one of the draft programs that I was. The EU Commission, of course, is based in Brussels and is the executive arm of the European parliament responsible for legislation.

So, having got that clear, I hope, if I could have the next acetate.

[Slide.]

I am going to cover three broad areas, first of all, say something about the background to this issue as it occurs in the EU, because I think there are some important differences that are worth mentioning; secondly, to talk about the requirements for authorization in the EU; and then, thirdly, to talk about some of the issues which, as I say, are going to be very similar to the issues that you are facing over here.

[Slide.]

As far as the background is concerned, I wanted to emphasize two points. First of all, that we have harmonized procedures in Europe in the 15 member states, and secondly, we have, and have had for some time, separate procedures for antimicrobials that are used as therapeutic products or as growth promoters.

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As far as growth promoters are concerned, they are regulated under Council Directive 70/524, and these are the substances that are currently authorized as antibiotic growth promoters in the EU. I will return to this because, as has already been mentioned, the first four of those will be disappearing later this year.

[Slide.]

Just to emphasize that growth promoters are authorized in the EU at sub-therapeutic levels. They are authorized for extended periods mainly in pigs and poultry throughout the growing period, and they are available without veterinary prescription.

[Slide.]

In contrast, the veterinary medicinal products authorized for therapy -- and I have listed the major groups that we have products, these I am sure are very similar, I haven't listed the individual products, but these are the major groups that we have. I am sure it is very similar here in the USA.

[Slide.]

There therapeutic products are authorized at therapeutic doses for defined, generally short periods, and on veterinary prescription. The requirements for

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authorization, if I can move on to that, and on to the next slide --

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The requirements for the additives or for the growth promoters include these sort of areas, and these have been set out for new products in Council Directive 87/153. This requires the applicant to provide data of MICs in various pathogenic and nonpathogenic gram-negative and gram-positive species of bacteria, studies on cross-resistance to therapeutic antibiotics by determination of MICs in mutants produced in vitro which exhibit chromosomal resistance and may be needed, and in the case of microorganisms which are resistant to therapeutic antibiotics, the genetic basis of the resistance should be shown.

Tests to find out whether the additive is capable of selecting resistance factors are required, which may be performed under field conditions in the animal species for which the additive is primarily intended, whether all factors may have been found, tests required to determine the effect of the antibiotic on the microflora of the digestive tract, colonization, and shedded or excretion of pathogenic microorganisms, and field studies to monitor the percentage of bacteria resistant to the additive should be provided

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before, during, and one month after use.

So, these are the kind of studies that are currently required. Council Directive 96/51 extends these to run specific approval, and there will be new guidelines, and particularly the review of products which have previously been authorized.

[Slide.]

In contrast, the therapeutic antimicrobials are authorized through a separate procedure. We have essentially three procedures - a centralized procedure which is used for biotech products and is obligatory, but is optional for innovative products, so if there was a new antibiotic coming forward, say, which had a biotech element in it during its manufacture, it will be obliged to go through the centralized procedure.

If it were an innovative product, then, the company could choose whether or not to go through that procedure. The centralized procedure essentially involves a single application to the European agency in London, assessment of the dossier against the requirements, and a scientific opinion by the Committee for Veterinary Medicinal Products, leading to if it's a positive opinion, authorization in all 15 member states.

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The decentralized procedure is a mutual recognition procedure. This would be available for a product that was not innovative, and the company would come say to a member state, say the UK, as the reference member state with its dossier, get an authorization in accordance with the procedure, and then apply for mutual recognition of that authorization in as many other member states that it wanted.

[Slide.]

The criteria for authorization for therapeutic medicinal products is very much the same as over here. Safety, quality, and efficacy are the three criteria that are required, and on to the next slide.

[Slide.]

The safety of the product involves the target animal, the operator, the consumer, and the environment.

[Slide.]

As far as consumer safety is concerned, we have the MRL procedure, the maximum residue limit procedure, which has been obligatory in the EU since 1990. All new actives have to have an MRL before they can be authorized, and we are also reviewing all old actives, so that by the 31st of December 1999, an MRL has been set for them, or any substances which don't have an MRL by then will be removed

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from the market.

We also use microbiological MRLs. This is based on the fact that the toxicological MRL for a substance may, for an antibiotic, for example, which may be relatively non-toxic, give a pretty high MRL and a short withdrawal period which could lead to significant residues passing into the human food chain, and therefore, we have a microbiological MRL procedure where the microbiological activity is assessed mainly in vitro, and if this leads to an MRL which is lower than the toxicological MRL, then, that will be the MRL that will operate and give a longer withdrawal period, which will obviously protect the human consumer.

We also have residue surveillance much as you have over here, of course, and I think that it is generally recognized that the residues of antibiotics that appear in the food chain don't pose a significant risk to consumers in terms of antibiotic resistance.

[Slide.]

The next acetate shows the regulatory requirement in 81/851 for the authorization of medicinal products, and again this just summarizes some of the major areas that have to be addressed by the applicant.

This would include data on resistance and the likelihood of

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resistance emerging, data where strains are passaged serially in subinhibitory concentrations of antibiotic and MIC values evaluated at various stages, MIC values for bacterial strains isolated under field conditions, information about resistance to related bacteria.

Data from clinical trials before and after treatment may be required, and data from different EC countries. There is also new information that is required, such as the degree to which resistance is developed, and the mechanisms by which it is developed, a commentary on the speed of its development and its geographical distribution and analysis, the likely effects of such factors on the efficacy of the product.

There is also a requirement for pharmacokinetic data to ensure that the dosage regime is appropriate, and for pharmacovigilance, although I will come back to pharmacovigilance in a moment. This is suspected adverse reaction reporting because this is an area where there is going to be quite a lot of development over the next year or so.

[Slide.]

Moving on finally to some of the issues, we have had a number of inquiries and advice given in the UK and in

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Europe. These are some of the UK committees that have been sitting. I suppose the most significant of those is the House of Lords Committee, which reported last April, and which recognized that the major problems relating to antibiotic resistance in terms of human infections was related to human use and medical use of antibiotics, but clearly, that there was an important issue as far as veterinary use is concerned, and they recommended the phasing out of feed growth promoters which were related to products which were important in human medicine.

It also commented on the need for prudent use of fluoroquinolones. The government has responded to that issue, to that report, and is taking it forward. I think one of the important things here is that it has emphasized to the government the multidisciplinary nature of this issue, and the Department of Health and the Department of Agriculture are taking this forward jointly.

The Advisory Committee on Microbiological Safety of Food has still to report, and the Veterinary Products Committee, which is an expert advisory committee that advised the licensing authority, is also due to report shortly on some of these issues. It held an open meeting last June, and its report will be published very shortly.

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[Slide.]

This acetate shows the committees operating on a European and international level, and some of these have been mentioned earlier. The WHO meetings on growth promoters and fluoroquinolones at the bottom, the European CMO's meeting which led to the so-called Copenhagen recommendations, but I wanted to mention the two others, the Scientific Steering Committee, which is a committee set up by Directorate General 24 in Brussels, a wide-ranging committee which is look at all aspects of antimicrobial resistance, and is due to report very shortly, and then just say a few words about the CVMP working group.

As I have mentioned, the Committee for Veterinary Medicinal Products advises the European agency on scientific matters and on opinion for applications, and the CVMP set up this working group in 1997 to carry out a risk assessment of antibiotic resistance, potential effect on treatment in animals, and the risks of transfer to man.

It would then advise the CVMP, who would consider what risk management procedures it should put in place. The group has been working for some considerable time now. Its initial challenge was to collect and review data across the 15-member states, and it has collected a great deal of data

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about products that are authorized, which is the easiest part of it, although even that caused some problems in some cases, the usage of products, and again this is where we started getting into real difficulties because there is very poor information available about usage, and then resistance, again, a lot of information available about resistance, but very, very difficult to analyze because of huge differences between laboratories in how the data had been collected.

The group then started looking at risk assessment and rapidly came to the conclusion that a quantitative risk assessment was going to be very difficult, and so it's currently looking to see, to make its best study of a qualitative risk assessment.

Also, I think the other important message that has come out from that is that you need to identify the question very precisely if you are trying to carry out a risk assessment. It is not possible to carry out a risk assessment, of the risk of antibiotics in animals to humans, you have got to identify it much more precisely than that to come up with any meaningful data, but the group is still working diligently and is expected to report within the next quarter.

[Slide.]

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This refers to a comment I made earlier about the withdrawal in the EU of virginiamycin, spiramycin, tylosin and zinc bacitracin as growth promoters, a recent decision taken in December 1998.

The background to this was that Sweden banned the use of growth promoters in 1986, and when it acceded to the EU in 1995, it received a derogation not to continue the use of growth promoters until the end of 1998.

This focused the mind of the commission as we came closer to that date, and the commission came up with a proposal in November to ban four growth promoters, these four growth promoters from the 1st of January 1999.

The Council of Ministers met in December, and they agreed that these four growth promoters should be withdrawn from the 30th of January 1999, i.e., in six months time, and that there should be further work carried out to consider how to deal with products from third countries who would, of course, be continuing to use these.

I think I would have to say that this decision was not based on a clear risk assessment or any scientific data in that regard except to say that there is a principle that has been operational in the EU since 1969, since the Swann Committee reported about the fact that growth promoters used in animal

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medicine should not be related to antibiotics that might have a valuable use in human medicine, and that really I think is the background to that particular decision.

[Slide.]

The next acetate just summarizes the areas where I think we are currently looking at this issue, regulatory approvals, and what changes might be needed to those as a result of the concerns that have been raised, getting better data about how much antibiotics and what sort of antibiotics are used, and how they are used on farm, better surveillance data of resistance preferably using standardized procedures, prudent use guidelines, we just heard from the AVMA representative, and the British Veterinary Association in the UK is carrying forward a similar sort of exercise on prudent use of antibiotics, and particularly getting in close contact with its medical colleagues, realizing that this is a multidisciplinary problem, and then finally, further research on a whole range of issues that are needed to take matters forward.

[Slide.]

This final acetate just sets out some conclusions that again, I don't think that these have got any blinding insights. Antibiotic resistance is a major issue, it's a

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global problem. The risks have not been adequately quantified.

There are very complex issues, a realization that some of the important problems in human medicine, such as MSRA and TB, have been primarily associated with resistance as a result of human use of the products, but, of course, we must as veterinarians play our full role in order to maintain the efficacy of drugs both for animal treatment and for human treatment, and to safeguard public health.

As I say, I don't think there are any blinding new insights in there other than to say that we haven't got quite as far as the framework document and the questions that are being debated today.

Thank you very much.

DR. STERNER: Does anybody have any questions for Dr. Rutter?

DR. ANGULO: I have just a comment and then a question. I think it's an overstatement to say that there is no scientific data to support the withdrawal of the four growth promoters. I think there is strong scientific data to support the avoparcin prohibition or withdrawal, and there was increasing data being built up to support the withdrawal of virginiamycin. I actually think there is convincing

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scientific data just on the virginiamycin itself, and then when you extrapolate the data on avoparcin, I think it was a very prudent step to just move and follow the WHO recommendation that no antibiotics used in human medicine be used for growth promotion.

My question is on the fluoroquinolone resistance situation or I will say fluoroquinolone decreased susceptibility situation in the United Kingdom, and your comment that has come to fairly high level attention, House of Lords' reports and others, and now an impetus to have prudent use guidelines for practicing veterinarians, but I have heard that there is also some active discussion about restricting some usages of fluoroquinolones in food animals in the United Kingdom.

Is that the case or to what extent is the discussion on the decreasing susceptibility of fluoroquinolones being held in the United Kingdom?

DR. RUTTER: Thank you. If I could just I think comment on the first part, the first comment that you made about the growth promoters. Yes, I think what I meant to say was that it wasn't based on a scientific risk assessment of the impact of the growth promoter use on the risks in human medicine.

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I think it is quite clear that both for avoparcin and for the other growth promoters, a potential hazard has been identified, the risk has not been adequately quantified. I think that would be the comment that I would make.

As far as the fluoroquinolones are concerned, there is, as I say, currently discussion in follow up to the House of Lords Committee, which is being taken forward on a joint departmental basis in the UK, and it would be premature, I think, to make any comments on that.

DR. STERNER: Further comments or questions?

[No response.]

DR. STERNER: Very well. We are moving along nicely on schedule here.

From the University of Illinois we have Abigail Salyers. She is going to talk about the importance of commensals and transfer of resistance from animals to humans.

Dr. Salyers.

Importance of Commensals in the Transfer of Resistance from Animals to Humans

DR. SALYERS: Before I start, I would like to tell you that I brought a small number of handouts which have what is on the transparencies and also an annotated bibliography that some of you might be useful.

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What I am going to talk about today is a issue that in some sense is much bigger than any of the issues that have been brought up to date. We have heard a lot about the zoonotic pathogens like Salmonella and Campylobacter, but I think we have to address ourselves to the question of is it possible that the use of antibiotics in agriculture could have an adverse impact on resistance in some of the more serious human pathogens like Streptococcus pneumoniae and in enterococcus species.

What I would like to do is to address that. This is going to take me, incidently, into the murky realm of horizontal resistance gene transfer, and so I am going to have to qualify my statements in a lot of cases, but I will try to give you a feeling for what people are finding out about horizontal resistance gene transfer and to explain to you how it is possible that agricultural use of antibiotics might have an impact on what we think of as mainly human specific pathogens.

So, I am going to be asking the question can commensals, that is bacteria, especially human commensals take up resistance genes, pass them on to bacteria that might be human pathogens, and how likely is this to happen.

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So, the first question is why is commensals, and human commensals especially, a food safety issue? Well, one example, and I will start with this because it's the easiest one to understand, is the enterococci.

Now, in the United States and many other countries in the world, sepsis is a major problem. We are talking now about hundreds of thousands of cases, not just 2500 cases, and vancomycin resistance is a real problem in some cases of enterococcal infections.

Now, in the United States, there is no question that that is coming from human abuse of vancomycin, so in the United States, our VRE problem is mostly in hospitals and was brought to us by the overuse of vancomycin by physicians.

So, in order to ask the question is it possible that you might get something happening to the resistance levels of VRE through the human food chain, I have to move to Europe where the European physicians were much more cautious than ours were with vancomycin's use in hospitals, and so they have not a problem with vancomycin, but enterococci in hospitals, but they have been conducting an experiment through the use of avoparcin, which has now been discontinued.

So, here is a place where if vancomycin resistance would

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come through the food chain, we might be able to see it.

So, let me start with that example and to say that there are some reports coming out recently. These particular figures are from the DANMAP surveillance program, but there are actually some other reports that have come out recently that put the incidence even higher, that the use of avoparcin in Europe has, in fact, produced vancomycin resistant enterococci.

So, there are a number of reports of that. Here we have 59 percent of enterococci in chickens supposedly resistant to vancomycin.

I would like to caution you a little bit on some of these figures I am going to give you, because people like to play around with the breakpoints between resistance and susceptibility, and moving the breakpoint a little bit either way can cause a big difference in the percent resistance, but when that happens, that's a signal to you that there are a lot of strains built up around the breakpoint and that they may be moving in the direction of resistance.

So, what would be the problem here? Well, the first question is could animal enterococci actually colonize humans, because if they could, then, conceivably if you got

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colonized with VRE, you go in for surgery, your chances of having a postsurgical VRE problem are somewhat increased. How much they would be increased is hard to say.

But let's suppose that that can't happen, let's suppose that the animal strains are different enough from the human strains that animal strains don't colonize the human intestinal tract or if they do, they don't cause diseases effectively.

Then, the question arises whether, as these enterococci move through your intestinal tract, they could transfer their resistance genes to human pathogens. That is a question I want to ask, and actually, I could substitute Streptococcus pneumoniae later on in that scenario and say, okay, what about vancomycin resistant enterococci coming through the food chain, getting into your intestine, and passing on antibiotic resistance gene to Streptococcus pneumoniae.

Now, you might say wait a minute, Streptococcus, the enterococcus faecalis, enterococcus faecium, or the colon, strep pneumo, when it colonizes, it usually colonizes in the throat, how could that possibly happen.

Well, the answer is we have evidence that that kind of transfer can happen, so my question is how likely is this sort of thing to occur, and what evidence do we have for or

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against that.

Before I go on to that, let me just show you some data that I got just before I came here. I got this from a European group, Vander Bogard's group.

[Slide.]

Now, I am not so sure about these figures myself because I haven't seen the data, and they are pretty small. Anyway, I thought I would show these to you because what is interesting is once again, they are saying in that first column on the left is vancomycin resistant enterococci, they are seeing again the high percent of VRE in animals, but the significant figure on here, which I will just read it to you, because I can see it even if you can't, is that in urban adults, they are finding significant, 12 percent they claim, of the enterococci or vancomycin resistant.

Now, this is something in the United States that we haven't seen, clinical abuse of antibiotics, of vancomycin in particular, is community carriage of vancomycin resistant enterococci.

So, it will be interesting to see -- as I said, I haven't seen the data -- but it will be interesting to see if this trend actually develops and if, in Europe, you begin to see VRE coming through the food chain and colonizing people.

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But back to the question of horizontal transfer.

[Slide.]

Now, there is another issue here that needs to be addressed, and we come now to the true human commensals, the bacteria that are the predominant one in your colon, and these are all the colonic anaerobes. Bacteroides is a gram-negative anaerobe, about 25 to 30 percent. The remainder are gram-positive anaerobes, which are not that distantly related to Streptococcus pneumoniae and Staph aureus.

So, the question is if the bacterium came through and transferred resistance genes to one of these organisms here, these are rounded, high numbers, they are around all the time, and then a pathogen comes through and another transfer occurs, how likely is this to occur?

[Slide.]

Well, how are you going to do that? Incidently, if I did a risk analysis on this, if you had asked me before I got the answer that I am going to give you in the transparency after this, I would have said that the risk of this happening are zero, very, very unlikely.

So, how do we do this kind of a test? Well, the best way to do it obviously would be to colonize a bunch of people with vancomycin resistant enterococci and see if the gene got

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transferred or do some of these other studies in a prospective manner, actually watch this transfer occur, and there have been a couple of animal studies where people have demonstrated in real time the transfer of resistance genes between bacteria in a test of mice, just to give you the impression that there is only really two or three cases in which this has been done.

So, all of the type of evidence that we have about these gene transfers comes from the second type of study, which is the retrospective study, which is on the second part of the transparency, where you look to see whether you can find the same resistance gene in different kinds of bacteria.

So, the argument here is that if you find virtually identical copies of the same resistance gene in two different species of bacteria, that was probably due to horizontal transfer, now, not necessarily between those two bacteria, it might have gone a more circuitous route, but that there is some sort of genetic corridor open between those bacteria.

[Slide.]

I am not going to go through this whole thing because it's kind of complicated, but this is the type of thing I am talking about. Let's take tetM there, which is the second

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one down. This is a type of tetracycline resistance gene. I am using this just now as an indicator as to what kinds of horizontal transfer can occur.

If you look, there are a lot of different genera and species in which that resistance gene, the same resistance gene has been found. There are some gram-negative ones like human Haemophilus and Neisseria strains. It has been found in Campylobacter. It has been found in Enterococcus, Staphylococcus, Actinomyces.

So, what this suggests to us, to me at least, is there is a lot of possibility, a lot more than I would have guessed for horizontal gene transfer. Now, where it occurs we don't know, how it occurs we don't know although probably by conjugation.

Incidently, this tetracycline resistance is a chromosomal gene, and it is transferred on conjugative transposons most of the time.

The next one down, tetK and tetL, have been found in soil bacteria, on the left, Bacillus and Streptomyces, but also in human commensals of Staphylococcus, so even between soil bacteria and human commensal bacteria, there is some evidence that there have been horizontal transfers.

I won't go over all the details of what we know about this,

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but there is now abundant evidence that horizontal transfers have occurred between oral bacteria and colonic bacteria, as well as between soil and human bacteria, and [Micro] found the first evidence that it was the same gene in Prevotella ruminicola from animals and Bacteroides from humans.

Now, sometimes we can't tell what direction this has been in, but sometimes you can, and in our case, by looking around the gene, at the DNA sequences around the gene, we were able to suggest that possibly the transfer of the resistance gene we were looking at, tetQ, between the human Bacteroides and the animal Prevotella, was from humans to animals, and not vice versa. But what ever happened, somewhere there is a genetic conduit open between those two groups of bacteria.

[Slide.]

Similarly, as is shown in this overhead, there have been efforts to trace vancomycin resistance determinants. What they are doing is -- this group found essentially identical genes in chickens, enterococci from chickens, from pigs, and from humans -- and what they are doing here is using the fact that the genes were almost identical, in some cases there was a single base pair difference, and so they looked at the pattern.

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Humans had one particular type, was that particular type found in animals, and in some cases, they were actually able to guess that the resistance gene had come from the animal to human, and sort of put this on a more firmer scientific footing.

Now, this is just the beginning, and I think you are going to see a lot more reports of this type where people are bringing out very compelling arguments for horizontal gene transfer and actually using more sophisticated tracking means to show the direction of transfer although this is still in its infancy.

[Slide.]

I used this to make the earlier speakers who complained about the complexity of their slides feel better. I could have made this simpler, but I want to impress you, I want to explain to you what this is.

We don't need to go through the thing, but I want to impress you with a number of examples. Now, the examples I have been giving you are not single isolated examples. They have been very easy to find, there have been very many of them, these putative horizontal gene transfer events.

This is the one that I think is so far one of the most chilling I have seen. What these people did was to look at

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isolates of bacteria from food. Over on the very lefthand column we have isolates from cheese, from sausage, and some of them are Enterococcus faecalis, but some of them are Lactococcus lactis, very harmless bacteria.

Then, they went in and they asked are these resistant, and where they were resistant, what was the resistance gene.

So, they found the resistance gene. You can't see it very well there, but they were identified.

Then, they asked, well, where else have we seen this resistance gene, and then over on the right you see human clinical isolates. These are bacteria that were, under some conditions, capable of causing disease, like Enterococcus faecalis obviously was not too surprising, but Staph aureus, other types of bacteria that we associate with human disease.

They found in those isolates the exact same gene, and we are talking about identities of 99.8 percent to 100 percent in most of these cases.

So, this doesn't prove that the resistance gene transferred from the food bacterium to the human bacterium, in fact, it might be that somebody colonized with the resistant bacteria, contaminated the food. We can't rule that out.

That is what I was talking about, the problem of direction,

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but once again, it shows that there is some evidence for a genetic conduit for resistance genes between these two very unlikely partners in an exchange.

So, to make a long story short, what I am telling you is that there are an accumulating number of examples of evidence at the genetic level that suggest that antibiotic resistance genes can be transferred, not just across genus and species lines, but transferred very readily in nature. The fact that it has been easy to find these examples suggests that they probably have occurred fairly often, and that this type of evidence is going to continue to accumulate, so it's very important that you think about what this means and to try to figure out how to interpret this information, but it certainly raises the question of whether it is possible that bacteria, antibiotic resistant bacteria from animals coming into the human intestinal tract could transfer their resistance gene to human pathogens, so this is not completely out of thinking about.

Many of you probably are very skeptical about this sort of thing. There are lots of caveats that you can make about this type of evidence, but one reason that I want to, that I think even if you don't believe a word of it, that you need to know about it because of what is on the last

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transparency.

[Slide.]

Public perception of food safety. Now, I wouldn't have even thought to talk about this except that to my sorrow I was involved in testifying about the safety of transgenic corn where the Europeans were very concerned about an ampicillin resistance gene that was used as a marker gene in corn, and they are obsessing about that while they are using avoparcin in animal feed, but that gives you an idea of the fact that the public isn't always really clear on risks and perceptions.

So, if we learn from this, first of all, antibiotic resistance is getting to be a very hot-button issue. This is something that the public is quite concerned about, but the public does not necessarily understand much about antibiotic resistance, tends to identify antibiotic resistance with virulence, and is going to be very confused about subtle arguments like whether human strains of enterococcus can colonize the human body or not.

So, I think that you are going to have to think about this from a public safety perception and especially if evidence emerges that some of these agricultural use antibiotics can compel cross-resistance, not just to vancomycin, but also to

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Synercid and some of the new antibiotics coming through the human use pipeline.

So, I think this is an issue, this gene transfer issue is not something that you should just brush under the rug because you personally don't find it too convincing, but really take a look at this, because this information is out in the literature now, it is being paid attention to, and at the very least you are going to have to answer questions about it.

I think I will stop there.

DR. STERNER: Questions from the committee for Dr. Salyers? Dr. Barker.

DR. BARKER: So, is the use of antibiotics in humans more of a hazard to animals than it is the other way around?

DR. SALYERS: Well, that is a possibility. You know, there are a lot of issues here. First of all, and I want to make this clear again although I know I said it at the beginning, there is no question that the pressure from physicians to develop resistant strains is the major problem right now, but I think the reason I am raising the question in the context of animal use is that the public is going to be a lot less forgiving for that type of pressure than they will be for human clinical pressure.

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Another problem that people perhaps should think about is people are handling these antibiotics in agricultural use, and that is something that I didn't address, but it is something that you might think about with respect to people who are colonized with resistant strains just selected by their use of the antibiotic.

It isn't impossible, though. I mean our finding that the resistance can go the other way is something that nobody really thinks much about, but is a possibility.

DR. BARKER: In terms of the framework document that we are working on, how might we incorporate these issues into our considerations about setting thresholds and determination of whether there really is resistance?

DR. SALYERS: I think the document -- incidently, I just want to say that I was impressed with this document in the sense that it showed more of a sophistication in terms of some of these issues like the more complicated ones of gene transfer than one normally sees, but I think that the document does address the issue of gene transfer, are these genes transmissible or not.

I think the document does address the issue of gene transfer, and one thing in the document that I think is not right is that you wouldn't expect to get gene transfer

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between the respiratory pathogen and intestinal bacterium. I think that we are beginning to find is maybe not the case, but I think the issue of whether the resistance is transmissible is a very important one.

Now, you have to be careful there, though, because sometimes one type of resistance gives you the idea that it is not transmissible, and I use the fluoroquinolone resistance as an example.

You know, people have been telling each other for quite a while that fluoroquinolone resistance is a mutation in DNA gyrase or topoisomerase, cannot be transferred, and yet recently, transmissible fluoroquinolone resistance has been identified. It is just now being studied.

So, it is a difficult issue to address because you don't know in most of these natural settings how the gene is being transferred. Probably it is by conjugation. Many conjugation systems are regulated. The one that we work on is stimulated by very low levels of tetracycline. Others are stimulated in other particular ways.

I think that what you are going to have to assume is that any resistance gene is transmissible would probably be the safest thing.

DR. STERNER: Other questions, comments?

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[No response.]

DR. STERNER: Thank you, Dr. Salyers.

Our last speaker before our break this afternoon is Dr. Sherwood Gorbach from Tufts University talking about the importance of in vitro resistance compromising therapy for diarrheal disease.

Importance of In Vitro Resistance Compromising Therapy for Diarrheal Disease

DR. GORBACH: My task was to talk about impact of low level antimicrobial drugs on the human intestinal microflora, as well as the changes in resistance that might have a role in the treatment of human diarrheal disease.

Let me make a few general comments. I will talk about the microflora first.

Antimicrobial drugs cause resistance in animal isolates of human pathogens, and they also create an atmosphere or an environment in the microflora where these resistant genes can be passed to other members of the microflora or to other human pathogens.

So, on the one hand, we have the problem of resistance all together.

[Slide.]

That is the microflora.

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[Slide.]

The second issue has to do with antimicrobial residues, very small amounts of antibiotic that might be present in the human food chain that somehow escaped surveillance, and the effects of these very low levels of antibiotics in terms of possibly inducing resistance.

Well, just to remind you about the localization of the microflora, the vast number of microorganisms are located in the colon, and as we go across the ileocecal valve -- I don't have a pointer here, but it is that line all the way on the right -- there is a dramatic increase -- these are log changes -- and so that we get to the human colon where anaerobic bacteria outnumber the aerobic or facultative types by a factor of about 1,000 to 1.

E. coli and the other gram-negatives are located starting in the mid-ileum and then moving down and are increased in the large bowel. The large bowel is so heavily compacted with microorganisms, 10^{11} or 10^{12} per gram that it approaches the theoretical limit that can fit into that given mass.

[Slide.]

Now, this is the result of changes in the microflora with therapeutic doses of oxytetracycline. It is obviously well known. These are called Finlandian graphs. These are the

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resistance of the E. coli strains. The graph all the way on the left is the normal, and the bottom there is the minimal inhibitory concentration. As the graph shifts to the right, there is increasing resistance.

[Slide.]

This shows that depending on the day as it goes out, that a therapeutic dose will have a tremendous impact on the antibiotic resistance, not very surprising. What is interesting -- these are studies by Tancrede from France -- what is interesting is that this is a very low dose, 20 milligram dose in a human, which is lastly sub-therapeutic, and again there is a significant shift of the graph, the one on the furthest left being pre-antibiotic, and the one on the furthest right being the changes in the resistance, an increase in resistance even with very low sub-therapeutic doses.

[Slide.]

These investigators, Tancrede and Barakat, noted that in the French population, 97 percent of normal untreated people are permanent or occasional fecal carriers of oxytetracycline resistant enterobacteriaceae. Enterobacteriaceae, of course, include E. coli and normal members of the flora.

[Slide.]

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So this is a tremendous amount of resistance. This was also shown in the studies of Stuart Levy, which are difficult to see here, but these are several antibiotics, ampicillin on the furthest left, and they show that people carry about 40 percent of the strains in their microflora have a resistance to one or another of these antimicrobials.

This is healthy human Americans, so the antibiotic resistance is very common, and these are the resistances to people on or off antibiotics, and the graphs on the left are the people off antibiotics, the controls, and it not only shows the 40 percent figure in people off antibiotics, but also shows that many, up to 10 percent have multiple resistances.

[Slide.]

So, when people are exposed to antibiotics, they not only get a resistant to one antibiotic, namely, the one they are exposed to, but they develop multiple antibiotic resistances. These are off of treatment, and these are the percent with four antibiotic resistances, 10 percent of their E. coli isolates had four antibiotic resistances.

So, antibiotic resistance is very common. Now, how much of this is related to human use and how much is related to agriculture or to veterinarian use? We really don't know

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that answer. All we can say is that not everyone is exposed to antibiotics, although it seems that way if we look at the antibiotic costs, but nevertheless, not everyone is exposed, and these people were not exposed, at least in the recent past. So, we have to assume that some of this may be coming.

[Slide.]

Now, what are the effects of a low dose? Well, this is a study done in mice where a very low dose of streptomycin, about 1 milligram, was given to these mice, and it shows the infective dose.

In the untreated mice, it required a million cells of Salmonella to produce a 50 percent infection rate. However, with this remarkably low dose of streptomycin, that sensitivity of Salmonella was reduced, the point being that even if small residues of antibiotics make their way into the food chain, they can have a major impact on the susceptibility to infection.

[Slide.]

The human counterpart was a study reported by the Centers of Disease Control, of an outbreak of Salmonella havana. It's a rather unusual strain, so they were able to track this, and they showed that the susceptibility was 31 percent in

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people who had had prior antibiotic treatment, that is, anywhere from one week to two weeks before the contact with the organism, versus 13 percent with no treatment, so it was about 3-fold increase in the susceptibility to Salmonella infection when people had antibiotic treatment in the past. This relates to the intrinsic resistance of the microflora to infection. So, you perturb the microflora with even very low amounts of antibiotics, and the susceptibility to Salmonella continues for at least one week and possibly more.

[Slide.]

Now, let me move to human disease. This is WHO data giving you some of the big human pathogens. This is Shigella, 600,000 deaths a year. This is out of a total of 2 1/2 million deaths that WHO has tracked. Enterotoxigenic E. coli, 300,000; the rotavirus, a huge number.

By the way, not considered a heavy-duty pathogen, mild disease, but nevertheless, it can on a worldwide basis responsible for a huge number of deaths, and typhoid fever for about 600,000.

Now, in the United States, the CDC has reported an annual mortality of about 500 cases per year, that is, deaths due to diarrheal disease. In the UK, the corresponding number

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is about 200 deaths per year. This is probably almost certainly vastly underreported.

Community-based studies have shown that acute diarrhea in the USA occurs in adults about one to two times per year. It is not a topic for polite cocktail discussions, but all of us are aware of these occasional intestinal assaults. In children, the number is about twice that, so it's around two to four cases of diarrhea per year, and if the child is in daycare, the numbers can be doubled yet again. Daycare is a veritable cesspool of pathogens. It's almost an immunizing event for a child. That is if daycare is generally over 10 kids in a daycare center.

Now, it is important to distinguish the organisms that are of human or environmental sources from those that are of animal sources, so among the pathogens causing diarrheal disease, those of animal sources are Salmonella, Campylobacter, Yersinia, and E. coli 0157.

Those of human sources, several of them are shown here. Shigella is human. The primary cases are mostly human to primate. Enterotoxigenic E. coli, as well as some of the other E. coli - enteroaggrative E. coli, and so on, are probably of human origin. Cholera is marine based, as well as most of the other Vibrios.

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The rotavirus is human. The human strain is uniquely human, and Salmonella typhi is also a uniquely human pathogen. So, everything on this slide is human, but these don't show the figures for the non-typhoidal salmonellosis, which is the major cause of food-borne disease in the United States, at least the bacterial ones - Campylobacter, which is very close to it, and all in all, causes a serious morbidity.

[Slide.]

It is often said that you really don't need treatment for these, and I have heard that comment, and I am showing you a study that was published about two and a half years ago in the Clinical Infectious Diseases by Dryden from the UK, in which he randomized people with severe diarrheal disease into receiving either placebo or Cipro before the cause of the diarrhea was known, and this is the outcome.

You can see the days of diarrhea were cut almost in half by the use of Ciprofloxacin, a fluoroquinolone.

The definition of diarrhea, severe diarrhea, in this study was four or more bowel movements per day for three or more days, and that is rather a heroic number of stools.

That should be accompanied by one other symptom, such as fever, abdominal pain. So these represent a small piece of the total diarrheal cases, but nevertheless, these are the

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ones that are sick enough to stay home from school.

Diarrhea is probably second only to respiratory disease as a cause of staying home from school or losing time at work.

Intestinal indiscretions can cause this, and it is clear -- this is the fourth of a series of studies from different places in Europe, and one from Chicago, as well -- that has shown the striking reduction in the symptoms of acute diarrhea by the use of Ciprofloxacin.

So, the point of this is Ciprofloxacin is a major -- these are just the pathogens, I won't go through all of those -- but suffice as to say that in this study, 88 percent of the cases of diarrhea had an identifiable bacterial pathogen.

The leading causes would be as you expect Salmonella and Campylobacter, and that last slide, which is difficult to read, in Salmonella and Campylobacter cases, contrary to popular teaching, there was a significant decline in symptoms in these severe cases.

Well, the point is that the fluoroquinolones are very important in treatment of Salmonella, not only the extraintestinal forms of Salmonella, Salmonella bacteremia and local tissue salmonellosis, but also the more severe diarrheal cases, and despite what the textbooks say, not to treat Salmonella, the fact is that practicing physicians,

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when they see a patient that qualifies with severe diarrhea, which generally means enough diarrhea to come to the physician's office, and you can usually spot them, they are kind of moving around on two legs, when a physician sees this amount of diarrhea that has gone on for three days or more, almost invariably they will treat, and almost invariably they will treat with a fluoroquinolone.

The four studies, one of which I have shown you, justify that. I would like to emphasize that while many of our resistance problems are surely related to antibiotics in human medicine, and I would include the pneumococcus and Staph aureus, tuberculosis, and with due respect to the honorable delegate in the front row, Abigail, I also include VRE as a problem of human proportions, at least in the United States.

It is rooted in the intensive care units, it is not found in the community, but we can argue that.

While those are clearly related to abuses in human medicine, that is not what this meeting is about. What this meeting is about is the problems in the veterinary medicine, and I don't think we can escape from the increasing incidence of Salmonella and Campylobacter resistance to fluoroquinolones, that has been seen in Europe, temporally related to a prior

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introduction the fluoroquinolones in veterinary medicine. The only way that you get is significant resistances in these organisms is through pressure, antimicrobial pressure at the animal source.

We don't yet have it although a recent study from Minnesota, published in The New England Journal of Medicine, suggests that fluoroquinolone resistance is increasing in our Salmonella/Campylobacter strains. In this country, we are still low enough so that a positive action by this committee I think can avert what is, now in Europe, a tremendous problem.

Spain is 50 to 70 percent resistance with Salmonella and Campylobacter. Granted, we don't have to treat all of them, but those that are sick enough to treat, we are not going to get a good antibiotic unless we can slow the resistance in these important pathogens.

DR. STERNER: Questions from the committee for Dr. Gorbach? I am going to at the risk of demonstrating my ignorance to this entire assemblage ask if you could help me in understanding the issue of increased susceptibility. When I look at antibiotic residues in foods of animal origin, in general, levels are set at the part per billion level, and violative residues that show up commonly would be at less

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than 100 parts per billion.

If I understood your statement on tetracycline dosage, you were giving a 20-milligram dose to a human and then demonstrated increased susceptibility.

DR. GORBACH: Increased resistance.

DR. STERNER: If you took at 45-kilo adult, you had about 0.44 milligrams per kilogram, so you were at half a milligram or half a part per million dose?

DR. GORBACH: I think the problem is it may be a little like the radiation effect, that you may be able to demonstrate resistance with very small amounts, but it gets harder and harder to demonstrate, but there may not be any bottom at which it is completely safe.

We don't really know that. All we know is that very small amounts, sub-therapeutic amounts can cause changes in the microflora, and I should say that does not relate to the problem with diarrheal disease.

It should be apparent that changes in resistance to the microflora would reflect themselves in increased resistance in urinary tract pathogens, E. coli or in infections, more deep-seated infections that we might see in the hospital, but I don't know what the bottom safety is.

I am not disagreeing, in fact, I was part of the speaker at

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the deliberations on antibiotic residues, and I agree with the position, but we don't know what the lowest level of safety is with antibiotic residues.

DR. STERNER: Well, that gets to the heart of the issue of the whole drug approval process as it has existed for every since I have been familiar with it, and the fact that we do, in fact, set some minimal level at which we consider it to be safe or a tolerance setpoint, and the data that you have shown would argue against anything other than what we can detect, in other words, zero. The smaller it gets, the safer we are.

DR. GORBACH: I think that is true, but I can't be sure. All I would say is I like the approach of the draft document in that it separates out antibiotics by importance. So, I wouldn't worry as much about the Class II or Class III, but I would worry about even low exposures to Class I.

DR. STERNER: So, for example, our AOAC says that they can detect a compound at a part per quadrillion. Even that level then would become unacceptable for a Class I drug?

DR. GORBACH: Well, we are talking about different issues now. We are talking about antibiotic residues which may impact the human to microflora.

DR. STERNER: Right.

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DR. GORBACH: There is another aspect of that question that relates to the changes in the intrinsic strains from animals, that is, Salmonella and Campylobacter, and that is a different issue. So, I am willing to accept, for antibiotic residues, a definable low level, but I am not very happy about using what the document defines as Class I drugs, because that in itself may influence the animals' microflora, which includes Salmonella and Campylobacter.

DR. STERNER: Then, if I may, by inference your philosophical opinion would be there would be zero Class I approvals then under any circumstance?

DR. GORBACH: I don't like the "under any circumstance," because there may be situations in animals where it is lifesaving in an animal, but for routine use, yes, that would be my position.

DR. STERNER: Thank you. Other questions?

DR. GERKEN: Yes. You stated that Spain has so much Campy and Salmonella resistance, I think it was to fluoroquinolones, is that correct, or was that in general?

DR. GORBACH: Yes, to fluoroquinolones -- well, it is actually in general. I mean they have resistance to pneumococcus, it is up to 60 percent. But I referred to Campylobacter/Salmonella.

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DR. GERKEN: Is there evidence that their food is contaminated with bacteria that have that type of resistance, and that there is a correlation between those two things?

DR. GORBACH: I don't know about the food, I am not an expert in it. I can simply say that there are a lot of reports from Spain about resistant cases of salmonellosis and Campylobacter. Maybe some of the experts on the panel could comment.

DR. GERKEN: In disease in people.

DR. GORBACH: Humans. Yes, in people. They do report increasing levels of resistant strains in people.

DR. GERKEN: Maybe you can shed some light on that.

DR. ANGULO: One of the background documents for this panel is the report from the WHO meeting last summer on fluoroquinolones in which all the data available then was reviewed, and there is clear evidence of quite marked fluoroquinolone resistance in Campylobacter from several European countries, most notably being Spain, and there is also literature that show fluoroquinolone resistant Campylobacter at retail, from poultry at retail and pork at retail in Spain.

The rates that have been just suggested for fluoroquinolone

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resistant Salmonella have not been seen. There have been case reports of fluoroquinolone resistant Salmonella around the world, but there are no countries that I am aware of that have a notable rate of fluoroquinolone resistant Salmonella.

There is evidence of decline in susceptibility to fluoroquinolones amongst Salmonella in several countries in Europe and in the United States, but there is not an emergence of fluoroquinolone resistant Salmonella of note.

DR. GERKEN: Does the meat in Spain mostly come from production facilities in Spain, and in those production facilities, are they using more fluoroquinolones than in other countries?

DR. ANGULO: That's right, and there are other members in the audience that participate in the WHO working group, and it was my impression the consensus that one of the items of concern was the unregulated use of fluoroquinolones in some southern European countries where there is over-the-counter usage of fluoroquinolones, and it was a conclusion of the WHO consultation on fluoroquinolones that the veterinary use of fluoroquinolones had contributed to the emergence of fluoroquinolone resistant Campylobacter. I should also point out that it was the conclusion, as stated by Dr.

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Vogel, of the WHO consultation that there was not then evidence of clinical treatment failures from such usage. In other words, the clinical consequence of this emergence, which there was agreement was the consequence of using fluoroquinolones in food animals, the clinical consequence of that emergence had not been seen yet.

DR. STERNER: Other questions?

[No response.]

DR. STERNER: Thank you, Dr. Gorbach.

Dick Geyer has some housekeeping announcements. We will at the end of his comments take a 15-minute break. I hope you have noticed we are keeping ahead of schedule, so that there is the prospect of you actually being able to take a meal this evening before every place has closed. When we do break, it will be 15 minutes. You can set your watches, and if you are not in here, we are going to press on regardless. Our next group speaking will be from the Animal Health Institute.

[Housekeeping announcements.]

[Recess.]

DR. STERNER: We are going to go ahead with the Animal Health Institute's presentations, but before we get to Dr. Brendan Fox, Richard Geyer has a few comments, housekeeping

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details that he needs to address before we get started. So, Richard, with that, we will call the meeting to order.

MR. GEYER: Keith, what I had to say applies to our public speakers, so I think I will just hold off until we start that section.

DR. STERNER: Our first speaker representing the Animal Health Institute is the president of Elanco Animal Health from Indianapolis, Indiana, Dr. Brendan Fox.

Testimony of Animal Health Institute

Dr. Brendan Fox

DR. FOX: Thank you, Mr. Chairman.

On behalf of the Animal Health Institute and its member companies, we appreciate the opportunity to appear before you today to provide our views on FDA's proposed framework document regarding the approval and use of antimicrobials in food producing animals.

As you have just mentioned, I am Dr. Brendan Fox, president of Elanco Animal Health, a division of Eli Lilly and Company. Since joining Eli Lilly in 1974, I have served in several research and management positions within the company, and my current responsibilities include both R & D, drug research and development, as well as the business side of our activities, but I am here today representing the

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views and concerns, not only of Elanco Animal Health, but of AHI's member companies, and I believe my comments will reflect the views of my fellow CEOs of Animal Health companies, those responsible for directing future investment in the animal health industry and in to antibiotics in particular.

Before proceeding, let me take a moment to describe how we would like to use our time this afternoon. I would like to make some opening remarks to give the committee a sense of the overall views of the animal pharmaceutical industry, and following that, I would like to turn to Dr. Richard Carnevale here.

Dr. Carnevale is the vice president of regulatory, scientific and international affairs for AHI. He will provide a more detailed examination of some of the specific scientific elements outlined in the framework document, and he will answer all the difficult questions.

Then, Alex Mathews, AHI's president and CEO, will offer our views on what we believe are appropriate measures, because we do believe there are appropriate measures to address the issue of antimicrobial resistance in food-borne pathogens. Those sort of steps will included: establishment of an appropriate risk assessment methodology to quantify the

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potential impacts of food animal antibiotic use on human health; secondly, strengthening and expanding the government's national monitoring and surveillance efforts to assess the potential human exposure to antibiotic resistant food-borne pathogens; additionally, joint government, industry, and producer efforts to educate the industries on judicious use of antibiotics in farm animals; and finally, the appointment of a blue-ribbon panel to advise FDA on the this whole question of antibiotic resistance in both humans and animals.

So, we will discuss those ideas later on, and once we complete the presentation of the three speakers, we would welcome the opportunity to take any questions or comments from the panel.

In setting out my part of the agenda, I would like, first of all, to state very clearly the worldwide concern over antimicrobial resistance is one which we, as manufacturers of pharmaceuticals for both human and animal medicine, strongly share. Health care both in humans and animals is our business, and it is very important to us to protect human health above everything.

From a public health viewpoint, protecting the long-term effectiveness of antimicrobial drugs for human medicine is

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critical, and obviously from a business viewpoint, we have a clear interest in prolonging the useful life of our products both in humans and in animals.

The development of antimicrobial resistance in pathogenic bacteria presents difficult medical challenges requiring both attention and action. To successfully address this challenge, it is critically important to fully understand the nature and extent of the problem in both human and animal medicine. In order to make sure we are proposing sound solutions, we must examine the basic issues in perspective, such questions as:

What is the risk to an individual of developing an illness from a food-borne pathogen which developed antibiotic resistance as a result of veterinary drug therapy? And what is the rate of treatment failure in such instances?

What is the relative contribution of human antibiotic use to the problem of resistance development compare to food animal use?

Finally, what is the cost to consumers and agricultural producers of changing current regulations regarding the approval and use of antimicrobials in animals?

Clearly, there are many, many more questions to be examined. And the questions, like this entire debate, are not new.

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We have known since antibiotics were first used that bacteria can employ defenses that allow them to survive drug therapy and that resistance to antibiotics is a logical consequence of their use in both humans and animals.

The questions before the advisory committee today are fundamentally no different than the questions that have been asked repeatedly in scientific circles and debated there for the past 40 years.

FDA has indicated that recent resistance data relative to food-borne pathogens have "rekindled concerns" and led to the development of this framework proposal, but as you will hear in our more detailed analysis, we believe the agency is overreacting, it is overstating the conclusiveness and the implications of the data that we have in hand and has put forth a flawed proposal.

We believe the framework document is, in practice, unworkable. It is not support by the scientific evidence, and it is based on too many faulty assumptions. In short, it proposes a solution to a problem that is as yet far from clearly understood.

The framework is based on five components designed to "evaluate and minimize the potential human health effects" of antimicrobial use in animals. But by starting the

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examination of this issue from that standpoint, implicit in the framework itself is the assumption that there is a risk to public health from the use of antimicrobials in agriculture. This does not provide a sound scientific objective from which to proceed.

There is universal agreement that any use of antibiotics in human and animal medicine represents a hazard that antibiotic resistance can develop. But the framework seems to suggest that the hazard is exactly the same as a risk, which is not the case.

Clearly, hazard identification and characterization are only two of the components in analyzing risk. In our view, any proposal for regulatory change -- and I would add that this is a major change -- in the approval process for antimicrobials in advance of a full evaluation of the nature and extent of resistance, and the actual risk as opposed to hazard, the actual risk of a public health impact from their use is, in our view, very premature.

The key issue is not whether food-borne or other pathogens develop resistance, it is what is the potential for such resistance to have a negative impact on human health, to result in infections that cannot be treated by antibiotic therapy.

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Addressing this issue requires the establishment of an appropriate risk assessment framework to examine the various uses of antimicrobials in food producing animals and identify and quantify any specific threats to public health caused by their use.

Contrary to the assertion in the framework document, this proposal does not set out a conceptual risk-based framework for evaluating microbial safety. It is, at best, a hazard-based framework, based on a potential risk.

What is needed first -- before any of the discussion of details of pre- or post-approval studies, resistance thresholds, monitoring thresholds, drug categorizations or pathogen loads -- is a quantitative risk and benefit assessment methodology with a farm-to-table approach to quantify potential impacts and establish acceptable levels of risk.

The importance of a comprehensive risk assessment in this equation becomes clear when you examine the number of points along the continuum from farm to table where something could go wrong in order for a food-borne pathogen to cause an antibiotic treatment failure in an individual.

Let's look at how the process is laid out in the framework document. I am quoting from page 3 of the document.

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It says, "If, (1) when using an antimicrobial in a food producing animal, (2) resistance occurs in such bacteria, and (3) the resistant bacteria are then ingested by and (4) cause an illness in a consumer who (5) needs treatment, (6) that treatment may be compromised (7) if the pathogenic bacteria are resistant to the drug used for treatment."

So, clearly, there are seven steps even in this document from the treatment of an animal on the farm to a compromised human drug treatment, and I would point out compromised treatment is not quite the same as treatment failure.

This example doesn't include the numerous food processing steps which affect pathogen levels, from the slaughterhouse all the way through to food preparation, and things that happen in the home or in the restaurant.

This example partially demonstrates the complex nature of the issue of food-borne pathogen antimicrobial resistance and suggests the importance of a more comprehensive risk assessment methodology to assist in making the important policy decisions in this area.

In order to develop better risk analysis understanding of food-borne antimicrobial resistance, the Animal Health Institute has provided financial support to Georgetown University's Center for Food and Nutrition Policy in their

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efforts to develop a comprehensive risk and benefit assessment of the impacts on human health of using antibiotics in food animals.

Our understanding is that the development of the risk assessment model is currently underway and that Georgetown Center will share the results with this committee and with the Center for Veterinary Medicine once it is complete.

Beyond this issue, however, there are other troubling aspects of the proposed framework document that deserve comment. As someone from a company which looks at this issue both from the context of human and animal medicine, and from discussions with my medical colleagues, I am struck by the difference in approaches within FDA to the problem of antimicrobial resistance in human medicine as opposed to that for animal medicine. This difference is especially striking in light of what we know about the public health impact of human versus animal use of antimicrobials.

If I may just depart for a second here. I had some very interesting discussions recently with my colleagues dealing with these issues, but one of the points they have pointed out is there is an increasing use of antimicrobials, antibiotics in humans that is driven by factors in society today.

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It is driven by the fact there are an increasing number of infections. This was mentioned a little bit earlier here. I think the number of cases of otitis media here in the U.S. has doubled in the past several years, and this is due to child care centers basically.

Those do require treatment, and in some cases, child care centers will not readmit children if they have not been treated with antibiotics, a clear example there of changes in society, but I don't think the Secretary or anybody will propose abandoning child care centers. The question is what can we do in that environment to ensure appropriate use.

We have an aging population susceptible to respiratory infections. Clearly, we will see more antibiotic use there.

We have a larger growing immunocompromised population, not just age, but also from transplants which are becoming much more routine.

So, clearly, in the human field, you are going to see much more use of antibiotics driven by those kind of factors, and those are the factors which we really ought to be focusing on that will drive human antibiotic use and the animal use, quite frankly, is peripheral as far as they can see in this whole issue, to say nothing, of course, of international travel and spread, and so forth.

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According to the U.S. Centers or Disease Control, there are 88,000 deaths annually from nosocomial infections. Of those, we have been advised that about a third or 30,000 deaths involve infections resistant to antimicrobial treatment. These deaths are not from food-borne pathogens, but from hospital-acquired pathogens, such as Staph aureus and Pseudomonas aeruginosa.

While the number of deaths in the U.S. from food-borne pathogens we are currently estimating is somewhere between 2,000 and 9,000 annually, we are unaware of any documented case of a treatment failure resulting from -- this much lower number -- of resistant food-borne pathogen disease caused by an animal drug.

So, up to this point we don't have any failures that we are aware of, so this perspective of what is happening on the human side, but the animal side, I think is a very important one that seems to be missing from the document and the discussions.

Now, clearly, resistant bacterial infections are a serious human health problem. There are extensive efforts underway in human medicine to address the resistance problem, from educating parents on the appropriate and inappropriate antibiotic therapy for their children, encouraging doctors

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and hospitals to use antibiotics judiciously, but I do not believe that FDA's Center for Drug Evaluation and Research, CDER, is proposing to impose drastic new approval requirements on antibiotics for human use as CVM is proposing to do for animal use here.

While I do not suggest that the issues are exactly parallel, this tremendous disparity in the public health impact of antimicrobial resistance caused by human drug use compared to animal uses raises serious questions as to why FDA is proposing an excessively restrictive and disproportionate kind of a regulatory approach for veterinary medicine, while relying still on largely educational and monitoring-based approach with respect to human medicine where the problem truly resides.

Now, make no mistake. This is significant change in terms as proposed in the regulatory document, the framework document. The regulatory approach in the framework document would have serious negative consequences for animal agriculture.

It is difficult to imagine any new antimicrobial that has a use in human medicine, now or in the future, being approved for food use animals under this proposal, and this is the proposal as it exists in the framework document.

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If we try and think, then, about how it will be applied in practice, reducing this to practice, to something of a debate between reviewers and companies trying to interpret this, to set out new guidelines, and set on, is a fiercingly complex process. So, it is a very complex bureaucratic process we are proposing here to deal with this situation. Quite frankly, to us it seems unworkable in practice.

The research and development costs and the time involved in bringing new animal drugs even through the current approval process already make it very difficult for companies to justify the expenses involved.

The extensive new requirements envisioned in the framework proposal, as I say, when they are reduced to practice, would, in our view, effectively prohibit companies from committing the resources necessary to develop new products.

We are all aware of FDA's workload. We have passed the Animal Drug Availability Act. We still don't have guidelines out in certain of the cases. There is a tremendous amount of work generated by each of these changes in regulations, and this one again would just add another layer of complexity and uncertainty about interpretation between reviewers within the agency, and so on.

It would also impose a very fixed framework, and as we all

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know, science continues to develop, and this could rapidly be outdated by progress in science, so we need something a lot more flexible to approach the real issues here.

Additionally, the concepts outlined in the framework clearly could be used to seek removal of existing approvals of many safe and effective animal antimicrobials.

Now, there is a need for new products and new entities for use in food animals. Enabling veterinarians to help to provide a healthy and safe supply of meat which the consumer requires, we should all keep in mind that the current drug approval process is extremely rigorous with the approval of very few new antibacterials. For example, we are estimating there is about only one new therapeutic product which has been approved for use in swine over the last 12 years.

A similar situation exists on antimicrobials for beef, dairy, and poultry, with a total of only eight new antimicrobial entities being approved for all food producing animals since 1986, so less than one new antimicrobial a year, and now a burdensome new process here being proposed.

Taken together, this question of an end of new animal drug approvals and removals of existing approvals, these developments would seriously harm the health of farm animals and would result in significantly higher costs to farmers to

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meet market demand, and these added costs would be passed on to consumers in the form of higher food costs.

And to what end? It is highly unlikely that the framework concepts would have any significant impact on reducing the problem of antimicrobial resistance in human medicine because the major resistance problem we are dealing with here is the result of antibiotic use in humans.

I must say we are also disturbed by some details of some more specific points. I won't go into too much detail, but it does talk about E. coli 0157 in the document, and it goes on to say, "The link between antimicrobial resistance in food-borne pathogenic bacteria and the use of antimicrobials in food producing animals has been demonstrated in a number of studies."

There are several things wrong with that, but more specifically, there are no studies regarding a link between antimicrobial resistance in E. coli 0157 and the use of antimicrobials in food producing animals.

Another disturbing argument is a discussion of vancomycin resistant enterococci and citing the European epidemiological evidence, the document says, "VRE in humans may have been related in part to the induction of cross resistance to vancomycin due to food animal use of the

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related glycopeptide avoparcin."

But VRE is a problem in hospitals here in the U.S., as well, and, of course, avoparcin has never been approved in the U.S. So, a major fault in logic there.

The fact that VRE is a problem both in the U.S., where avoparcin isn't used, and in Europe, where it has been approved and used, would seem to argue against not for the proposition that VRE is related to use of the glycopeptide in food animals, and the only common denominator between the U.S. and Europe on this issue is the widespread use of vancomycin in human medicine.

As an aside, my scientific colleagues in Lilly have produced a paper which showed that the kilos of vancomycin used in human therapy, both in the U.S. and in Europe, increased very significantly over the 1980s and into the 1990s. It increased, the original parenteral form increased very, very significantly, and an oral form was introduced into the marketplace with, of course, direct exposure to the gut flora.

So, clearly, here was a major increase in vancomycin usage both in the U.S., both in Europe, but completely ignored, and somehow this relationship to a very peripheral issue is sort of justified as being the major cause of some of the

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problems. So, again, the logic does not seem to be there.

Finally, before I turn to Dr. Carnevale, let me say what I find perhaps most troubling about the framework proposal is that FDA has looked at the same evidence as numerous other bodies, this is not the only body which has examined this issue, but it has arrived at sharply different conclusions. The proposal is based on the assumption that we know antibiotic resistant pathogens can and do pass from animals to humans, that means there is a public health threat that requires extensive new, and to our mind scientifically questionable, regulations.

But many others have looked at this problem, affirmed the existence of resistance transfer, but found the evidence to suggest major changes was not there.

Specifically, last summer, the National Research Council examined the resistance issues in its report entitled, "The Use of Drugs in Food Animals: Benefits and Risks." This report, which was requested by USDA and FDA's CVM, does not recommend the regulatory changes proposed in the framework document.

On the contrary, the NRC called for an oversight commission to advise FDA on both human and animal antibiotic resistance issues and for the establishment of an integrated national

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database to support sound scientific decision-making processes for regulatory approval and use of antibiotics. According to NRC, "Until more accurate data on animal antibiotic use, patterns and rates of resistance transfer to humans, and occurrences of actual disease emerge, and mechanisms of resistance are available, actions aimed at regulating antibiotics cannot be implemented through a science-driven, well-validated, and justified process."

The report also contained the following comments which seem especially relevant to the issues under discussion by VMAC, as follows:

"Substantial information gaps contribute to the difficulty of assessing the effect of antibiotic use in food animals on human health. First, it is uncertain that the observed or perceived increases in transference of antibiotic resistance to humans is associated with the use of antibiotics in the food-animal industry."

The report does go on to cite several other information gaps which I won't quote in the interests of time.

Finally, it does say, "Finally, although conservative measures in the food-animal drug approval process might be prudent until these questions are answered definitely, the quest for new antibiotics for use in food animals must

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continue. Mechanisms must be instituted to increase research funding to discover new mechanisms of antibiotic-drug action; to increase and expedite FDA approvals of new drugs; to provide base funding for aspects of long-term experimental resistance-emergence research and surveillance research, which are not likely to be funded by short-term competitive grants; and to develop much more precise and accurate and quick tests of microbial, pathogen, and antibiotic-resistant organisms for monitoring purposes. Also, in 1998, the Institute of Medicine issues its report on "Antimicrobial Resistance: Issues and Options," and it looked again at a whole bunch of issues on both human and animal medicine, and the IOM report, like the NRC report, did not recommend regulatory changes along the lines proposed in the framework document.

On the contrary, the report called for increased research, more and better surveillance, collaboration between government, industry and agricultural producers on the development of educational materials and strategies. Finally, at a World Health Organization meeting, a panel of international experts examined the issue of quinolones, et cetera, and I think we have already referred to that, the use of fluoroquinolones in food animals has led to the

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emergence of fluoroquinolone-resistant Campylobacter and Salmonella with reduced susceptibility, but the report goes on to say, "There has been little documented impact of this resistance on human health" -- this has been referred to earlier here -- "but there is a concern about potential human health consequences if it were to increase. Again, further research and data gathering are essential to quantify this." And it goes on to specify a certain number of things, but nothing like the very bureaucratically complex restrictions and regulations we are talking about in this document.

Let me close my comments by saying simply that we, along with many others, have examined the issue of antimicrobial resistance, concur with FDA's goal, which is reducing the rate and development of resistance to protect the viability of antimicrobial drugs, but we don't believe the concepts outlined in this particular document provide a workable basis from which to address this issue.

So, for a more detailed analysis and the proposals that we think are more realistic, I will now pass on to my colleagues, Dr. Carnevale and Mr. Mathews.

Thank you.

Dr. Richard Carnevale

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DR. CARNEVALE: Thank you, Dr. Fox. Good afternoon. I am Rich Carnevale, vice president of scientific and regulatory and international affairs for the Animal Health Institute. Dr. Fox has provided you with an overview of the animal drug industry's concerns regarding the issue of antimicrobial resistance. At this time, I would like to comment on some of the more specific aspects of the framework.

In the introduction to the document, the CVM claims that new reports, particularly from Europe, have renewed concerns for the contribution of animal antimicrobial use to the development of resistance in food-borne bacteria.

Several literature references have been cited to support their conclusions, and some of those have been commented on today. Their conclusions are that immediate action is necessary to change the regulatory approach and the approval of antimicrobials in food producing animals.

AHI believes that the citations provided do not in all cases represent new information, and moreover, do not provide the compelling scientific justification for such a significant change in animal drug approval requirements.

We would like to briefly comment on some of these publications as it builds our foundation for further comments on the specific framework proposals.

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One of the key reports that is referenced in the document is that of Threllfall et al., from the Central Public Health Laboratory in Great Britain published in 1996. In a series of articles, the authors suggest that temporal increases in "resistance" levels of Salmonella typhimurium, Determinant Type 104, are directly tied to veterinary use of fluoroquinolones.

This and other reports from this laboratory were what the industry viewed as the trigger which set CVM on their current path to propose sweeping changes to the regulatory process.

While we viewed this information as important regarding an emerging a food-borne threat, we did not believe that the information was sufficient to cause such a significant disruption to the current approval process for veterinary drugs.

First, the use of the term "resistant" has been used by the authors not to describe clinical resistance, but rather a shift in susceptibility. They have chosen lower breakpoints than the standards set by the National Committee for Clinical Laboratory Standards (NCCLS) and the British Society for Antimicrobial Chemotherapy. What have been reported as "resistant" isolates are in reality clinically

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susceptible according to the NCCLS and BSAC guidelines. Second, as far as we know, there has not been a documented case of a human fluoroquinolone treatment failure in the UK because of DT104 as a result of the treatment of animals. Third, reports from that same laboratory over the last two years demonstrate a marked decline in the incidence of Salmonella typhimurium DT104 and no clinical resistance to the fluoroquinolones has yet emerged. At the same time, the incidence of DT104 with increased MICs to fluoroquinolones has really not changed.

Another study concerns fluoroquinolone resistance levels in Campylobacter species in poultry in the Netherlands published in 1991. This information was considered by the 1994 FDA Joint Advisory Committee prior to it recommending that the fluoroquinolones were approvable for therapeutic use in food animals with certain restrictions.

The Advisory Committee did not consider the Netherlands experience adequate evidence establishing a public health risk to preclude the approval of quinolone animal drugs in poultry. For one thing, a high level of resistance was already present in Campylobacter prior to the introduction of fluoroquinolones for use in poultry.

The study from Spain was mentioned earlier, where increases

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in resistant strains of Campylobacter species were, in fact, observed, however, Spain is a country where manufacturing, distribution, and sales of relatively low quality generics do abound, and other veterinary and human pharmaceuticals are generally less controlled.

In particular, these products tend to be more readily available, as was mentioned, for human and animal use without prescription, in contrast to the limited and veterinary controlled uses in the United States. It is important that we make that difference.

This report also failed to demonstrate that there was a direct link between the use of fluoroquinolone in animals and the actual development of resistance that was determined in people.

Another reference from the Minnesota Department of Health has also been referred to here today. That data is yet to be published, so we really don't know exactly what it says, but we have heard at various meetings pieces of it.

From the information we know about, only a very small percentage of human clinical cases were associated with the fluoroquinolone-resistant Campylobacter, and the majority of these were attributed to foreign travel.

The same author has reported that fluoroquinolone-resistant

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Campylobacter has been increasing in human isolates since 1991 in Minnesota, and that is four years prior to the approval of any fluoroquinolone in food producing animals. Now, the document also points out concern for development of antibiotic resistance in non-pathogenic enteric bacteria, which may under certain circumstances be pathogenic. References are appended from several studies in Europe suggesting a link between vancomycin resistant enterococci and glycopeptide use in animal feeds. We have heard a discussion about that this afternoon.

These references represent a significant research effort in Europe to incriminate the use of antimicrobial growth promoters as being responsible for transferring resistance to humans.

I would comment that these and other studies have been considered by the Scientific Committee on Animal Nutrition, an advisory body to the European Union Commission.

They have reviewed the situation with several drugs, avoparcin, virginiamycin, tylosin, and spiramycin, all the drugs that the European Union has decided to ban. In every case, their conclusions have been that the data falls short of being able to conclude that the use of these drugs in animal feed represent a significant public health risk.

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However, as we know, the European Union moved ahead with their ban.

Now, there is no question that common resistant isolates or resistance determinants can be found in humans and animals as a result of antibiotic use. Clearly, animals and humans can exchange bacteria carrying these properties. I think we have seen evidence for that. However, the cited evidence in the framework document, in our view, simply does not rise to a level which justifies the extreme measures being proposed here by CVM. This does not mean that we shouldn't take safeguards, and we will try to discuss what we think is our approach to the problem later in this presentation.

Now, let me talk a few minutes about some of the specifics on the proposal, so you can get our views of it.

With regard to categorization, the agency is proposing that the human health impact will be evaluated on two factors: one, the importance to human medicine; and two, the potential human exposure. That was discussed earlier by Dr. Sundlof.

Based on this evaluation, FDA proposes placing the antimicrobials into three categories based on their value to human medicine and their exposure.

Now, AHI shares the concern for preserving the usefulness of

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antimicrobial drugs for treatment of human infections, while at the same time balancing the need to assure the availability of needed antimicrobials in food animals. However, we believe the plan proposed by CVM will likely assure that development of important new antimicrobials for food producing animals may not even be attempted, as Dr. Fox alluded to.

A significant problem with establishing pre-approval and post-approval requirements based on the categorization is a dynamic new process by which pathogens emerge and new antimicrobials are discovered and developed.

Because new drugs in discovery require 10 or more years to develop, it won't be possible at the time of discovery to really project the importance of a new antimicrobial to human medicine.

That, of course, will be dependent on diseases of importance to humans and availability of other effective drugs at the time of expected commercialization of the new antimicrobial.

Because virtually any class of antimicrobial that has the potential benefit for animals will have similar benefits for human medicine, it is really difficult to imagine that any innovative antimicrobial would be developed for animal use without really having to meet the criteria of Category I,

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and we recognize there are several categories, but to us it appears that most drugs are going to fall into Category I, and this is obviously going to lead to a reluctance by companies to invest in their development.

The result, of course, will be more reliance on the older products, and hence, more resistance selection for those older products.

Now, some might suggest that animal health companies should just develop drugs for animal use, and avoid anything related to human medicine. Well, as I said before, this is rather difficult because any drugs that have a potential for treating human disease will probably have applications in veterinary medicine, and, in fact, most animal health companies share their discovery research with their human counterparts.

The economics of trying to do discovery research for animal drugs only simply doesn't make sense and certainly can't be justified economically.

Further, what might not be important today for medical uses might become important in the future. So, it is a very difficult balancing act - how do you determine what is important to human medicine today, so that you have that vision for the future.

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CMV also talks about exposure scenarios, and AHI certainly agrees that potential exposure of humans to resistant organisms is important to consider. In fact, we believe it is the primary factor to consider.

FDA states, and AHI concurs, that antimicrobial resistance transfer is determined by a complex chain of events. The proposal lists many factors that should be considered when classifying potential exposure.

These include attributes, product use, and potential human contact. Although food processing is mentioned, the emphasis is clearly on the attributes of the drug and how the product is used on the farm.

The industry sees a problem with this. The number of animals treated, for example, has little relationship to actual human exposure to food-borne bacteria.

Clearly, the most critical factors in determining potential exposure take place after the animal or food products, in the case of milk, leaves the farm. For example, consider the use of antimicrobials in dairy calves. Exposure to pathogens, whether they be susceptibility or resistant, is eliminated with pasteurization. The risk essentially is zero assuming there are no failures in the pasteurization process.

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So, drug attributes, product use, potential human contact, manure management practices, a lot of these factors are essentially non-factors.

Of course, we have a different situation with meat and eggs. These products are not pathogen-free. However, we are all aware of steps that are being taken, such as HACCP, steam sterilization, irradiation, that should have a major effect on reducing food-borne pathogens from a number of animal sources.

AHI doesn't believe that this important aspect relating to exposure has really been given adequate consideration by CVM in the development of their proposal.

Let me comment a moment on pre-approval studies. The framework proposes that pre-approval studies would be necessary for all Category I and II to assess the rate and extent of resistance development in enteric bacteria.

The document also talks about resistance thresholds and monitoring thresholds. For Category I, the agency says it may be possible to establish a level of resistance that will not cause a significant transfer to human pathogens. However, lacking that data, the agency would consider any level of resistance change to be a cause for the drug not being shown to be safe. In other words, the drug sponsors

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must demonstrate by pre-approval studies what level of resistance is safe prior to approval.

We believe the concept here proposes a standard that simply can't be met. Aside from the fact that the document is unclear as to whether these thresholds are based on susceptibility shifts or clinical resistance, the Center is acknowledging that in many cases it won't even be possible to define a safe level of resistance.

Since there is very little correlation between in vitro susceptibility of enteric bacteria from food animals and impacts on human health, there is little likelihood that you could ever set a safe level of resistance. Therefore, the agency, we believe, is proposing a rather prohibitive standard given the fact that resistance development is a natural response by bacteria.

Furthermore, it appears that CVM may be using a similar concept -- and I think others have commented on this -- to the way animal drug residues are handled, but there are important differences which make that an unworkable approach. I think Lyle Vogel commented on that.

At least with drug residues, we have assays, we have safety factors, statistics can be applied. The scientific basis and protocols for establishing resistance standards that are

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similar to drug residue tolerances simply haven't been developed. There isn't a long history of toxicological research that has gone into antibiotic resistance. It simply doesn't work to really quantify resistance by the methods used to establish residue tolerances.

Pathogen load. We have some concerns about pathogen load. FDA suggests that this is necessary to determine the time required for the pathogen load to decrease following treatment. We question the basis for this requirement. Implicit in the requirement for pathogen load studies is the assumption that quantitative viable counts of pathogens, above a baseline normal, will present a greater risk to public health.

We are not really aware of evidence that correlates increased on-farm gut concentration or prevalence of food-borne pathogens to increased human disease from those pathogens, nor are we aware of data which indicate that shedding of gram-negative bacteria, which are sensitive to a drug under test conditions -- and that would be the case with any new products -- should even be of concern with broad spectrum antimicrobials.

I think we heard this morning the use of a resistant strain. Well, that seems to be imprudent to develop resistant

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strains just to do studies.

There are a number of inherent difficulties that can be pointed out if one attempts to acquire the information, and I think it was already mentioned that there are some studies in swine, I won't go into that, but these on-farm studies that USDA has collected have shown a multitude of factors that contribute to pathogen shedding, and transportation is certainly one of those.

Establishing a relationship, a clear relationship between pathogen load and the use of the drug, we think is a very difficult thing to do, confounded by many factors.

Let me move to post-approval studies. It is clear that FDA believes that on-farm studies to monitor antimicrobial resistance development will be necessary for all Category I and Category II drugs, again, to ensure that thresholds are not exceeded.

The proposal would have drug companies collect such data on a drug-by-drug basis to establish and monitor these farms to meet the established monitoring and resistance thresholds, so that intervention and mitigation strategies could be investigated and initiated in a timely fashion.

AHI has serious concerns with this concept. We don't believe that on-farm isolation and susceptibility testing of

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food-borne bacteria, in particular pathogenic organisms, represents the best or most efficient location for assessing exposure.

Because of the relatively low prevalence of pathogens, numerous animals would need to be sampled in order to gather meaningful statistically valid data upon which to determine changes in susceptibility.

Now, in order to get around these problems, CVM has suggested that surrogate organisms might be used as sentinels for pathogen changes. We are concerned that the use of a surrogate removes the relevance of the results even further from what we are trying to accomplish, that is, to assure food safety.

The framework lays out FDA's belief that it would be appropriate to evaluate mitigation measures. Now, we are certainly interested in determining mitigation measures that could be used to decrease the rate and extent of resistance development. The information would be helpful to our companies in prolonging the effectiveness of antimicrobials. However, we don't see how such studies can really be justified as part of the approval process.

Information from these studies should be used in the judicious use initiative, and this is an area where

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industry, the veterinary profession, and government should work together, but we don't think it belongs in the drug approval process.

Now, as you will hear in a few minutes, we believe the best early warning system to monitor for changes is not on the farm, but in the slaughterhouse and closer to the consumer of meat and poultry. Further, we view testing for food safety purposes to a federal government responsibility as it is with other food-borne hazards, such as animal drug residues and pesticides.

The costs of on-farm testing should not be underestimated, or the logistics of even trying to collect representative data to determine if a pre-determined quantitative threshold has been exceeded. Estimates run more than a million dollars per drug per year even if studies could be adequately designed and conducted, and that is probably an underestimate.

The scope of testing that CVM has in mind, we believe might be beyond even what the federal government is capable of doing in the surveys that FSIS and APHIS have conducted over the years.

Thresholds. It is not clear in the document what is meant by a "threshold," whether it's a resistant or monitoring

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threshold and how the two may differ. We are assuming a resistance threshold might be a higher value than established for monitoring. If that is the case, then, we have complicated an already difficult process and added yet another set of assumptions to the approach. We have not only one threshold, but multiple thresholds. It is getting very difficult.

The use of in vitro susceptibility data as a regulatory tool, I believe has many drawbacks. Now, susceptibility testing is very valuable for evaluating trends and useful as an indicator for selecting therapeutics, but it is a measure of in vitro activity and in no way assures therapeutic outcome. It's a laboratory test. When in vitro susceptibility testing is used as a monitoring tool, we have been told by experts in the field that several years of data are really necessary to establish trends before you could tell whether something is occurring, and although shifts may be detected in the short term, more time is needed to confirm these trends.

The Salmonella DT104 situation in the UK, that I have mentioned earlier, is a good example of that, whereas, shifts initially were seen, and they seem to be leveling off.

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With that, I think I will close and turn to my partner, Mr. Mathews, but as you can see, FDA's proposed framework for regulating antimicrobials, AHI does not believe can be practically implemented.

In closing, I want to urge you in your role as advisers to the Center for Veterinary Medicine to request that the agency reconsider its proposal for a change in the regulation of animal drugs as they have suggested.

Thank you.

Alex Mathews

MR. MATHEWS: Thank you, Rich.

Mr. Chairman, in closing -- when you are having this much fun, time really flies. Dick, how much time do we have left?

MR. GEYER: It has expired.

MR. MATHEWS: Thank you all.

MR. GEYER: You have time to finish your prepared remarks. We have turned the clock off. You will stay on green until you finish your script.

DR. STERNER: However, don't construe that as license to carry on.

MR. MATHEWS: Okay, we won't run it up, but I appreciate the indulgence of this committee very much. I do think at this

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point you all deserve an award. You have been very patient and tolerant with the number of speakers and the amount of material that has been covered. I will be very brief.

As Rich said, we would now like to present our views, AHI's views on an effective strategy to deal with this issue, given our industry's concerns with the overall approach that CVM has proposed.

Antibiotic resistance is a problem that FDA and the medical and veterinary communities have struggled with for many years. Numerous studies have been conducted in an attempt to better define the causes, the degree of potential risk, and ways to manage it. The fact that we are here today debating what to do about all of this indicates that the problem is not easily solved, there is no magic formula which, if followed, will assure regulators that they are preventing a public health problem.

Every health concern that may present itself need not be dealt with by an overly zealous regulatory approach which simply adds additional burdens for both industry and the government to deal with.

Absent a defined health crisis that can be clearly prevented by specific risk management strategies, there are usually other options that can be examined. We have previously

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indicated that risk assessment is the first and necessary component to judge how great a risk there may be and whether a public health crisis exists.

Clearly, expert review of the issue, the current literature, and documented instances of health problems has led most scientists to conclude that there is a potential risk, but that the evidence has not risen to a level which indicates that there is an immediate health concern.

We refer to recent reports of the 1998 WHO meeting on the medical impact of fluoroquinolones, as well as the recently completed National Research Council report, "The Use of Drugs in Food Animals: Benefits and Risks."

The fact is the long history of antibiotic use in animals has generally failed to turn up compelling examples of where antibiotic use has significantly impacted human health that would justify the implementation of overly stringent controls.

Moreover, there are a number of regulatory safeguards currently in place for antimicrobials. All new therapeutic antibiotics are now only permitted by or on the order of a licensed veterinarian whether they be prescription dosage form products or the new veterinary feed directive drugs as recommended to FDA by this advisory committee in 1994.

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For certain drugs, such as the fluoroquinolones and glycopeptides, FDA has established a policy prohibiting extra-label use which has been widely publicized and endorsed by veterinary and practitioner groups.

As you know, the approval process for veterinary drugs is already extremely rigorous for all aspects of animal safety, effectiveness, and human safety. FDA establishes strict residue tolerances and withdrawal periods for animal drugs. USDA reports low level of residue violations in the National Residue Program indicating that animal drugs are, in the overwhelming majority of cases, being used correctly. Producer and veterinary groups have had a major impact through quality assurance programs by instilling the principles of proper use. It has been said that veterinary drugs may be among the most regulated consumer products in the country.

The animal health industry supports strong science-based regulation of its products, regulations which thereby improve confidence in the safety of these products. On the other hand, these policies must be based on an objective risk assessment, the scientific validity and practicality of the proposed measures, and a determination of the economic impact on the affected parties.

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We do not see these factors having been considered by the agency in the development of the framework document, nor do we see that FDA has considered the extensive efforts of three prestigious groups of scientists - the National Research Council, the Institute of Medicine, and the World Health Organization - and the conclusions they reached after their recent in-depth evaluations of the resistance issue. Instead of building additional requirements of dubious scientific value into the approval process, we endorse building on what has already been learned and recommended, and on approaches currently in place for evaluating and controlling the spread of antibiotic resistance. We believe the concerns that we all share can best be addressed with a program encompassing the following elements:

1. Risk Assessment. Dr. Fox has previously emphasized the importance we place on objectively assessing the potential for harm before any decisions can be made to impose new regulations. Risk assessment has become a fundamental principle in developing public policy.

Trade agreements negotiated within the World Trade Organization have embodied this approach for resolving food safety policy debates. In fact, I think it is worth relating the recent comments of a high USDA official, Gus

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Schumacher, as many of you know, the Under Secretary for Farm and Foreign Agriculture, who, when speaking about U.S. concerns over attempts to restrict foreign trade through nonscientifically-based sanitary and phytosanitary standards said, and I quote, "We want to make sure that science, not politics, is the guide when countries adopt measures relating to health and safety. Belief in the scientific method also must be the foundation of informed public policy. A policy based on public perception, rather than fact, will ultimately fail."

We believe that the risk and benefit assessment methodology being developed by Georgetown University's Center for Food and Nutrition Policy could serve as the basis for this effort. A sound, science-based, risk and benefit assessment approach is critical in assessing the impacts on human health of using antibiotics in food animals.

Monitoring and Surveillance. Strengthen and expand the National Antimicrobial Susceptibility Monitoring Program. Subsequent to the hearings on fluoroquinolones in 1994, the FDA and USDA established an antibacterial susceptibility monitoring program which focuses on carcass sampling in slaughter facilities. AHI strongly supports this program since in our opinion it is the optimum place to assess

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potential exposure from resistant food-borne pathogens. However, the program is in need of additional and continuing resources to maintain testing of all available isolates coming from governmental food safety testing programs, and the addition of new compounds to the program as needed. This will improve the sentinel value of the data in detecting changing trends in susceptibility with important antibacterials. Current HACCP sampling provides isolates of Salmonella obtained from short term focused testing by FSIS to determine a plant's compliance with pathogen reduction standards.

Testing of these isolates is useful and should be continued. However, it should be supplemented by susceptibility testing of isolates obtained from more routine national baseline surveys that FSIS plans to reconduct on a species-by-species basis in the future. Improving the national monitoring program to be a better indicator of what is occurring nationally is important in addressing the potential human exposure to resistant food-borne bacteria.

Appoint an expert blue ribbon panel of scientists to evaluate data from the national monitoring program, examine current research and the need for new studies, and make recommendations to FDA on resistance issues.

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The FDA should form this blue ribbon panel composed of, as we envision it, microbiologists, epidemiologists, public health experts, and other appropriate experts to regularly review data from the susceptibility testing of animal isolates, and report to the agency their findings regarding whether or not any patterns or resistance or decreased susceptibility are appearing.

This group could work with CDC on findings from the human sentinel site testing program in order to compare results with the animal data. The panel of experts should also analyze and critique the scientific knowledge of predictive studies for assessing antibiotic resistance, examine current model studies, and make recommendations to the agency.

Based on analysis of the national monitoring program, government agencies should then conduct focused epidemiological investigations to determine location and causes of susceptibility changes.

This is currently listed as one of the objectives of the national monitoring program as stated in its 1998 report.

We support this approach in using the monitoring program data as it uses resources appropriately and where necessary when problem are encountered. Under the President's Food Safety initiative, follow-up investigations could be

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conducted through the auspices of APHIS and ARS to determine the source and possible causes of susceptibility shifts.

Establish an action team composed of veterinary, producer, industry, government representatives and other scientists to propose specific mitigation steps to control problems identified in epidemiologic investigations.

These steps could range from efforts to communicate and educate producers and veterinarians on changing the pattern of use of an antibiotic, to more stringent measures such as labeling changes or temporary or permanent suspension of use.

The key concept here is that by involving and seeking the commitment of all stakeholders in addressing a potential problem, we can achieve a swift, focused solution. It was mentioned earlier the efforts that are underway in human medicine the control the development of antibiotic resistance through the efforts of public health agencies, industry, health care facilities, and practitioners. There are strong parallels with those activities and what we are proposing here.

Education. Encourage, promote, and help to fund efforts to develop and integrate judicious use principles and guidelines as standard operating procedures for all

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veterinarians and produces.

AVMA has undertaken to develop judicious use principles for antibacterial use in animals and is currently supporting efforts to develop more detailed species guidelines. These efforts have involved not only practicing veterinarians, but also producer groups, FDA, and Centers for Disease Control and Prevention.

AHI is also encouraging development of judicious use principles and guidelines for antibacterials used in animal production. Through these efforts we believe the principles of judicious use will become more deeply integrated and embedded in the practice of food animal medicine and animal production.

In closing, I would like to reiterate that we in the animal health industry share the concern over the development of antibiotic resistant bacteria, and we support comprehensive efforts to assure that the use of antibiotics in animal agriculture does not harm public health.

We believe the programs we have outlined here - establishing a risk assessment methodology to quantify potential impacts of antibiotic use, educational efforts to promote judicious use, strengthening the government's national monitoring and surveillance efforts to assess potential human exposure,

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increased epidemiological investigations, and appointment of a blue ribbon panel to advise FDA on resistance development - are the appropriate measures to address this issue.

We are committed to helping find effective means for monitoring and controlling antibiotic resistance that may arise from animal use while still making sure we maintain the availability of needed therapeutic and production tools. For the past 58 years, a key part of our mission has been to help America's farmers produce the safest, most nutritious, high quality food supply possible. The steps we have outlined will continue that important mission while assuring that the health of the American people are not compromised in any way.

Thank you, Mr. Chairman.

DR. STERNER: We will now entertain questions from the panel of the three speakers that we heard, and I will exercise the Chair's prerogative by asking about the Georgetown report and when will it be due out.

MR. MATHEWS: We understand that we don't have control over the timing of that, Mr. Chairman, but we understand it's a matter of months before it's out. There may be a preliminary report out within the next month or so, but I think that Dr. Crawford is slated to be a speaker tomorrow,

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and may be able to provide more specific information about that, though it should be a matter of months.

DR. STERNER: Dr. Bell.

DR. BELL: Our three colleagues have raised a long list of issues, some technical, that could probably be addressed, some more philosophical, that we basically don't agree with. I guess my question, though, is as I tried to indicate in my talk this morning, the real challenge is how are we going to get off the dime and more forward, and I would like to ask Rich and your two colleagues, your proposals to do a more comprehensive risk assessment and appoint a blue ribbon panel, well, first, how would this blue ribbon panel manage to do what multiple blue ribbon panels in the past have never been able to do, which has been produce something that both the human and animal health people could agree on, and second, the risk assessment, you know, I mean it really sounds good, but the problem we have is that risk assessments are dependent on assumptions, on modeling, on methodologies, and I perceive this notion that if, oh, we just waited for the risk assessment, then, the clouds overhead would part, the light would shine through from the heavens, and the way would then be clear, and we would all agree, and I guess, it seems pretty clear to me that

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whatever the risk assessment's conclusions were, the people in either human or animal health who disagreed would challenge the assumptions and the methodology and everything else, so I am at a loss to see how we move forward based on the admittedly laudable principle of waiting for scholarly risk assessments.

You know, we at CDC, we like surveillance because we feel like surveillance measures, what is going on in the real world, and it enables us to leapfrog ahead of some of these debates as to what would happen if we did this or that.

So, my question is how are the blue ribbon commission and the risk assessment that you proposed really going to help us move forward now, whereas, this kind of thing really hasn't helped in the past, in my opinion?

MR. MATHEWS: Richard, you may want to respond, as well, but let me take a stab at that.

I think with respect to the risk assessment, let me address that first. I think the need to have that can't be overstated. What we don't have, what we lack is a quantifiable risk assessment from farm to table, what is the risk to public health.

What we are proposing here, what is being proposed in the framework is an extraordinary shift in terms of how animal

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drugs are approved, and what Dr. Fox talked about is absolutely spot on it. It will squelch R & D, it will squelch production, it will cause a shift in husbandry practices, it will have far reaching residual impact.

To get to that point, to reach those kinds of judgments and decision that that has to be done, first, a risk assessment has got to be conducted. Now, how it is done, I think it requires, as I indicated in my remarks, it requires the commitment from all the stakeholders involved focused on this issue.

I think that leads me into the blue ribbon panel. The blue ribbon panel needs to be focused exclusively on this issue, but I think again with science driving it, and I think that there may have been other panels, some termed blue ribbon and others, but they haven't specifically focused on this issue in terms of how it can go forward.

DR. STERNER: Any other comments from the panelists? Okay. Dr. Norden.

DR. NORDEN: I think I would like to follow up a little bit on Dr. Bell, but I have a couple of comments. I mean what I keep hearing in a sense is what I call a smoking gun hypothesis - show us a case in a human organism that was acquired from an animal with resistant flora, and I think

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everyone who knows about epidemiology and surveillance knows that that is virtually impossible. It is almost impossible with a nosocomial infection in the hospital to find out exactly where it came from.

Maybe a risk assessment will give you great value, I am not sure. I am like Dr. Bell on that.

The other is simply to say that I think that in terms of regulation of drugs for human use and resistance, speaking as a member of the FDA Anti-infective Advisory Committee, not as an FDA member, that CDER is struggling with exactly the same issues that, in our evaluation of a drug like Synercid, one of the major questions is how do you achieve regulation, how do you approve a drug with a major emphasis on resistant organisms, and I think that my impression is that FDA is moving toward more stringent regulatory involvement with drugs for human medicine that are going to involve resistance.

There are requirements for postmarketing surveillance that don't exist presently that have been proposed. So, I don't think there is quite the discrepancy between "human" and "animal" medicine that was cited by our colleagues.

DR. STERNER: Dr. Angulo.

DR. ANGULO: My concern is that certainly the negative tone

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of your presentation, first, you discount much of the background material that is provided in the framework document, which although not extensive, we could point you towards extensive evidence, and please be assured that the Centers for Disease conclusion clearly is that there is an increasing trend of antimicrobial resistance in food-borne pathogens, and the use of antimicrobials in food animals is the driving force behind this increasing antimicrobial resistance.

Yes, it is true that we do not yet have human treatment failures because of completely resistant in food-borne pathogens, but we are rapidly approaching that arena or that situation, and we believe strongly at the Centers for Disease Control that we need to mitigate this problem now, not in 20 years.

That being said, and I would be happy to discuss with the panel, the critiques made of the background documents, I would be happy to offer a different impression of the background documents, but my first comment is about the negative nature of the critiques of the framework is because I just am wrestling with what is the alternative.

Although you can say many negative things about the framework, I just don't see an alternative, and no

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alternative was offered. The Animal Health Institute did provide an outline of a risk assessment, increased epidemiological investigations, increased monitoring, a blue ribbon panel, where is the public health safeguard? There is no safeguard there. Is the a public health safeguard if we increase monitoring? No.

If we do more investigations, where is the safeguard? Where is the consumer of the United States protected by any of those actions?

Now, if we do increased monitoring, and if we respond to certain things we see on increased monitoring, then, we begin to have a safeguard, and now we begin to start sounding like the framework document.

So, rather than throwing the baby out with the bath water, rather than throwing the whole framework out, your comments and critiques about the framework are well taken, and the framework needs to be fine-tuned and the details have to be worked out, but the framework of the framework document provides for the first time light at the end of the tunnel that we can begin to assure the consumers of the United States that the public health is being protected, the public's health is being protected.

DR. STERNER: Respondents?

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MR. MATHEWS: If I can make just an initial reaction to that. The point is well taken. I am glad I have a chance to respond to it.

I think in the question, what you are saying is how do we protect the public health, and I come back I think to our original fundamental point, which is what is the risk to the public, what is the risk to public health, and circle then back to an examination of understanding what that risk is from beginning to end, complete with intervention steps along the way, what is the risk that we need to address here and how best to address it in an effective means.

DR. ANGULO: A 30-second response is that is why the framework document is so visionary because if, as you present, there is no risk, then, you shouldn't be afraid of the framework document because when we put thresholds in, we will find no effect, and there will be no effect upon the industry.

If you are so certain that there is no effect, then, why are you so concerned about threshold and corrective actions? In public health, it allows us to go forward confidently with new approvals and assure the public that they are being protected because there is going to be corrective actions later on if it should emerge.

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I don't understand why you can be so vehemently opposed to the framework document if you are so insistent that there is no risk. If there is no risk, this framework document is not going to influence you.

DR. STERNER: Dr. Angulo, we have other panel members who want to ask questions also, with due respect.

Richard, I believe you were next.

MR. WOOD: I also am concerned about the global perspectives, the point you are raising, but I want to look at a specific item that was in your comments, but not referred to, and that has to do with reporting.

You are, in this one section, identifying that you are not supportive of reporting sales information, and I wish you could address that, particularly in light of you do in steps that you would like to take, you want to increase monitoring and surveillance, and the NARMS, you know, susceptibility and monitoring program, and in the framework document it identifies the value of having the sales data to be able to identify more strongly mitigating steps.

So, to me, it's a disconnect if you don't have those two together.

DR. STERNER: Respondents?

DR. CARNEVALE: We didn't comment on that, and I think it is

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because, you know, taken together with everything else, that was just another overwhelming piece of the whole puzzle.

Sales data right now is collected by companies, and certain information is reported to FDA on units distributed. There is really no system set up at the moment that most companies have that can track the kind of information that seems to be envisioned in this document, but we are not entirely clear what FDA has in mind.

The fact is that to implement such a monitoring system that they have in mind would be enormously expensive if it could be done, and then the question arises of what real value is it, and I think it is just another piece that has to be taken within the whole framework.

So, we have concerns about it, not from the standpoint of the request itself, but really in context with what is its value, and then what is the economic cost to the industry of having to try to develop a reporting scheme like this, which they may not be able to practically do, but I don't know all the details of the problems with that.

We put it in there as a concern we had, but we didn't elaborate on it in the talk.

DR. STERNER: Dr. McEwen.

DR. McEWEN: I just wanted to emphasize that I think that

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you should bear in mind that there are different types of risk assessment, and I think the question out there is whether we have to wait until the absolute ultimate quantitative risk assessment is done before any action is taken. That is one extreme, I guess.

The other one would be to do a qualitative risk assessment based on the information that is available and then make a decision on actions. I think there are gradients of assessing risk, and it is not entirely an all or nothing thing the options that the committee is facing.

DR. STERNER: Dr. Galbraith, you had a question?

DR. GALBRAITH: Yes. I would just like to add a comment about risk assessment. I think it's laudable that you are supporting the development of risk assessment, but I wonder what in the history of risk assessment and regulatory affairs makes you optimistic that this will help be a resolution?

DR. FOX: Let's just say, for example, it is now mandatory in WTO actions, GATT actions, I think there is a lot more now, it is becoming a lot more sophisticated, and clearly, there are different models, and so on.

It is used in a fair number of regulatory decisions on toxicology, and so on, and even more recently, I think in

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the UK, at some of the BSE decisions, when it came down to the beef on the bone, and the 1 in a billion kind of thing, that was something that began to get talked about much more publicly, so I think we are on a journey here, but I do think the whole question of the involvement of risk assessments, the sophistication, the understanding is steadily building.

DR. STERNER: Dr. Barker.

DR. BARKER: One man's vision can be another man's nightmare. It is obvious that there is a big of difference between the perceived vision of one and the hallucination that it appears to be to another. We are better to deal with the issues than with personalities.

I would like you to respond to this issue. Now, the FDA has already established a fair amount of requirements for approval of antibiotics that include determination of safe levels, determination of an ADI, flexible labeling, which would permit lower and higher dose administrations, there were a range of concentrations that often exceed proven effectiveness, and that the role of the FDA is to provide safe and effective products and to assure the health of the American public in the use of these compounds.

When we look at antibiotics, we start to see shifts in

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effectiveness. We start to see susceptibility changes. It is still an effective drug, and under effectiveness, it would still meet the requirements.

We seem to be starting to bump up against the other requirement that FDA make, that it also be safe.

When do changes in susceptibility become perceived or actual differences that define resistance, and then can be interpreted as being unsafe because of the perception that it could somehow be passed on to the American public?

DR. CARNEVALE: I think the question is how do you establish thresholds?

DR. BARKER: Pretty much.

DR. CARNEVALE: I don't know that I can answer that. That is exactly the question we are asking. The threshold concept, you know, I understand how CVM came to that, how the thinking got them to that point, because it is a very nice tool to use.

The problem is you are raising a very essential point - when does susceptibility change or resistance change in a certain number of pathogens in a certain study mean that you have got a problem, and I don't know how to make that determination, and it is one of the problems that we have in this document.

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It has to be recognized that it is a diagnostic tool. MIC changes are affected by how you do the test. MICs are only an approximate measure of whether a drug will work or not work. There is some correlation with a number of antibiotics. I recognize NCCLS has set clinical breakpoints, and related that to clinical effectiveness, but the bottom line still is an approximation.

It doesn't mean that the patient won't respond. It means there is a likelihood the patient might not respond. There are a lot of other factors in the patient that dictate whether they are going to respond to the disease or not, and you can look in the literature and see where drugs that have been fully effective, supposedly fully effective by in vitro tests have not worked. Why? Because they were treating a patient that had an underlying immune compromised state.

So, the problem we are having is, yes, where do you set those threshold values, because the correlations simply haven't been developed that show that you reach a certain point, and that means you have a human health impact.

Now, one could argue that, you know, you don't need that to regulate products, and getting back to what Fred was saying, we are not discounting the literature, we are not suggesting the literature doesn't show that there have been resistance

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transfer and there has been development of resistance. We are simply saying that the literature doesn't rise to a level at this time to change what we are currently doing. We think there are other ways to control antibiotic resistance because we don't envision that the literature says that there is a crisis occurring at the moment. Now, that is a point that obviously certain people are disagreeing with us on. Some people are saying there is a crisis. We don't think there is a crisis that would dictate massive changes to the regulatory approach. Do we think there should be things done? Absolutely. There are things being done now. We just think they ought to be strengthened. We think we ought to look for alternative approaches other than always looking to the drug approval process to try to correct a perceived problem.

DR. STERNER: In fairness to our next speakers, I will give Dr. Barker his last opportunity to comment or a question.

DR. BARKER: Thank you.

Just to kind of follow up on that, is it clear to industry based on the framework document exactly how they are to proceed in trying to get an approval at this point?

Was that too obvious?

DR. FOX: How long have we got here? No, I think as I said

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in my comments, seriously, there is a very big concern because I think it is one thing to talk about a framework document here, and speaking as one of the other drug sponsors, who has been through this process many, many times, it is very difficult right now to get drugs cleared. Taking a framework document and putting it into something in practice, how reviewers are going to interpret it, how the lawyers are going to get involved, how you get a reviewer to review variations, how is FDA going to write guidelines?

It is truly a nightmare, and this is a very big shift. I can only close with one comment, which was from one of our very senior corporate research people, and it was, "It seems to me that in veterinary medicine, the more innovative the drug, the less likely it is to be approved." That, I think has serious consequences for veterinary medicine in the U.S. Thank you.

DR. STERNER: Thank you, Dr. Fox.

That concludes remarks from AHI at this time. There will be perhaps an opportunity tomorrow morning to further address questions to them.

We are going to take a 10-minute break, at which time we will open with some housekeeping announcements from Dick

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Geyer, and then we will begin our public commentary and try and keep people on task.

Thank you.

[Recess.]

DR. STERNER: If I could have the attention of the audience, the floor is now Richard Geyer's.

MR. GEYER: If you all would take your seats, we need to run through just a few procedures for the public session.

For the public speakers, for the benefit of the committee, we would like for you before you start with your remarks to answer two questions. First of all, do you have any financial interest in or financial support from any manufacturers of animal drugs, and number two, have your expenses to attend this meeting been paid entirely or in part by animal drug manufacturers.

So, if you would respond to those questions, we would appreciate it. I might run real quickly through the list. If you have the list of public participants in front of you, we are going to make just a few changes in it.

Dr. Rebecca Goldberg, who is now No. 13, we are moving up to No. 2. These few changes that we are making are to accommodate people's schedules.

Tom Burkgren, who was No. 2, his time will be 12 minutes

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instead of 10 minutes for the benefit of those who are setting the clock.

No. 12, Jim Jarrett, will be speaking tomorrow. No. 14, Dr. Robert Walker, his time allocation is 10 minutes.

No. 17, Ran Smith, will be speaking tomorrow.

We have added to the end of the list Dr. Barbara Glen with 10 minutes, and she will be speaking this afternoon.

So, our present plan is to have just two speakers tomorrow, but I think that depends upon how rapidly we move, and I am going to turn it over to our Chair to talk about that.

DR. STERNER: In fairness to the committee and given the workload that we expect and the discussions to go tomorrow, we will ask you to adhere strictly to the time allotted, and I will be very unceremonious in saying time is up when that right light comes on. That is just a common courtesy to the other speakers who have all tried to prepare their remarks and fall within the time frame.

So, with that, we have our first speaker from the public sector, Margaret Mellon from the Union of Concerned Scientists with 10 minutes, Margaret.

Public Speakers

Margaret Mellon

MS. MELLON: Well, I will start by saying that I am

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receiving no money from any animal drug manufacturer, nor have my expenses been paid by anyone other than my own organization, the Union of Concerned Scientists. I also congratulate the committee for asking the question. I think eliciting the interests of speakers is a very important part of taking testimony from the public.

My organization, as I said, is the Union of Concerned Scientists. We are a Boston-based, nongovernmental organization with an interest in the interface between technology and society. I am here as the director of our agriculture and biotechnology program.

We are very pleased to be here today to comment on CVM's proposed framework for the use of antibiotic in food producing animals. The emergence of antibiotic-resistant pathogens is a looming health issue of major proportions. Scientists, physicians, and public health agencies around the world are raising the alarm and, in some cases, taking action. It is certainly time for the U.S. to step up to the bar.

We applaud the FDA for taking the initiative in addressing the issue both in the medical and the animal settings, but particularly for this, the neglected area of the animal uses of antibiotics.

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We do not in any way underestimate the problems of dealing with the antibiotic resistance. Dealing with this problem runs counter to the most human of predispositions, dispositions to favor benefits today over problems tomorrow that may never emerge, but nevertheless, this is an important problem and will require strong leadership if we are to stave off the resurgence of untreatable infectious disease.

As a national sort of aside, I hope that the U.S. is in the forefront of addressing that problem, and that it is not only those in Europe that are going to take it seriously.

Since time is short, I will make brief comments. First, is that the FDA's policy should encompass existing drug use, and should start with sub-therapeutic uses of antibiotics. The policy with a few footnotes aside seems to focus on new therapeutic drugs for use in animals.

Well, it leaves completely untouched the existing use of antibiotics and particularly those that are used for growth promotion. In our view, a risk-based policy ought to be like bank robbers, the they ought to go where the money is, and in this case, the money is with the existing annual use of antimicrobials.

From our perspective, a prospective use-only policy is

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something like two decades too late. It might have made sense before there were multi-drug resistant pathogens, before resistance had been shown to emerge on the heels of initiating use in animal systems, perhaps when people still believed that resistant strains of microorganisms were not going to be virulent or that they were carrying such an energy cost as a result of carrying antibiotic resistance that they would revert to susceptibility.

We now know that that is not true. We believe the U.S., we believe the CDC when it says that use of antimicrobials in animals is the dominant cause of antibiotic resistance in food-borne organisms.

We know that resistant strains are virulent and we know that they are not likely to revert to susceptibility on discontinuing the use of the antimicrobial. So, in our mind, this puts us in a situation where we need to act and where the burden of proof has been shifted from those who say that there is no problem to those of us who ask, you know, not to be told that there is no proof that there is a problem, we now want proof that there is no problem.

I think there is enough scientific evidence on record for that to be the responsible public response. Now, we do understand that there are lots of places where we need more

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data, that there are lots of holes, there is a lot of uncertainty, but as we said, I don't think that that is enough anymore.

That was enough 20 years ago, that is not enough now. We also understand that medical settings are primarily responsible for the overall problem of antibiotic resistance, but again, that doesn't get us very far. It doesn't mean that agricultural use is not a problem. It seems to us that it is.

I mean with all of the data that have been brought forth, I have seen no scientific explanation for why prolonged exposure to antimicrobials in animal settings would not lead to an antibiotic resistance problem.

So, pointing out that animal use isn't as responsible in medical use doesn't mean that animals aren't a problem.

Third, we are really troubled by this notion that we ought to wait for therapeutic breakthrough before we act. I mean we don't want to wait until there are dead bodies in clinics before we act. If we can see antibiotic and antimicrobial resistance rising in pathogen populations, that ought to be enough. We need not wait until we have gone through all the antibiotics and people are actually dying in clinical situations. I think that is an irresponsible position for

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us to take.

We suggest that we need a new antimicrobial policy, one that would basically eliminate nonessential uses of antimicrobials and one that would shift the burden of proof to those who want to use antibiotics to prove that their uses are essential, are required.

We think that we need to save all of our antimicrobials, our crown jewels, for use in human medicine, that we can't afford to compromise their efficacy unless there is a compelling public benefit.

Turning to the framework specifically, we would like to -- well, first of all, we would like to say that if resources are limited at the FDA, we think that the better focus is on reviewing and eliminating existing uses of antimicrobials rather than doing a lot of work with review applications for new ones.

Second, we certainly recommend that the FDA adopt the CDC recommendation that antimicrobials used in humans or those that select for cross-resistance in humans be banned. We have a number of reasons for that.

The first is that it is the easiest way of accomplishing major public health benefit. It is the easiest way, much easier than controlling medical settings to limit our use of

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antibiotics.

The second is that the economic benefits are completely tenuous and, in fact, may not exist at all, but even if the National Research Council's estimate, probably a high one, of 5- or $10 per year per person is the cost of eliminating sub-therapeutic antibiotics, I suggest that it is a cost that most people are willing to pay.

Finally, I would say that the handwriting is on the wall in Europe, that the public will begin here and there to demand a livestock industry that is not dependent on antimicrobials, and that it is time to get started with the new animal management research that will make that possible.

We would like to recommend, in addition, that the aquaculture, that the committee recommend that FDA take up aquaculture specifically and not let it be wrapped into the other parts of its livestock program, and that it consider all the uses in aquaculture as sub-therapeutic because all of them are going to be or most all of them, it seems to me, are going to be broad in duration, and they are going to have very wide environmental exposure.

In conclusion, I want to say that the landscape, the policy landscape under which the FDA is undertaking this inquiry is changing. The public wants antibiotics for themselves, for

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their children, for the communities, and they do believe that they are at risk.

They are no longer going to tolerate a compromise in the efficacy of those drugs for any but the essential uses.

Now, some of those essential uses will certainly --

DR. STERNER: Ms. Mellon, unfortunately, time.

MS. MELLON: Half a sentence. We will include treating animals in pain and animals who are diseased. They are not going to, however, include an overly productive export industry.

Thank you.

DR. STERNER: Thank you.

Next, from the Environmental Defense Fund, we have Dr. Rebecca Goldberg, and she has 10 minutes.

Dr. Rebecca Goldberg

DR. GOLDBERG: Thank you. I will begin by saying that I have no funding from the pharmaceutical industry. I came here with money from my own organization.

I would also like to say that I am trained as a biologist and that I work as a senior scientist at the Environmental Defense Fund, sometimes known as EDF, which is a large, nonprofit organization that does research and advocacy on a variety of environmental issues.

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I am here today to comment on FDA's draft framework because the Environmental Defense Fund has become extremely concerned about the threat to public health from antimicrobial resistance bacteria. The heavy use of antimicrobials in animal agriculture is clearly an important component of this health problem.

I want to begin by saying that the Environmental Defense Fund applauds the Food and Drug Administration for beginning to consider the role, the issues of antimicrobial resistance should play in evaluations of new antimicrobials used in food animal production.

We agree with FDA that new uses of antimicrobials should be evaluated and, as appropriate, restrict it to ensure that they do not pose a threat to human health via the development of bacterial resistance.

In addition, EDF is extremely pleased that the Food and Drug Administration has proposed that detailed drug sales information be submitted as part of drug experience reports. Such information, which has been heretofore unavailable in the United States is essential to more fully understanding relationships between drug use and the evolution of resistant bacteria.

We urge that the FDA make such information publicly

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available to the fullest extent allowed under the law, so that researchers have access to it.

These points made, EDF has some significant criticisms of the framework, and in the interests of time, I would like to limit myself to articulating concerns about three items.

The first item that EDF would like to take issue with is FDA's assertion that the framework is risk based. Within the narrow confines of new uses of antimicrobials in animal agriculture, an argument can be made that the framework has a risk basis in that FDA's proposed actions are at least related to the likelihood and threat to human health from particular new uses of antimicrobials.

However, if one looks broadly at the problem of antimicrobial resistance, it is apparent that at least in the near term, the greatest risk to human health from agricultural uses of antibiotics comes from the very considerable existing uses of antimicrobials in animal agriculture, not future uses.

Yet, these existing uses are ignored by the framework and, as a result, it makes it extremely hard for EDF to view FDA's proposed framework as truly risk based.

The second point I want to make is that EDF disagrees with FDA's priorities as expressed in part in the new framework.

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In other words, where there are tradeoffs between allowing antimicrobial use in food animal production and protecting public health, we believe that FDA gives too much priority to food animal production. EDF would give much more priority to protecting the bacterial susceptibility and therefore protecting the public health.

In our view, the most troubling example of this difference in priorities concerns FDA's proposed categorization of antimicrobials. FDA's proposed Category I includes those drugs whose efficacy is immediately critical to human health. This category includes drugs that are -- and I quote -- "essential for treatment of a serious or life-threatening disease in humans for which there is no satisfactory alternative therapy.

In other words, Category I includes drugs for which the loss of bacterial susceptibility would likely result in human deaths. Yet, FDA proposes to allow Category I drugs to be used in food animal production albeit with some evaluation and often, I assume, with considerable limitation to prevent the spread of resistance, but even limited use of Category I drugs carries some use and will likely increase the risk that bacteria will evolve resistance to these antimicrobials.

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Thus, FDA's proposed framework potentially jeopardizes human lives, and we are frankly appalled that FDA would propose to allow such uses of Category I antimicrobials in animal agriculture.

We believe that few members of the public would make such a tradeoff between animal production and protecting human health if given the choice, and we urge that FDA take a similar perspective.

Our third point concerns some of the science underlying the policy. In particular, FDA distinguishes between enteric and non-enteric human pathogens in its categorization scheme, suggesting that it would not be expected or biologically plausible for resistance to be transferred from animal enteric pathogens to non-enteric pathogens.

This is hogwash, if you will excuse the pun. The more that scientists learn about patterns of bacterial gene transfer, the more it becomes abundantly clear that bacterial genomes are extremely plastic and that bacteria exchange genetic material frequently and across substantial taxonomic distances.

There is no reason to expect that genes from enteric bacteria will not be transferred to non-enteric bacteria.

As someone with at least a little background in microbial

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ecology, I can tell you that antimicrobial resistance genes are extremely common among all sorts of bacteria in the environment including those in soil, those is water, and those on the surfaces of leaves of plants.

In other words, it is abundantly clear that non-enteric bacteria frequently acquire antimicrobial resistance genes.

There are probably a variety of reasons for this. These include linkage of antimicrobial resistance genes with heavy metal resistance genes, and perhaps selection pressure from some antimicrobials that are persistent in the environment. But what it all boils down to is that FDA's argument that non-enteric pathogens will, for practical purposes, not acquire resistance genes from enteric pathogens doesn't stand scientific scrutiny.

In short, FDA should concern itself with the effect of antimicrobial use in animal agriculture on the development of resistance in non-enteric, as well as enteric pathogens.

Finally, because I think I probably have a minute or two more, I would like to make a comment on a point made by the previous commenter, Margaret Mellon, concerning aquaculture and uses of antibiotics or antimicrobials in aquaculture as fish farming is actually something I have some personal expertise in.

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Unlike most forms of livestock production, one cannot directly administer antimicrobials to fish that are being farmed. You can't dive into the water and inject a particular salmon or a catfish with an antimicrobial drug, and therefore, outside of hatcheries of fish antimicrobials are almost invariably given to fish through feed, which is put directly into the water.

Since most aquaculture facilities in this country have no effluent treatment of any sort, that means that low sub-therapeutic doses of antimicrobials from uneaten feed and that have survived a fish intestinal tract, which is rather different than that of higher organisms, are probably in the water and present at sub-therapeutic level providing selection pressure for spread of antimicrobial resistance genes. We, therefore, are very concerned about even therapeutic uses of antimicrobials in aquaculture.

Finally, in closing, EDF would like to congratulate the Food and Drug Administration for at long last stepping forward to consider the threat to human health from the use of antimicrobials in animal agriculture.

However, FDA's proposed framework falls short in a number of critical ways, three of which I have elaborated. We urge the agency to take an approach that is far more protective

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of human health.

Thanks a lot.

DR. STERNER: Thank you. Actually, time has just elapsed, so you have done well. You have set a good template for the rest of the public speakers.

Next, from the American Association of Swine Practitioners, is Dr. Tom Burkgren, and he has 12 minutes.

If you would state your associations.

Dr. Tom Burkgren

DR. BURKGREN: Yes. To the two questions, I have no financial interest in pharmaceutical companies, and my expenses to this meeting have been paid by my association.

I would first like to preface my remarks about our association. We are a practitioner-based association of veterinarians, and in our contact the past year with Dr. Bell in our judicious use guidelines, I would have to say that we appreciate his professionalism and his passion for this issue.

We understand his frustration because my comments today are as a result of deeply rooted frustrations on our part as practitioners and not knowing if we will have a drug approval process in the future, if we will have the absolutely necessary tools, antimicrobial tools for us to do

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our jobs on the farm.

The AASP recognizes and appreciates the efforts of the FDA in keeping the nation's food supply safe. We recognize the complexity of this issue. We are not naive in thinking that this framework will not be instituted, however, we do have severe and significant concerns about this framework.

The framework proposed to manage a risk that has not been adequately assessed. It fails to recognize the need to separate hazard from risk. The FDA has identified a hazard, but they have not addressed the issue of risk and how likely the hazard is to occur, and what the magnitude will be.

The AASP agrees with the FDA that the impact of animal uses of antimicrobial drugs on human health should be reexamined, however, we disagree that the proposed framework is the appropriate approach. The evaluation of the issue should be done within the scientific risk assessment whether qualitative or quantitative. The risk assessment process has value even if you do not meet your preordained measures of success. It does help you fill data gaps and address research agenda.

Risk assessment should not be implemented until the risk has been laid in proportion. To undertake risk management before risk assessment has no basis in logic, nor within the

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accepted parameters or risk analysis in the absence of a clearly identifiable severe risk.

In the worst case scenario, this framework could appear to be a thinly disguised regulatory application of the precautionary principle. Objective risk characterization would enable this issue to be evaluated within the broader context to which the hazard relates, that is, the societal cost and the benefits of regulatory restriction of antimicrobial use in all arenas.

The FDA states that its primary public health goal must be to protect the public health by preserving the long-term effectiveness of antimicrobial drugs for treating human disease. By this statement, can one assume that the FDA is acting in proportion to the relative magnitude of the problem from the use of antimicrobials in the treatment of humans?

At this publicly, it seems FDA's actions to protect the public health with respect to antimicrobial use in the human arena have been limited to education and non-binding guidelines, and we have heard the opinion that these are not successful. Why, in the absence of a credible risk assessment should animal agriculture bear the brunt of FDA's regulatory interventions?

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As the document was examined for its scientific merit, two immediate concerns were evident to our review panel. The first eight references were anonymous, and did not represent peer-reviewed science. Yet, we feel that if there is something worth citing, then, it would be more convincing to cite original peer-reviewed sources from those documents. Secondly, the examination of the document reveals the words, "FDA believes" or some variant of this phrase appears 47 times. The complexity of this issue requires that belief be founded in science, and the document is less than convincing on this matter.

The framework fails to adequately define many scientific terms. This lack of clarity invites subjective and misleading interpretation and raises further questions of the scientific foundation.

Examples of the terms we would like to see defined would be pathogen load, human health effects, induction of resistance, significant baseline of colonization. This list is not exhaustive, but we feel that a reference glossary of scientific citations would be useful to further discern the scientific basis of this framework.

There are examples given within the document which tend to mislead and bias the reader. Other speakers have E. coli

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0157 as being included. Actually research has shown this bacteria to be transient in individual animals, and not a persistent colonizer of intestinal flora of various food producing animals, and certainly not in swine, but E. coli 0157 has considerable emotive impact on the public, but its pertinence to this discussion is questionable.

Vancomycin resistant enterococcus has been mentioned in Europe, but in the United States we have no glycopeptide use in animal agriculture. We fail to see the relevance for this discussion other than, once again, emotions are raised.

There are other instances where scientific citations would be useful. The document often associates pathogen level with duration of therapy. There are statements in the document where the use of antimicrobials, especially for long duration, is inferred to disturb the normal intestinal ecosystem in the animal resulting in an increase in the bacteria that could cause human infections or prolong the duration of the carrier state.

In a cursory discussion of this point, our review panel identified several papers on antimicrobial use in swine that contradict the position of the FDA in the document. Our minimal expectation is that the FDA would conduct a credible review of the scientific literature before proposing

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demanding expensive requirements for the pre-approval testing based on a belief that appears to have a very questionable and very narrow scientific basis.

We are troubled by the categorization of human antimicrobials. We believe them to be plagued with subjectivity and built-in bias.

In our review of the scheme for categorization and in reference to the context of this discussion today from several experts, it becomes clear to us that this subjectivity allows a majority of significant antimicrobials in swine medicine to be placed in Category I immediately or in the near future. The subjectivity questions the credibility, and, in fact, the clinical usefulness of this categorization.

Other instances of bias comes through in terms of all food-borne disease becoming elevated to the same status as serious or life-threatening disease, when we know that the vast majority of food-borne illnesses are not serious nor life-threatening, and most do not require antibiotic treatment, in fact, it is contraindicated.

In more general terms, the discussion of the evaluation of potential exposure to humans centers more on the exposure of the bacteria in the gut of the animal to the antimicrobials

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than on the exposure of humans to resistant human pathogens and the subsequent clinical human health impact.

The examples that are given base potential exposure of humans to resistant human pathogens on the duration of treatment of the food animal. Once again, we ask for scientific basis for this assumption. The use of this type of surrogate measure for human exposure may be, in fact, easy, but it has no potential for measuring true clinical significance to public health.

The FDA has not revealed any valid model to link exposure of bacteria in the animal gut to the human exposure to the pathogens.

Now, we agree that the effects of antimicrobial resistance transfer from animals to humans involves a complex chain of events. The document lists only four parts of this chain. We would add the following: the likelihood the transfer will cause illness, the likelihood that the illness will require antimicrobial treatment, and the likelihood that the resistance will result in treatment failure.

Other biases found within the discussion of the example for the high potential human exposure, the label claim of improved growth or feed efficiency is highlighted in the example in the ensuing discussion. We question how the

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label claim is relevant to this discussion for potential human exposure to resistant pathogenic bacteria other than the emotional value of placing that in the document.

Bias is also revealed within the evaluation of the potential exposure of humans to resistant bacteria when they state that drugs are -- and I quote -- "administered in feed throughout the life of the animal on a flock or herdlike basis."

This would mean, in a swine herd, that the entire herd would be fed from birth to death antimicrobials, and would be on a continuous basis. I know of no swine farm today that could sustain that economic impact, nor clinical science background to warrant that.

This statement is inflammatory and blatantly misleading and has no place in this scientific document.

Monitoring and threshold levels and resistant threshold levels must be tied to measurable public health outcomes to be clinically important to the projection of human health.

We would cite the following questions needing more data: how the FDA intends to measure the rate of resistance transfer in vivo, what measure of resistance will be used, if used, how MICs will be used to determine clinical human health impact, and what constitutes sufficiently sensitive

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tests.

Lastly, on farm post-approval monitoring programs, we would ask that they carefully correlate measurable public health outcomes to proposed thresholds from on-farm monitoring before they come on our farms and disrupt our production. We would ask that models that validate on-farm monitoring be revealed.

In closing, we would propose the following to the FDA: the scientific risk assessment before attempting risk management, and we would offer our white paper that we have jointly commissioned with NPPC, the National Pork Producers Council, as helping to set the model and identify the research needs; risk characterization of the issue, strengthening of the NARMS program, continued and open meaningful dialogue between the FDA experts and stakeholders, and as part of this dialogue, identification, prioritization, and funding of an aggressive research agenda to help fill the data gaps.

Thank you.

DR. STERNER: Thank you. You probably have 30 seconds in which to field a question from the panel.

Any questions?

[No response.]

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DR. STERNER: Thank you, Dr. Burkgren.

Next, from the Colorado Animal Research Enterprises is Dr. Diane Fagerberg.

Dr. Diane Fagerberg

DR. FAGERBERG: First of all, I have not received financial support from the animal drug industry with regard to what I am going to present. In my presentation, I will mention how I am, however, and otherwise involved with the animal industry. As far as expenses, the Animal Health Institute will defray my travel expenses.

[Slide.]

This who I am now. I am the president and executive general manager of Colorado Animal Research Enterprises in Fort Collins, Colorado. I am involved in numerous types of FDA-required research for the approval process of new animal drugs.

I have conducted numerous studies, in fact, probably 99 percent of all of the feed additive antibiotic studies that went through the 558.15 regs for pathogen loads and microbial resistance.

[Slide.]

This is who I was 20 years ago. I sought and was awarded an FDA contract that extended over a four-year period. It was

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intended to be the baseline for comparison to future years, the baseline for comparison to today, to the 20 years later. The contract number was 223-77-7032, and its title was Database for Drug-Resistant Bacteria for Animals. It was basically FDA's reaction to the European Swann Committee.

[Slide.]

During the four-year period of 1978 to 1981, we sampled on-the-farm broilers, beef, and swine, and we sampled live swine at slaughter plants. We sampled 312 total units that represented 7- to 10,000 animals.

[Slide.]

From fecal samples of these animals we tried to isolate any Salmonella that were there. We isolated out 10 coliforms primarily which were E. coli, and we isolated out 10 enterococci, calling them streptococci at that time.

We performed antimicrobial susceptibility testing on all of those isolates, any of the Salmonella, all of the coliforms and all of the enterococci. It represents over 3,000 coliforms and enterococci.

[Slide.]

Before proceeding to relate to you some of the results of that work, I would like to relate to you -- and I will relate it as best that I can -- that the trend of drug usage

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in animals, food producing animals, during the most recent 15 years has increased. Sulfonamide usage has increased approximately 10 percent, streptomycin by approximately 63 percent, tetracycline by approximately 18, and penicillin type drug usage has increased approximately 150 percent. If of that 150 percent we eliminate the 70 percent that can probably be attributed to dogs, cats, and intermammary cow infusions, we are down to about a 70 percent increase in penicillin type usage in food animals.

These figures are very generalized and do not exclude companion animals. I am unable to tell you where this information on usage came from because along with that information, I was told it was confidential and that this strict confidentiality is key to the continued data quality, integrity, availability, and value.

[Slide.]

But the important thing, and I don't think anyone will argue with me that the animal usage of antimicrobials has increased over the last two decades.

[Slide.]

I am going to concentrate only on the Salmonella portion of that survey that we did 20 years ago. I would like to compare the past to the present. Basically, the present is

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represented by the NARMS data that was generated for 1997. Comparing all of our Salmonella to all of the NARMS Salmonella, we see a decrease in resistance from the then to now in most of the prevalent resistances, in sulfonamide resistance, streptomycin, and tetracycline.

[Slide.]

Increases have occurred with ampicillin and kanamycin. We saw no resistance to gentamicin, chloramphenicol, trimethoprim sulfa, nalidixic acid, or amikacin 20 years ago, whereas today, there is some resistance to all of them except amikacin. Again, a reminder, however, that decreases occurred in spite of increased usage of the sulfonamide, streptomycin, and tetracyclines.

[Slide.]

This is obviously difficult to read. I will tell you that what it is trying to show is the number of antimicrobials that were in a resistance pattern in the past, Salmonella isolates versus the current isolates, as well as what the patterns were.

There are 10 common antimicrobials between the past data and the current data, and I have only compared those. What has basically happened is we saw only 18 percent of the Salmonella isolates 20 years ago had no resistance. Today,

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the majority of Salmonella from the NARMS data have no resistance, 65 percent have no resistance.

The greatest majority of resistance then and now was either none or patterns that had just one or two antimicrobials in them. The shift to no resistance today is due to fewer Salmonella with resistance to one, two, three, or four drugs. There has been a slight increase in the number of isolates with five drug patterns. This is primarily due to adding kanamycin or chloramphenicol into the pattern, neither of which is used in food producing animals.

Probably the best Salmonella data to compare between the then and the now is that of slaughter swine, because the numbers of Salmonella tested were fairly similar between then and now. There were 128 tested back in the late seventies, early eighties, and in 1997, there were 110 HACCP Salmonella isolates from swine. Thus, their source was fairly similar also.

In neither case was amikacin or nalidixic acid resistance found. Twenty years ago we found no resistance to several of the drugs, gentamicin, trimethoprim sulfa, chloramphenicol, and kanamycin, and very little resistance to ampicillin, whereas, there are more with these resistances today.

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Tet resistance appears to have increased by about 20 percent, but sulfonamide and streptomycin resistances have decreased by 25 to 30 percent. Despite the increased usage of sulfonamide and streptomycin, there was this decreased resistance. Despite that kanamycin, chloramphenicol, and trimethoprim sulfa are not used in livestock, their resistances have recently appeared.

Gentamicin is used in swine primarily in very young pigs, and it was approved for such beginning in 1983, but seeing that other resistances have appeared without relationship to any drug usage in the animals makes on wonder if gentamicin usage in pigs had anything to do with finding gentamicin resistance in them now.

[Slide.]

These are just a few more comparisons of the types that are possible between the historical data and the NARMS data. This is cattle and swine on the farm, past and present. Salmonella antibiotic resistance on the farm cattle and swine show a major decrease in all of the major resistances, sulfonamide, streptomycin, tetracycline, ampicillin, but non-understandable increases in kanamycin, gentamicin, and chloramphenicol.

[Slide.]

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The same general pattern is seen when we compare cattle and swine and chickens. This is comparing to the NARMS data of the clinical and non-clinical isolates.

[Slide.]

When we talk about attributing animal antimicrobial resistance to animal antibiotic usage, food animals that is, we find that in the FDA survey, during which we gathered information on antibiotic usage, there was no correlation, and we tried all different ways, and could find no correlation of antibiotic resistance to antibiotic usage. When we compare the past to the present, we find that despite the increased usage of sulfonamide, streptomycin, and tetracycline, there has been a decrease in these resistances. Despite no usage of kanamycin, chloramphenicol, and trimethoprim sulfa in food producing animals, there has been an increase in these resistances. Despite no change except increased usages or new usages, there has been a major shift to finding that most of the Salmonella have no antibiotic resistance.

[Slide.]

If we can't even make antibiotic usage in food animals correlate to animal antibiotic resistance, how can we make a far greater leap of animal antibiotic usage affecting human

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antibiotic resistance?

[Slide.]

We gathered 20 years ago a wealth of baseline resistance information. FDA ran out of money, so the data was never summarized. If it is believed that surveys are important, I think the E. coli and enterococci data would provide even more, much more information than just the Salmonella data because there were numerous isolates tested. FDA has the data somewhere. They even should have the actual isolates somewhere.

They were provided to them. I urge VMAC to insist the data be found and be reviewed.

[Slide.]

I would like to interject my personal opinion about the proposed framework document. Despite the fact that I probably only have to gain from its implementation because so much more research will be needed, I believe that it will only be a costly adversity to food and food animal well-being, and will be very ineffectual towards preserving human health safety. In my opinion, it should not be implemented.

DR. STERNER: Does that conclude your remarks, Dr. Fagerberg?

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DR. FAGERBERG: Yes, it does.

DR. STERNER: Dr. Angulo.

DR. ANGULO: So, if we don't implement this framework, what would be your alternative suggestion, to continue with the current approval process?

DR. FAGERBERG: Yes. I think it has been very acceptable.

DR. ANGULO: And so the current state of the approval process, which was most of us familiar with the fluoroquinolone approval discussions, I think it is interesting because other representatives have a very different impression of the current approval process. So, I would just comment perhaps that our impression from the human data is very different than what you have presented, and it is very clear there is an increasing trend of antimicrobial resistance, and I think, to remind the panel, that that wasn't a question for discussion at this advisory committee, it is taken as a background statement that where antimicrobial resistance in food-borne pathogens come from.

DR. FAGERBERG: I think it does indicate that we do not have all of the answers.

DR. ANGULO: We don't have all the answers, but we certainly cannot stand still. We have to move forward if we don't

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have all the answers, but we have to assure the public health, and standing still and doing nothing is a statement that is not -- that is, in fact, not a safeguard.

DR. STERNER: Further questions for Dr. Fagerberg? Yes.

DR. SHELDON: Susceptibility test methods have changed quite a bit in the last 20 years, and therefore data derived from those methods may not be comparable.

What can you tell us about the susceptibility test methods that were used 20 years ago and those that are being used in the NARMS studies to assure comparability of the interpretation of results and therefore that one can compare them?

DR. FAGERBERG: I think that Paul and I would have to sit down and do comparisons. We used NCCLS 1979 standards for breakpoints. For the last three years of the study, we did MIC determinations. We used those breakpoints. SensiTiter did not exist then, we prepared our own MIC plates by the Anderson system.

They were manually read type plates for breakpoints.

DR. SHELDON: As a member of the NCCLS Committee, I can tell you that methods have changed quite a bit, inoculum effects. We now have documents to assure the quality of the media being used.

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So, I think that before we can accept -- that one can compare the information that you have here, we need to have assurances that the methods are comparable.

DR. FAGERBERG: The procedural information is available somewhere with FDA.

DR. STERNER: Thank you, Dr. Fagerberg. Unfortunately, time moves on.

Our next speaker from NCCLS is Dr. Thomas R. Shryock, Ph.D. He currently is employed by Elanco Animal Health.

Dr. Thomas R. Shryock

DR. SHRYOCK: That's correct, as a microbiologist with Elanco, obviously, my financial interests are obvious, and my expenses have been paid by an animal health current company.

[Slide.]

However, I am here today wearing as the hat as the chairholder for the NCCLS Veterinary Antimicrobial Susceptibility Testing Subcommittee. I needed 20 minutes just to get that out, so if I can abbreviate, I promise the presentation will that much shorter.

All day today we have heard the terms resistant, susceptible, MIC used. My purpose in coming before you today representing NCCLS is to provide some background on

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the techniques as was just discussed here and set forth by the NCCLS to help VMAC in addressing specifically Questions 3, 4, and 5.

[Slide.]

Just a real quick word about the NCCLS. More information certainly is available on their web site, but basically, it's an independent standards and guidelines writing organization, primarily focused on the human, clinical, laboratory and hospitals, and as you can see, one of the chief areas of responsibility is with microbiology.

[Slide.]

This particular talk will deal just with microbiology, terms of veterinary antimicrobial susceptibility testing.

The process for the NCCLS is to have a tripartite participation involving the professions or academia, regulatory involvement, as well as industry, representing a variety of type of industry. It is a consensus process which means basically more than just simple agreement, but all parties have an opportunity to review and comment on the variety of documents which are elaborated, and there is assurance that comments will be given serious competent consideration.

[Slide.]

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Now, the Subcommittee on V-AST, if I may abbreviate as such, was first proposed in 1992, and has since developed two approved level documents over the course of the year.

The first document, the M31, deals with the specific methodology to determine susceptibility test methods, and we will talk a little bit more about those momentarily.

The second is the M37, which is a guideline for manufacturers of animal health antibiotics, to set the quality control and breakpoint information. I should point out that the AAVLD, the American Association of Veterinary Laboratory Diagnosticians, has accepted this approved level document for diagnostic laboratories as part of its accreditation process.

[Slide.]

Just to give you a quick show of the members who have voting privileges and the advisers who do not that comprise the committee currently. There is also a third category of observers which I have not listed.

[Slide.]

The M37, which is the document to guide manufacturers of animal health products, contains, first of all, guidelines for quality control development. The idea here is to devise a valid reproducible methodology that can ensure

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comparability of tests from time to time, and this is done using ATCC, American Type Culture Collection strains which are appropriate to the drug spectrum, and comprises both disk and minimum inhibitory concentration, or MIC, testing, and obviously, the value to doing this, to establish the test validity.

I should point out that the concentration gradient to strip test has not been included in NCCLS guideline development.

[Slide.]

In terms of setting guidelines for MIC breakpoints and zone interpretive criteria, three different aspects are evaluated, and these include a pharmacological evaluation, which attempts to take that information and establish a tissue or serum concentration which is in excess of the MIC on a population basis. That population basis is derived on an epidemiologic ground where we are looking at a scattergram which plots for the same isolate an MIC and a zone or of an inhibition on the millimeter basis.

Finally, the third component is on the clinical efficacy, which is derived from data during the NADA process.

[Slide.]

So, those are the three key components that go into the establishment of interpretive categories, and these are the

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terms that have been used frequently today - resistant, susceptible, and in your intermediate.

I should like to point out that resistant implies that the organism would not respond to treatment with that agent. It doesn't necessarily imply that there is a genetic resistance determinant associated with it.

In the context of what the committee sets forth, it reflects back on the achievable tissue concentrations relative to the MIC, and would predict that those organisms with that particular MIC or zone of inhibition size would not respond to clinical treatment.

Susceptible obviously implies that there would be a clinical success that would be favorable for the host, and intermediate is kind of that category that's a bit gray to account for day-to-day variations.

[Slide.]

Finally, to accommodate some of the newer legislation, a flexible labeling category has been established to account for that recent bit of activity.

[Slide.]

The M31 document, this is the one that the laboratory would use, the actual technician at the bench, to guide the conduct of the studies. The focus then is on that

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diagnostic end user.

Now, originally, our scope was to limit the document to therapeutic claims, but as some as these products came before the committee and were approved for the breakpoints, quality control, et cetera, the Working Group on Non-therapeutic Claims was formed to address other uses in animals of antibiotics, and fuller discussion of the outcomes of these are included in the full M31 document, but on the next slide, I can share with you how that was basically delineated.

[Slide.]

The first item would be the control claims for a group with therapeutic claims, primarily with the objective that early treatment was viewed as therapeutic for those member of a population with disease signs. So, if you had a few animals showing disease in a flock or herd, that would be acceptable for triggering a control claim.

Now, prevention and growth promotion claims, we felt that susceptibility testing was not relevant. The reason for this is that these are healthy animals, there is no target pathogen which can be identified or recovered, so it didn't make a whole lot of sense to try to predict a clinical outcome.

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You can't predict better growth or predict that you will prevent disease from some unknown pathogen, however, any epidemiologic studies could well use these M31 methods, but putting them into sensitive, intermediate, or resistant categories does not appear to make a great deal of sense.

[Slide.]

Finally, with the actual susceptibility testing methodology, there really are two components, the quantitative or MIC, and the qualitative, agar disc diffusion test, and the purpose in this document is to describe standardized procedures that all labs can adhere to with strict quality control guidelines to validate the testing in order to have inter- and intra-laboratory reproducibility.

The second component would be the interpretative criteria list, and this deals with specific host pathogen drug-specific data. This would mean that, for example, for swine, you might have swine actinobacillus pleuropneumoniae and a specific antibiotic listed.

[Slide.]

I would like to share with the group that the subcommittee is now expanding its scope and has decided that Campylobacter species would be something that would be of value to further explore for defined methodology.

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Dr. Bob Walker from Michigan State University is heading up this working group, and it is comprised of an international collection of microbiologists. It also has representatives from the Human Medical Microbiology Committee, as well as regulatory and veterinary diagnostic laboratories associated with it. So, this working group is quite unique in its scope, not only on a national and international basis, but also bridging the human, as the veterinary groups.

The objective here simply is to standardize the test methodology to define appropriate and quality control strains, relevant antimicrobials, and appropriate tests and incubation conditions. This all would seem relatively boring except for the fact that it can be useful for epidemiologic purposes. So far as one might read literature, there are a variety of techniques that have been conducted.

The last point that I kind of skipped over there, but was the fact that no breakpoints will be set by the V-AST to put antimicrobials into the category of susceptible, intermediate, or resistant because there are no antibiotics for Campylobacter claims. That would be a job the Human AST group would need to conduct on its own initiative.

[Slide.]

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As far as some future tasks that are before this group, we do have a number of interpretive criteria for which we have excerpted human data and incorporated those for animal outcomes. This is recognized as a surrogate, and we encourage the replacement of these with veterinary specific guidelines as that information becomes available, and there is a Working Group on Generic Antimicrobial Agents to get this testing done or to scour the literature and come up with an approximation for making these conversions.

Secondly, a future task here is looking at specific test methods for other vet pathogens, you can see which are listed there, and we certainly encourage, as the final point, additional sponsors to present data on their existing antimicrobial compounds. I hope that they will come forward very soon.

[Slide.]

So, again, what is the value of the NCCLS V-AST Subcommittee to the deliberations of the VMAC? It would be for addressing Questions 3, 4, and 5, to provide an accepted methodology which is available to ensure quality data generation throughout the United States.

I should point out that some countries in the EU are using these methods, as well. Obviously, this has implications

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for clinical diagnostic laboratories in terms of what they can provide to the practitioner in support of judicious antibiotic selection, and it also implications on surveillance application, assuring the quality of the methodology.

That concludes my remarks, and I would be happy to entertain any questions that the VMAC may have.

Thank you.

DR. STERNER: Thank you, Dr. Shryock.

Questions from VMAC or panel members, invited speakers?

[No response.]

DR. STERNER: Hearing none, we will press on regardless.

Our next speaker is Barb Determan from the National Pork Producers Council, and she has been granted 20 minutes.

Barb Determan

MS. DETERMAN: I have no interests or income from an animal health company, and my expenses are being paid by my organization, which is producer funded. Every time a producer sells a hog, they contribute to our organization.

Good afternoon. I am Barb Determan. I am a pork producer from Early, Iowa. My husband Steve, myself, and our three children have a family farming operation in northwest Iowa.

Our furrow to finish operation produces about 2,000 head of

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pigs each year. As a volunteer on the National Pork Producers Council, I donate my time to represent producers from across the nation.

The policies and programs of the National Pork Producers Council are overseen by a series of volunteer producer committees. I am the chairperson for the Pork Safety Committee.

NPPC is one of the largest commodity organizations in the nation. Our headquarters are in Des Moines, Iowa, and we also have an office in Washington, D.C. The council works to build a strong and vital pork industry by solving problems efficiently for the nation's pork producers.

There are approximately 85,000 producer members in 44 affiliated state associations, and the NPPC draws its strength from the nation's grass-root pork producers.

Our members account for the overwhelming majority of the nation's commercial pork production. The pork industry is the fourth largest agricultural sector in the country. We generate approximately $11 billion in annual farm gate sales, and while creating an estimated $66 billion in economic activity, employ 764,000 people.

As many of you and certainly the agency knows, we have been very involved in this issue. We appreciate the agency

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calling this meeting and the opportunity to make comments on the proposed framework.

It is the hope and expectation of pork producers that the agency will carefully consider all the comments that are offered, and we are glad to hear that the program and direction of the framework has not already been decided on.

From the perspective or pork producers, we are like any other animal agriculture sectors. We need timely, economical availability and access to effective products.

We need this because we need to keep our animals healthy. This is the right thing to do from the perspective of animal welfare, environment, and doing all that we can do to provide a product that is safe and wholesome.

We are very serious about food safety and public health, and I can tell you personally, as a producer and a mother of three children, I am very dedicated to producing a safe food for my family at home, as well as families throughout the world.

Another reason we need these products is because they are a tool that we have to be able to use to raise our animals efficiently and make a living to do so.

You probably have read about how difficult that has been for the last six months. Well, it still isn't a whole lot

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better today. Another reason we have been so involved is because of the long-term effects the drug approval process will have on our producers and their animals.

We believe that the best process is an open one, that is scientifically based. The proposed framework is a thoughtful document that no doubt took a lot of hard work to think through and what had to be very difficult to write, but this is very important. We see it as an extension of a lease and don't feel that it gives adequate scientific justification to substantiate such a broad encompassing program.

Because of this, there is a concern that it will not result in an effective mechanism for protecting public health. What we need is the assessment that will lead us to what appropriately must be done to manage that risk.

The proposed framework is presented as ideas that would be used to evaluate, but instead they are actually ways to manage, not evaluate, risk. It is a risk management document which, in numerous places, exposes the bias of the authors with statements about the impact that antimicrobials in our animals have on human health instead of the risk of this happening.

If the agency believes the hazard is great enough that it is

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compelled to develop new regulations, then, this means that you must have already assessed how great that hazard is, but we contend that the agency can't measure the size of the hazard, because the hazard is either there or it's not. It has to have measured the size of the risk to be compelled to take that action.

Again, what the agency has given us is a risk management program, one that is built on regulations. The agency's risk assessment that compels it to propose this framework is what most of us here are asking for, so we can see if the framework is an appropriate response.

Understand, we do not deny that there is a hazard, but what we need is a risk analysis, which includes risk assessment before we have the regulatory risk assessment program put into place.

I want to offer some comments on some of the questions that the agency has asked about the framework. We will be submitting written comments that will include our views on the validity of some of the statements and assumptions that are in the framework also.

The agency asks for public input in developing the criteria for categorizing drugs as to their importance in human medicine. The criteria and categorization that are proposed

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are subjective. The Category I criteria talks about drugs that are essential and important, and not having satisfactory alternatives and limiting therapeutic options. It also talks about resistance being rare among human pathogens and the potential for long-term therapy. How is propose to measure all of these? What is needed is measurable objective criteria that can be objectively applied. Without them, these would be black box decisions, black box decisions that would ultimately come down to belief.

We also see the framework as a clear indication that despite attempt to rationalize criteria for Category II and Category III, and given reasonable advances in scientific ability to analyze resistance mechanisms, we believe all present or future antimicrobials that are used in pork production and animal agriculture will eventually be classified as Category I.

This apparently is not what the agency intended, but if you read the criteria very carefully, that is what the outcome will be.

The agency asked for comments on the factors set out with respect to evaluating human exposure. This begs the question about a quantifiable link between enteric pathogen

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levels and some measurable public health risk. Without it, you have a regulatory program without purpose because you don't know that it will have any effect on public health, and we certainly don't know if it will have a positive effect on public health.

The effect that the quantity of bacteria in the animals intestine have on human health is a researchable question, but it is also one that is so full of compounding factors that realistically, it may not be able to be answered.

Pathogen load, as presented, is a HACCP issue. The USDA data shows that HACCP has been successful in reducing pathogens on our carcasses. It is a program at the USDA FSIS, not the FDA, and yet, it is not at its end point. We, at the National Pork Producers Council, as producers, are funding preharvest food safety research projects that will help us answer the appropriate questions about pathogen load, and if we can affect it on the farm, but at this time we simply do not know enough to be able to make those decisions.

Another very important point is that exposures may also be dependent on advances in food processing technologies, such as radiation. The framework correctly mentions the ability of processing technologies to affect human contact, but this

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is much more important to public health than what the document gives it credit for.

Finally, the agency is proposing a system of post-approval resistance monitoring that includes extensive on-farm collection of samples. We question the agency's authority to instruct companies to come onto our farms. The proposal in effect holds the approval process hostage, demanding the payment of an off-farm, post-approval monitoring program, which the agency knows that in itself does not have the authority to conduct.

I guess we question the agency's full consideration of these actual costs and logistics needed to gather this valid and usable data. Who would collect the samples?

The health of our animals depends in part on the biosecurity of our farms. Often, we even ask our veterinarians not to come to our farms if they have had recent contact with other pigs. Is the agency proposing to ask a producer to take samples on the farm to show the FDA that a product should be taken away from us as producers?

How would sample quality be assured? Who would pay for the program? I believe we do know the answer to that question.

Animal agriculture would ultimately be required to pay for a program which neither we, the agency, or other public

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health agencies know whether or not it will make a difference to all of animal health, to all of public health. I will say that we believe that the framework is a good-faith effort, but as presented, it must be rejected in favor of goals and objectives that are defensible and attainable. The bottom line is that what has been laid out cannot be accomplished for these reasons.

Categorization is subjective, and by the document's own admission, will be changing according to whoever the decisionmaker is. Research has to answer the question of quantifying a link between the number and characteristic of bacteria coming in to the packing plant and then testing the animals and the bacteria leaving on the meat.

There are strong concerns about logistics of post-approval monitoring - what would it cost, who would do it, and how would the health of our animals be protected. Remember, HACCP is designed to prevent microbial contamination, and it is working, and there are other concerns that can't be presented because of the allowable time for these comments.

Multiple scientific bodies have told us that the hazard is there, but the risk is not quantified or is it imminent. We need to answer these questions before committing the massive resources that would be needed for this.

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We have the time to develop a comprehensive program that will work, and we support that, forums, such as this, that will start that process, and we committed to continuing it to a logical workable endpoint.

If the objective is food safety, then, let's develop a process that will change the framework to meet these needs. As Dr. Bell said, we need to think outside the box and change the proposal, so that it can work. If the agency understands what they are proposing, then, they are intending to eliminate the use of antimicrobials in food producing animals.

It is our contention that this will actually have the opposite effect on both our animal welfare, the environment, and food safety than what we actually are intending for this.

What do I mean by that? We will not be able to quickly and effectively address animal disease, and there will be more manure produced, and alternatives like heavy metal feed additives that will contaminate the environment.

The framework will eventually increase food safety risks because of our loss of ability to effectively treat disease. The agency has repeatedly and publicly said that one of the best ways to ensure food safety is to ensure the

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availability of a variety of effective products. We agree with this position. Has the agency changes its position? We believe that eliminating or limiting product availability will increase resistance, not decrease it, because we will be forced to rely on, at best, a very limited, narrow supply of products.

Finally, all of these factors will have an effect on the ability of our pork producers to make a living and stay in business. If these outcomes are not the agency's intent, then, it should reevaluate the framework. Input from all stakeholders is needed to do the job right.

The VFD process set a precedence for cooperative effort that led to reasonable outcome in which all stakeholders could claim some ownership. This was a successful example of Dr. Bell's outside-the-box thinking. It was said then that the VFD process was a model for a new FDA paradigm, listening to stakeholder input.

The agency worked with its constituents openly and cooperatively, and this is what we need in this case.

Points that we need to consider include strengthening the monitoring program. We support a scientifically defensible NARMS program.

One possibility that NARMS is planning is to take more

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samples in the packing plants and monitoring that pathogen resistance. This could make the program similar to the residue monitoring program including adequate and anonyme safeguards.

There are other possibilities also and they should be carefully considered. We need to have reasonable discussions about the alternatives. The point is to dedicate the money and resources available to make a NARMS program that is statistically significant and meaningful.

We think that the AHI proposal of advisory panels is sound. This would give stakeholder input and ownership of the process. Then, we could use that data to design focused studies to help the advisory panel and the agency.

Why is there so much concern about the framework? The second footnote in the introduction says that after evaluating input on the framework, the agency will take appropriate procedural steps to develop and implement any resulting policies.

It assumes that the framework is the correct approach. It doesn't acknowledge that the agency could review the proposal and decide whether it is appropriate as it is, whether it should be amended, or whether it should be completely reworked.

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It says the agency will take appropriate procedural steps to develop and implement policy. The footnote says the agency is interested in stakeholder input, but it does not suggest that it will listen to or act upon that input, and the language of the document is all that we have to go on.

We, as pork producers, do not want to be obstructionists to developments of food safety, and we have a very good history to show that we are not obstructionists.

A few of those examples are we have actively participated in the national and international discussions and the development of the AVMA's judicious use principles. We have committed our own producer checkoff money to funding research.

Last summer alone, we awarded over $200,000 to antimicrobial research. I earlier mentioned our extensive pre-harvest food safety research. This is a lot of producer dollars going into research for both antimicrobial resistance and pre-harvest food safety.

We have formed a pharmaceuticals issues task force with the AASP. The intent is to examine the science of resistance and how it affects the pork industry and human health. We haven't accepted poor quality assurance program that is used by the industry. Over 40,000 producers have gone through

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the program. Major packers are not asking for this, but now are requiring producers to be at PQA level 3.

We are preparing a revision that will include judicious use and resistance information. I am very pleased to report that our PQA program is working. Education works with our producers. The evidence is in the decreased residue incidence since the PQA's inception. Our producers are voluntarily being involved in this program and getting a lot of good out of it, and producing a safer product because of it.

There is a necessary caution and deliberation because our constituents' livelihood depends on the outcome of this issue. We are talking about real life people who are doing their absolute very best to provide the safest product possible to you.

Multiple scientific bodies have said that there is a need to gather more information to make an informed decision, and that this is not an imminent hazard.

As the chairperson of the Pork Safety Committee and a member of the NPPC board of directors, I have to go back and give the producers the scientific justification for spending their tax dollars on this program, and right now I don't have that information.

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We have been trying to help gather the needed food safety information. We owe to our constituents the consideration of risk assessment for risk management.

Again, I would like to thank you for the opportunity to give the pork producers' view on the framework, and I offer our help and resources in working with the agency and the other stakeholders towards developing a doable, reasonable system that we can all consider successful.

Thank you.

DR. STERNER: Are there questions from panel members for Ms. Determan?

[No response.]

DR. STERNER: Thank you very much.

Perhaps our next speaker will avail himself of the answer to the question that I posed to the AHI people with regard to the risk assessment report. Dr. Lester Crawford goes back with CVM many years as a former director, in fact, I think he is responsible for the name Center of Veterinary Medicine, if my memory serves me correctly.

Dr. Crawford.

Dr. Lester Crawford

DR. CRAWFORD: Plead guilty to all that.

With respect to funding, our university and our center are

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underwritten by industry, government, and also foundations, and the study that I will mention is underwritten by the Animal Health Institute.

I appreciate the opportunity to be here and also would like to congratulate the agency for conducting this hearing and also to responding to the current concern about antibiotic resistance.

I would like to begin by talking a little bit about my personal involvement over the years with risk assessment on products like this. The question was earlier posed what would risk assessment do for us, and are there any regulatory issues that have been adjudicated or addressed by risk assessment.

In fact, of course, there are. When I was with the agency, starting in the middle seventies, and then off and on for some years, we did risk assessments on diethylstilbestrol, which eventually came off the market as the result of a fairly comprehensive look, and also nitrofurans, which came off the market after an 8,400 page outlook.

Those were then the subject of special studies by the National Academy of Sciences, as previously mentioned, and an engaging series of consultations, many conferences, and also a pamphlet, the risk assessment with respect to

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regulatory responses was memorialized by the Academy in a series of publications using those two and two more that were done in other parts of the government as examples of what was to come.

The Deputy Associate Commissioner for Scientific Affairs in FDA, Dr. Joe Rodericks, was the author of many of those papers and also co-chairman of the NAS study.

Following that, there were some more Academy looks at risk assessment, and as many of you in the room know, out of that grew HACCP, which is considered on-the-farm or in-the-plant risk assessment, and certainly regulatory decisions are made by that always.

And then in 1988, both FDA and USDA exceeded and funded an external risk assessment which involved a number of agencies and also some universities and others of Listeria monocytogenes, which formed the basis of the current policy, which is still being employed.

The risk assessment that we are doing, we start out, as you do in all risk assessments, and as all of you know, we create a fence around the problem, and with ever narrowing concentric circles we tried to get to a doable assessment that still will have sufficient validity and breadth to add some light to the issue.

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In our case, after starting out fairly broad, and with the impaneling of an advisory committee, some of whom are here in the room, we narrowed our study down to fluoroquinolones as they are used in beef cattle.

It happened that during the time we were putting the early analyses together, that one of those compounds was approved for use in beef cattle in the United States. It was a watershed event as far as public health mensuration is concerned because there was no fluoroquinolone used in beef cattle prior to that time, and then from that point there was. So, it lent itself very well to what we were doing.

Then, we started looking for target organisms to assess, and after some fits and starts we narrowed down Campylobacter jejuni and also Salmonella typhimurium, Definitive Type 104.

Our look at the literature has revealed that we do have sufficient information upon which to conduct these risk assessments. The first study is out to the internal review committee, and will be submitted for publication shortly. It comprises an analysis of the effects on Campylobacter. The second will be the Salmonella study. The first one should be published by late spring or early summer, the second one by early fall or late fall.

As to what they will say at this point, obviously, it is

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premature. I would mention, though, that just this past week, I visited colleagues who are doing a broader study in the United Kingdom, at the Central Veterinary Laboratory at Waybridge, where they have considerable risk assessment expertise, and we are going team with them in terms of trying to provide them with what we have and also hopefully learn from the study that they are doing.

As you know, risk assessment is an ever-changing field. The question is are your assumptions sufficient and valid, and also, on a topic like this, you know, how fast can you complete it.

A risk assessment in a field like this, that takes three years, it is probably excessive. We are mindful of that, and we hope to accomplish what we are doing in a year and a half or, in other words, about another six to nine months, but that is certainly using all the resources that you have, and also you have to, in our case, avail yourselves of outside consultation and also professional risk assessment groups, which we are and have done. So, more to come in that respect.

Also, here, there has been some conversation about when will it be done and why should we wait for it, and what is the necessity of waiting, and so forth, and since FDA first

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started trying to regulate these issues in the seventies, and particularly when I was on board in '75, '76 and then again in '78 through '80, things changed.

Diane Fagerberg talked about her excellent study and some of the conclusions that she came up with. Incidently, Diane, with respect to your slides, I was around when those were first shown. I hope I haven't faded as much as your slides have, with all due respect.

So, I don't think we are in a position to tell anyone, certainly no regulatory agency, to wait until we finish our study. That is not our position at all. As you know, there are key meetings that are coming up. The World Health Organization is having one March 15 through 19 on the transmission of resistance through food, not on their veterinary public health side, but on their food safety side.

Also, OIE, the international veterinary parliament is having a similar meeting a few days later. So, those I think would be worth incorporating, but we are not standing as a barricade the you and your deliberations. I think you have plenty to do without that.

Thank you.

DR. STERNER: Questions from the panel for Dr. Crawford?

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Yes, Linda.

DR. TOLLEFSON: Lester, can I just a question for clarification? The Georgetown risk assessment is looking at use of fluoroquinolones in feed lot cattle?

DR. CRAWFORD: Yes.

DR. TOLLEFSON: Is that all you are going to look at?

DR. CRAWFORD: Yes, precisely.

DR. TOLLEFSON: Thank you.

DR CRAWFORD: We don't believe in extra-label uses, so that is what we are confining ourselves to. I don't know where that term ever came from anyway.

DR. STERNER: Other questions for Dr. Crawford?

[No response.]

DR. STERNER: Moving on then, Joel Brandenberger is from the Coalition for Animal Health, and he is allotted 10 minutes.

Joel Brandenberger

MR. BRANDENBERGER: Thank you all very much. I know it is late in the day, so I thought I would come talk to you all about something you haven't heard about to this point, risk assessment.

My name is Joel Brandenberger, and I am speaking here today on behalf of the Coalition for Animal Health. The Coalition is comprised of more than a dozen organizations. We

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represent every major livestock and poultry association in the U.S., as well as the commercial feed industry, veterinarians, and animal pharmaceutical companies.

We were formed in the mid-1990s to promote public policies that ensure the availability of the widest possible variety of safe and effective animal drugs to help treat those animals in our members' care.

We have worked with FDA on several issues in the past, but most notably a few years back to reach consensus on the Animal Drug Availability Act of '96. That effort remains a model of how stakeholders and CVM can work together to address complex and difficult issues, and we hope that maybe we can enjoy the same cooperation as we address the antimicrobial resistance issue that is before us today.

The Coalition, first of all, wants to commend CVM for bringing the committee together to discuss the scientific evidence regarding the use of antibiotics in food producing animals and antimicrobial resistance.

It is a complex issue, one that deserves the committee's attention, and the Coalition is pleased to be able to comment on the proposed framework.

A lot of the Coalition members have been here today or will be here later offering individual presentations. These

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remarks that I am making are designed strictly to highlight our areas of common concern and interest.

The Coalition members share FDA's and the public health community's concern about antibiotic resistance whether in humans or animals. The safety of the food supply is of the utmost importance the all of us, and as is the continued effectiveness of antibiotics.

We hope to continue working with FDA and all relevant government agencies to ensure we are providing the safest possible products to our consumers while minimizing the incidence of illness and other suffering and farm animals.

Our policy toward the framework needs to be clear. The Coalition for Animal Health will find it difficult to support any change in the policy for approving antibiotics in food producing animals if that change is not preceded by a comprehensive assessment of the actual risk posed by antibiotic use in farm animals or the risk of resistant bacteria in those animals.

This position should not be misinterpreted as indifference on the part of the Coalition toward the antimicrobial resistance issue or unwillingness to work with FDA toward policy change. The Coalition shares the goal FDA stated in the recently released framework document. We are absolutely

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committed to protecting the public health and to ensuring the use of antimicrobial drugs in food producing animals does not result in adverse health consequences to humans.

We also are pleased that FDA agrees with the Coalition that the use of antimicrobial drugs in food producing animals is important to promoting animal health and providing an abundant and affordable supply of meat, milk, and eggs.

Coalition members also would agree that this is an appropriate time to examine the antimicrobial resistance issue in further detail and to contemplate potential changes in the FDA approval policy for antibiotics.

We understand the seriousness of the issue, as well as the need to develop appropriate measures both to protect the use of antibiotics in humans and minimize the negative consequences to animals and the food supply.

There is no doubt bacteria can develop resistance to some antibiotics whether they are used in humans or animals or both. However, the likelihood and extent to which antibiotic resistance occurs in the farm setting and is then transferred to humans has been neither adequately assessed nor established, and that is the crux of the Coalition's concern.

Neither FDA nor any credible scientific organization has

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conducted a comprehensive risk assessment with regard to this issue. We don't see how FDA or any other agency for that matter can look at data and studies that are incomplete or contradictory and come to the conclusion that the recommendations in the proposed framework represent the best possible public policy solution to the danger of antimicrobial resistance.

FDA cannot give in to the temptation to regulate based on scare headlines and studies that have yet to stand the test of peer review.

We would remind everyone here that three recent reports from the National Research Council, the Institute of Medicine, and the World Health Organization do not come to the same conclusion that FDA did in this proposed framework document. All agree that there is cause for closer scrutiny, but all recommend additional data to determine the appropriate course of action.

Indeed, the 1998 NRC report on "The Use of Drugs in Food Animals: Benefits and Risks" acknowledges the possible link between antibiotic use in farm animals and the development of bacterial resistance in humans, but the report says, "Information gaps hinder the decisionmaking process for regulatory approval and antibiotic use in food animals. A

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data-driven scientific consensus on the human health risk posed by antibiotic use in food animals is lacking." According to the NRC, "Until more accurate data on antibiotic use, patterns and rates of resistance transferred to human, occurrence of actual disease emergence, and mechanism of resistance are available, actions aimed at regulation antibiotics cannot be implemented through a science-driven and well validated and justified process." Let's put it simply. Really, what we are saying here, if we are only contributing 10 percent to the resistance problem, we don't want 75 percent of the solution put on our backs. That is really our bottom line.

Dr. Crawford just talked about the study that Georgetown University, Center for Food and Nutrition Policy is conducting, and we think this is a model and a step in the right direction to determine the actual risk and subsequently develop an appropriate plan of action.

I think it is important to look just real briefly at what we don't know here. While some animals unquestionably carry resistant bacteria, we have very limited information about how many animals with such bacteria ever make it to the processing plant.

We have no clear idea how much resistant bacteria actually

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survives all the critical control points in modern food processing and packaging and we have very little data about how much of that bacteria survives because of mishandling or undercooking of meat and poultry products by the end consumer.

While science is still trying to determine how many people actually get sick each year from food-borne illness, we do know that to date no death from food-borne illness ever has been connected to a resistant bacteria derived from the use of antibiotics in animals.

Given this dearth of information, how can we be sure the policies in the proposed framework actually will reduce the incidence of antimicrobial resistance?

What is far more certain, unfortunately, is that these policies will reduce the availability of antimicrobials to food animal producers, and we have got to remember that there also is a risk associated with narrowing the spectrum of available antibiotics.

I saw an article recently where Dr. Mitchell Cohen from CDC was quoted as saying one of the reasons why we saw antibiotic resistance rise in recent years is because of the lack of antibiotic development on the human side in the 1980s, and that doctors now have fewer alternative available

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to counter drug resistant infections.

So, my question here is what do we think is going to happen if livestock and poultry producers have fewer and fewer and antibiotics to utilize and drug companies find the regulatory cost of bringing new antibiotics to market prohibitive. We are going to have the same problem begin to develop on the animal side.

But -- and I think this is the important thing here -- the Coalition understands it isn't enough just to come to you all and say do a risk assessment. You have been hearing that all day, and you are probably going to hear it more before you are done.

So, what we want to promise is that we will work tirelessly with FDA, everybody in the Coalition, to develop an affordable risk assessment plan that provides -- and this is the important part -- in the shortest time frame possible all the data needed to make science-based policy changes, and we will go one better than that, too. When a consensus analysis of that data is complete, you have got our pledge to work with the agency to make all changes dictated by the risk assessment.

I am going to talk real briefly about some of the specific concerns we have in the proposal because we do find it

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troubling that the framework appears maybe to ignore some proactive steps that are being taken right now by stakeholders in this process.

On the meat and poultry processing industry side where I come from, for example, we are in the midst of a significant effort to control pathogens in food supply. We are in the middle of implementing the new HACCP inspection system in the plants, and we think that will minimize exposure to food-borne pathogens.

In addition, other steps are being taken including steam pasteurization and educational campaigns to reduce the incidence of food-borne illness, all of which must be taken into consideration in a risk assessment.

We are also troubled that the framework doesn't seem to really fully recognize or consider the efforts that are underway by the nation's producers and veterinarians to develop judicious use principles for industry.

The first phase of that is already through. The next phase is scheduled to move forward very quickly. I think AVMA has done an outstanding job of leading that effort.

We are a little perplexed, I guess would be the best way to put it, that instead of working with producers and the industry to ensure these principles properly address the

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issue and are fully implemented out there, less than eight months into sending us off on that quest, we have suddenly got this major change in the regulatory approval process before us, and that confuses us maybe even a little more because the educational approach is not only considered acceptable, but is being emphasized in human medicine. Animal and human medicine are different, we understand that, but there are similarities, and the animal and human medical approaches right now do not appear very consistent.

DR. STERNER: Joel, your time has expired.

MR. BRANDENBERGER: Okay. Fair enough. Thank you very much for the time and for the opportunity. I would be happy to answer any questions.

DR. STERNER: Dr. Bell, I have not made this exception for anybody else. I regret, you will have the opportunity if Joel is here in the morning, to press your question.

MR. BRANDENBERGER: I may not be here in the morning, so I will be around for a while this evening.

DR. STERNER: Our next scheduled speaker is Clyde Thornsberry from MRL Pharmaceutical Services. He has 15 minutes scheduled to him.

Clyde.

Dr. Clyde Thornsberry

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DR. THORNSBERRY: I promise to give you back some of those minutes.

Let me say first that MRL doesn't have anything to do with residue levels.

DR. STERNER: Could you give us your affiliation or your disclaimer first?

DR. THORNSBERRY: Yes, I am about to. My name is Clyde Thornsberry. I work for MRL Pharmaceutical Services. Fortunately, we have lots of contracts with most of the pharmaceutical companies that make antibiotics for animal health service, and fortunate I say because they can pay for me to come here and do this.

Before I go on to what I really came to talk about, I want to say to David Bell that the first half of your talk was the most remarkable talk, and it's about time someone said what you said.

I totally agree with you. I don't think that any scientific or nonscientific studies are likely to change the status quo. We do, because this is totally a political process, and, in fact, I thought that is why Monica was here, but it is a political process, and I agree with you there has to be bridges built and spanned, but -- you may not like this one -- I would suggest to you that CDC build some bridges,

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because if you ask a lot of these people around here, CDC is the biggest bully on the block. But I totally agree with you, and thank you for saying that.

The other, to take that a little bit further, I might even go further than David and say to the FDA get rid of every one of your consultants, put your program into action because if it's untenable, you will hear about it, because some congressional aide will be sitting on your desk, because one of the things that FDA does is they are always responsible to somebody, very unlike most of the other government organizations that we know about.

But anyway, that is not why I came. I want to thank you for letting me address the committee and the rest of you, and as some of you know anyway, my group and I have been interested in surveillance of antimicrobial resistance for a long time wherever it is, whether it's human or whether it is an animal population, and that is my main reason for being here.

Upon reading the framework document, I certainly wish to compliment the FDA for recognizing that surveillance of resistance is the basis for most any actions that you would ask for or objectives that you would intend to reach.

If I understand the document correctly, the major steps

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which you wish to take, is to determine how many drug resistant enteric bacteria exist and the effect of changes in pathogen load on the host.

I suspect the first one could be done, I think that the second one might be more difficult, but I think that if you read the document, you come to the ready conclusion that this is a microbiological problem.

I thought it was very interesting as I looked around this table, I see only two card-carrying microbiologists, and if the rest of you are, forgive me, but I only know two of you that are, and I think this is a microbiological problem, and I think one of the ways that this must be approached is from a microbiological viewpoint.

I also wish to compliment the FDA and their sister organizations for promulgating the NARMS program as a sentinel surveillance system in animal health, but even as I applaud you, however, I do not believe that you have developed an ideal or an adequate program.

Before I express my reservations and concerns, let me elucidate a bit on items which are discussed or alluded to in the framework document.

First, in the document, there are many references to inducing antimicrobial resistance. Although this is

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correctly explained in some areas of the document, I believe that the naked references to inducing resistance could create some false impressions.

Antibiotics do not cause resistance, but rather select for resistant mutants as indicated. I think this is a fundamental principle that must be remembered.

Second, let's discuss a bit about the factors that influence the number of drug resistant strains that we find in a host or in an institution, and I should say that those of you who know me, also know that I am a human microbiologist, not an animal microbiologist, so much of what I have reference to will be in humans.

Let me mention four things that I think have to do with the number of resistant strains. The first is that obviously, we have resistant mutants and have created a selective pressure with a drug to which the mutant is resistant.

The second effect of infection is the effect of infection control. Now, obviously, that is a human term, but I think it can be transferred to the animal health system, and horizontal transfer -- and both of those have been talked about today -- I want to talk about horizontal transfer in terms of patient to patient, and not bug to bug, and it is probably certainly better understood in humans than in

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animal environments, but there are many, many cases in many hospitals in the United States where the resistant rate for a bug and a drug far exceeds 50 percent, yet, the national prevalence of resistance is less than 10 percent.

It is easy to blame this on antimicrobial abuse, but in reality, in most cases it is the failure of the infection control programs to control spread of any infections.

The third factor that affect the number of resistant strains, and probably the least understood although it has been mentioned several times here today and was talked about by Linda to some degree this morning, it involves the number of drugs to which a strain is resistant.

This can be best demonstrated with methicillin-resistant staphylococci. As you know, MRSA are resistant to almost every drug except vancomycin. As a result, every drug is a selective agent for itself and for every other drug except vancomycin. It does not have to be Ciprofloxacin that selects for resistance to Ciprofloxacin, it can be penicillin, it can be a cephalosporin, it can be a tetracycline. It can be any of this list of 40 or 45 drugs.

Today, in the U.S. human hospital population, MRSA population, 80 percent will be resistant to fluoroquinolones, but if you look at the methicillin

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susceptible population, or that is, MSSA, less than 50 percent are resistant to fluoroquinolones.

This is because the MSA strains, the only selective agents are probably fluoroquinolones and a penicillin. A similar but less severe situation exists with S. typhimurium DT104, but not to the level seen with the MRSA, because in DT104, if you get fluoroquinolone resistant, the fluoroquinolone will be no more selective than the other four or five drugs that it is resistant to.

So, if you are talking about getting rid of one of these, you are talking about getting rid of six drugs, because every one of them is a selective agent.

Lastly, the rapidity with which resistance develops is a bug, and a bug and drug varies greatly between species and between drugs. Certain species seem to have a capacity to circumvent these pressures, which leads to a resistant population.

For example, in the human side, we have used gentamicin for several decades, and we have used ceftazidine for almost two decades, yet, the incidence of resistance in Pseudomonas aeruginosa for each of those drugs is about 10 percent. Clearly, Pseudomonas aeruginosa does not develop resistance very rapidly to those agents.

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In addition to determining the level of resistance in drugs and bugs, these factors also may influence what are considered Category I drugs. It would seem to me that if one of the criteria here is lack of selective pressure, then, if you were talking about MRSA type resistance, you are talking about making almost every drug a Category I drug.

So, I think you are going to have difficulty fitting many of these agents into the Category I.

But anyway, let me get back to what I really came for and what I asked the time for, and talk about surveillance.

Although I am happy that the FDA recognizes the value of resistance surveillance and that they have their own surveillance system, I do not believe that what you are recommending or what you are doing is adequate.

I strongly believe that resistance surveillance should be done for its own sake, and should not be hidden as a part of the food safety program. Let them exist independently. I further believe that the surveillance should include the vast majority or organisms and antimicrobials that are used in animal health, and that strains should come from all stops between the farm and the butcher shop.

In the past, I have advocated programs in which the

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organisms are collected throughout the country and tested in a central laboratory. I still think that is probably the most viable and the best way to do it, but with the adoption of the NCCLS methods that Tom talked about, by more and more veterinary labs, and the availability of good results from a standardized method, I believe that we could also begin to do electronic surveillance as we have done in human medicine.

The central lab program should, of course, be done annually, and the electronic system would be a continuous program which would do surveillance every day, every week, every year.

It is only with these kind of data, I think, that you can answer all the questions and do it in timely manner. Let me give you an example or two before I quit.

There is much concern expressed about fluoroquinolone resistance in E. coli, including here today. In the U.S. in 1998, we used almost one billion dollars worth of Ciprofloxacin in the United States alone. If you ask me where I got that number, I would have to think about it, but it is not in confidence, but almost a million dollars of Cipro was used, and yet the resistance of human isolates was 2.2 percent.

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Is E. coli the best enteric organ to use in indicator species? Maybe not, because P. mirabilis had 5.8 percent resistance. There were no fluoroquinolone resistant Salmonella in 1998.

So, should we be concerned about fluoroquinolone resistance in Pseudomonas aeruginosa? Probably so, since it is now about 23 percent. Is it increasing? Probably, because last year it was 20 percent. A year before that it was 18. So, my point for bringing this up is if you know that you have a drug and a bug that is increasing every year about 2 percent, is that a point at which you, as an FDA, would make a move to stop or would you say that that is okay?

Clearly, if we have the right kind of surveillance, we can answer those questions. So, I would urge that we do resistance for resistance sake, and use the data where they are needed, be it food safety or the need to develop methods of intervention of resistance.

Thank you very much.

DR. STERNER: We have a brief period of time, a window of opportunity for questions of Dr. Thornsberry.

[No response.]

DR. STERNER: Hearing none, at this point we will press on relentlessly.

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DR. LEIN: One, if I could.

DR. STERNER: Donald.

DR. LEIN: Dr. Thornsberry, what about fingerprinting something like Salmonella basically to be more exact what we are finding as we look from the animal to the butcher shop that you are talking about?

DR. THORNSBERRY: I think the way that that has to be approached is that you use your surveillance system to identify where you have the problem, and then I think that becomes a side research issue, because, you know, I think it would probably be too difficult and expensive to do.

DR. LEIN: And use the antimicrobial resistance patterns.

DR. THORNSBERRY: To identify, yes, but obviously, the fingerprinting would be better.

DR. LEIN: Thank you.

DR. STERNER: Our next public speaker is Harless A. McDaniel. I don't know what the acronym AVID is. You have 10 minutes, and I assume you will explain that to us after you give us your disclaimer.

Harless A. McDaniel

MR. McDANIEL: No funds from any drug company, and no funds for paying any expenses to attend this meeting.

AVID is an acronym for American Veterinary Identification

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Devices. However, I hope that my comments today apply more across the board to the electronic animal identification technology, as well as the database development and management for animal production records.

I urge the Center for Veterinary Medicine to provide leadership to the livestock and poultry industries by developing a database format for electronically compiling and submitting information on use of antimicrobials and other regulated products in food animals prior to and during slaughter, throughout slaughter.

This process would provide CVM and other agencies, as well as industry organizations, industry needed about animal slaughter for human food. Many animals, not many poultry, but certainly quite a number of cattle and quite a few hogs now are being electronically identified and produced using software management programs.

Computerized management reduces production costs by 15 to 23 percent according to several experts, not me. Data on feed, treatment, and other production activities are available and could be electronically compiled and submitted to a central database if an appropriate program can be developed including definitions and so that everybody is talking about apples and oranges, or whatever it is, and the

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information becomes so much more meaningful if we have national and perhaps even worldwide standardized definitions.

Now, the database to me is far more important than your electronic identifiers or readers, or any other component in the system, and the database should extend from conception through the entire slaughter, sampling process, so this is the data for one animal and everything that is known about this animal or, in the case of poultry and perhaps some pigs that are produced in the same lot, in the same environment, of the same genetic stock, you may be talking about electronic identification for a sampling of these animals, or even in the case of poultry where they are all from one premise, you don't have to put it on any animal, but you just put it into the computer.

Certified production data could be useful for export and domestic marketing, plus a variety of other uses. It could be developed so production premises could be located, the premise data compiled, coupled with the individual animal identification could be used to evaluate exposure to infectious diseases of animals or human if diseases, such as mad cow disease occurred in this country.

Other less devastating animal disease outbreaks or in this

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case antibiotic resistance could be managed quickly without costly disruptive programs.

European Union has spent millions of dollars developing an animal identification system to be coupled with a database also under development. In 1998, the animal identification part of this alone, the budget exceeded $25 million. So, they are several years ahead of us.

We might not have to do all the work to develop an identification system, definitions, database management, electronic, and so forth, and so on. I suggest that we might find that much of this has already been done by the Europeans, and the more of this that we could standardize would be a great asset to the global marketing of animals and animal products.

I included in my submission the name, address, and so forth, for the European organizations that are managing the animal identification project, and I believe the same people are also involved in the database development.

That concludes my prepared remarks.

DR. STERNER: Are there questions from any of the panel members? Yes, Dr. McEwen.

DR. McEWEN: Just a comment. I would like to say that I think the sort of traceback studies that Scott Holmberg did,

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and John Speka, and others, on resistance issues would have been made a lot easier if there had been an I.D. system in place, and so I would like to endorse the concept as a way of helping to address some of the issues that we are talking about today.

DR. STERNER: Other questions or comments from panel members?

[No response.]

DR. STERNER: Thank you.

Our next speaker is one of my feathered friends, Dr. Dennis Wages, who is here to represent the American Association of Avian Pathologists. Dennis, you have 10 minutes, and the meter is about to run.

Dr. Dennis Wages

DR. WAGES: Thank you. Sorry about the cold. I usually can tell people that my voice will never get any worse, but I think today it might.

First, I guess Animal Health Institute has paid my expenses to this meeting, but I do not have any financial interest nor am I supported in my research at North Carolina State University by any of the pharmaceutical companies.

Today, I wear the hat of a poultry clinician, a teacher at the College of Veterinary Medicine, specializing in poultry

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medicine, as well as chairman of the Drugs and Therapeutics Committee representing the American Association of Avian Pathologists, which represents both turkey and chicken veterinarians.

Since the Swann report in '69, and in the much publicized Holmberg report of the Salmonella smoking gun in the early eighties, poultry veterinarians have realized the importance of a safe and an economic, healthy source of protein for the United States and the world.

Since that time and those reports, without fanfare and without publicity, the poultry integrators and poultry veterinarians withdrew penicillin, tetracycline, and sulfonamides from low-level or growth-promoters in their operations.

We, not like our counterparts in swine and cattle, had alternatives. We had the bacitracins, the virginiamycins, as well as some of the antimicrobials that were not used in human medicine.

Little did we know that today, 20 years later or 25 years later, we would be looking at two of those, being bacitracin and virginiamycin, which are on the cutting stone in our European neighbors to be pulled off the market for the potential for cross-resistance.

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So, we don't know now what is going to happen 20 or 30 years from now, and our decisions may reflect that ambiguity, if you will, on what might happen.

From 1994, I have agreed and I have spent many occasions defending the use of fluoroquinolones in poultry and other food animals. As this meeting has shown, and other meetings like it, to say this is a controversial issue would be the understatement. Prescription only, detailed records, HACCP, food safety initiative, FoodNet, post-approval monitoring, and I will say HACCP two or three times, the committees on judicious therapeutic antimicrobial use, and now the WHO initiative for the code of therapeutic use are all vocabulary terms that we know well because of fluoroquinolone use in food animals.

All of the above programs that I have mentioned are in stages of development. HACCP is in place, FoodNet, food safety initiative is in place, and I guess my first question when I saw the framework is why another one.

I think at some point in time we must look at merging or marrying these programs together. It appears that we have the framework and the nidus in place with HACCP and the antimicrobial monitoring that is going on, NARMS, I omitted, we have these in place to be able to integrate this type of

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a framework document to better suit our needs.

I am afraid that if we don't integrate what we have got, then, four, five, six, 10 years from now, when the budgets are cut, what program is going to be pulled, and it is going to leave the rest of them naked.

As far as concern on the document itself, and I can echo a lot of things that have been said from my food animal counterparts, and probably will be said, that I look at the categorization of drugs and I feel a little bit of an apprehension.

First of all, there doesn't seem to be any way to improve your categorization. If you are pulled into a Category I, it doesn't seem like there is very much way that you can go to a level 2 or 3, and it seems if you are a level 2 or 3, the only place to go is up, and up is bad.

I shudder to think at some of the comments that were made for veterinary medicine to prove that it does not cause the problem. I am not a statistician, and I am not a Rhodes scholar, but to prove a negative has never been very high on my list to be successful and to prove that we cannot or will not or cannot do something would be very detrimental to the antimicrobial industry and to our animals.

Another thing that bothers me about the antimicrobial

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categorization is there is nothing on there about the importance of those antimicrobials in the food animal itself.

Folks, from 1988 or in the eighties when [noctafurzone] was pulled off the market and was the only E. coli drug I had left, and the poultry industry had left to treat E. coli, I had nothing to treat E. coli infections until the fluoroquinolones were approved, not that I had an option, not that I could combine drugs, I had nothing, and so the fluoroquinolones were a godsend to us.

But even though you would think that with such an impact on E. coli infections, when you are only dealing with 5 to 6 percent of the flocks in our industry getting sick, an 18-month survey period has shown that in the broiler industry, only 1.2 percent of our flocks are treated with fluoroquinolones.

Yes, they are important, yes, they minimize the disease impact going into the plant, but, no, we don't over-abuse them in our opinion.

So, those are some problems that I see with the categorization. On-farm monitoring, I think that if you are going to do on-farm monitoring, it has got to be focused. I think if you do a national on-farm monitoring, that in my

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opinion could be disastrous.

I think if you are looking at the on-farm monitoring to actually try to point out where the resistance and if transfer resistance from either food-borne bacteria to non-food-borne bacteria, and the antimicrobial resistance resulting, if that is going to be found and finger-pointed, I think you need to have a very focused attempt, and not in this global picture.

Also, I think we have kind of missed the boat on something that may have already told us a lot. One of the big questions and concerns is veterinary use of antimicrobial as it impacted the treatment of food-borne pathogens. We have a perfect example with erythromycin.

My understanding is even though we screened humans with fluoroquinolones for nonspecific diarrhea disease, once we find that it is a Campylobacter, erythromycin is the drug of choice. Erythromycin has been used very heavily in turkeys for 30 years. It has been used in chickens, not as heavy, but if you are looking at a trend, let's track erythromycin and the resistance that has even been developed or not developed in Campylobacter.

It may be something that is sitting right there that we haven't utilized, we have been looking at fluoroquinolones.

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Campylobacter, Salmonella, and E. coli are target organisms. Five years from now listeria may be the target organism for food-borne illnesses that we need to be concerned with.

I guess one thing that I think of that probably hasn't been expressed in the food document is if you can take something out of the equation to minimize exposure to humans, I think irradiation and stopping the exposure of the humans potentially to that food-borne pathogen as the comes off the carcasses, an important area of consideration.

It doesn't stop cross-contamination. It doesn't stop the cross-contamination from the alfalfa sprouts and the vegetables, but it may go a long way in helping us out.

Everywhere that I find information that tells us antimicrobial cross-resistance doesn't occur, I find information that says that it does, so it is conflicting.

I guess to close, I would like to say that I am personally convinced that the intent of the framework document that has been presented is not to deter the development of new animal drugs in veterinary medicine, but I think the reality, if I am sitting back in the back of this auditorium, and I am an R & D person for a pharmaceutical company, that is exactly what this framework document will do.

If I have my options and I have the potential of putting a

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small animal drug on the market or an equine drug, or a food animal drug, I will guarantee you with some of the framework documents and the hoops and the barriers that we have to go through or would have to go through, I would not do it, especially to potentially treat 1.2 percent of the broilers or the turkeys that we are talking about.

I say let the programs talk. I think that when you look at a framework and a document, such as this, that not only can VMAC be involved in it, but you need to integrate a lot of the other stakeholders before you present this framework to the public, and maybe some of the controversy can be laid to rest.

Thank you very much.

DR. STERNER: Thank you, Dennis.

Our next speaker is from Iowa State University, Dr. Mike Apley, his presentation representing the Academy of Veterinary Consultants, and if you will start with your disclaimer also, Mike.

Dr. Mike Apley

DR. APLEY: My name is Mike Apley, and my expenses to this meeting are being paid by the Academy of Veterinary Consultants, whom my comments today represent.

I am on the faculty at the Iowa State University College of

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Veterinary Medicine, working in the areas of food animal production medicine and clinical pharmacology.

The Academy of Veterinary Consultants, or AVC, is a group of approximately 400 veterinarians involved in beef cattle production systems. Our objectives include to promote the profession and maintain high standards under which the members conduct the services of the public by holding meetings for the exchange of ideas and the study of the profession of herd-health consultation, and to cooperate with veterinarian agriculture organizations and regulatory agencies.

The commitment of the AVC to the issue of antimicrobial resistance has been demonstrated by recent presentations at our meetings by Dr. Angulo from the CDC, Dr. Thompson from the CVM, and Dr. Lieberman from the CSPI.

We applaud the recent visit of Drs. Bell, Webber, and Angulo to Colorado feed lots where they were introduced to our production system.

The AVC is committed to animal health, public health, and the viability of the beef industry. The delivery of a safe wholesome product to the consumers is our ultimate goal.

The AVC recognizes, as do producers, that this is a vital component of the longevity of the food animal industry.

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In keeping with the requested topic of this meeting, we would offer our comments on a proposed framework document. This framework document requires us to emphasize our animal obligations in order to achieve balance in the approach. As written, the document contains the potential to severely compromise our ability to fulfill our obligations to animals and animal health. While the AVC agrees that the relationship between antimicrobial use in animals and humans must continue to be close examined, we must also remember that antimicrobials are a major component of delivering a safe product to our consumers.

Upon initial reading by one concerned with issues, as the AVC is concerned about, the agency appears to have assumed the stance of if we can conceive it, you must disprove it. While the widespread application of the precautionary principle to this issue may be expedient, we must also consider the potential negative impacts on public and animal health.

In document Section II, the introduction, the following statement in the document, we would like to propose comments on. I will read the statement.

"In addition, bacteria can become resistant indirectly when resistance traits are passed on from other bacteria by

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mechanisms which allow the exchange of their genetic material. In this way, resistance can be transferred between nonpathogenic and pathogenic bacteria and from bacteria that usually inhabit the gastrointestinal tract of animals to those that infect humans."

The reference for that was Dr. Levy's article, 1998 article, Multi-Drug Resistance, a Sign of the Times.

This concept is brought up later in the introduction, as follows:

"Alternatively, the bacterial resistance genes can be transferred to pathogenic bacteria in the human gastrointestinal tract or in the environment and these newly resistant bacteria may then cause human infections in the immunocompromised host."

While this statement is conceptually understood, I could not come to grips with that reference being the source for that statement. We have had an excellent presentation on this subject earlier today that outlined many possibilities, but in my opinion, few certainties.

We do not dispute that pathogens in food animals with altered susceptibilities may be passed to humans through improper hygiene, whether personal or in the food preparation system. In fact, preventing the zoonotic

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transfer of pathogens and minimizing any bacterial transfer to the absolute lowest point possible is a major effort on the part of the producer and slaughter industry.

However, we encourage the agency to carefully examine the concept of indirect transfer of altered susceptibility from nonpathogenic food animal isolates to enteric pathogens in human for a specific drug pathogen combination before using this concept as the basis for policy.

Adoption of this concept is reality without justification for each application. It would allow the hypothetical linkage of almost any drug use in animals to an important therapeutic application in humans.

A major assumption that will be necessary to enable this document is some idea as to the amount of change in susceptibility required to have an adverse effect on human therapy or to at least have an idea of how to determine this threshold for effect.

Committing to fulfilling the requirements of this framework document with no direction in this area relies on a very optimistic view of the relationships we will be able to work out agreements on.

This framework relies on developing information for much of which the agency does not possess reasonable methods of

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discovery at this time. This framework establishes required decisions and policies that, by their design, will require subjective judgments on the part of the agency.

We appreciate the opportunity to comment today and ask that the agency continue this transparent method of development.

In the section on importance in human medicine, we realize the agency cannot consider animal welfare in the pursuit of human food safety, however, we ask the agency to consider the point that some antimicrobials may be very important in controlling pathogen occurrence, and by this manner have a positive effect on food safety.

Regarding the Category I criteria, we would ask the agency start by indicating anticipated cross-resistance categories.

We encourage the agency to safeguard against errors based on overgeneralization. As a pharmacologist, I routinely run into misconceptions based on generalized concepts concerning antimicrobial drug groups.

We propose the agency designate a review period after which a drug standing in human medicine is reviewed. Under the current proposed framework, it is hard to envision a drug ever moving down a category unless a periodic review inviting public comment is required.

The "new class statement" should be better defined. As

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written, the agency has wide latitude as in no definition for designating a novel drug class as having potential for long-term therapy in human medicine.

Other definitions required are those for a rare mechanism of action and/or the nature of resistance induction is unique, as well as resistance is rare.

The issue of category placement is extremely complex in itself. We would anticipate a transparent process whereby the reasons for each drug placement would be disclosed and comments would be received.

In the part of the document that addresses evaluating the potential exposure of humans, the following example from the agency document is referred to in the comments below. This is a section from the document.

"An antimicrobial drug administered in drinking water ad libitum is used for 7 days to treat E. coli infections in a herd of swine and the drug has been shown, in vitro, to induce resistance to an antimicrobial used in humans to treat food-borne pathogens such as Salmonella species. This drug is administered to all of the animals in the herd in the production class that is susceptible to the disease when a disease outbreak occurs. However, outbreaks occur in only a small fraction of the herds brought to market."

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Pivotal determinations required for categorization of exposure for this example include what is a small fraction of the population, what is the definition of resistance, and what in vitro standards are to be applied, does the change in susceptibility patterns constitute resistance.

Additional questions from this section of the document include what does the agency intend to use for the definition of a significant baseline incidence. Obviously the 6 to 21 days for a medium exposure drug is put out for discussion, which you are welcome to take part in.

We do not hold these up as reasons that such evaluations are impossible, but as examples of the complexity of the documents that will require multiple inputs.

Regarding microbial safety, the agency requests comments on whether and when it would be appropriate to set resistance thresholds on human data, animal data, or both. By setting resistance thresholds based on human data, the agency would be contending that the vast majority of resistance development for that pathogen drug combination is due to antimicrobial use in animals.

The agency is confident that the majority of human Salmonella infections are of food origin. How would this framework address other pathogens? For example, vancomycin

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resistant enterococci has been referred to as a pathogen "that may now be essentially untreatable in the United States."

The relationship between animal use of the glycopeptides and appearance of VRE in humans in Europe is used extensively through the framework document as justification for this approach.

Under the proposed framework document, it appears that if glycopeptides were used in U.S. food animals, the current VRE incidence in the United States would be at least partially attributed to food animal use.

I can see no provision in this document to attempt to discern between effects of widespread use or misuse in human medicine and use in veterinary medicine. The food animal industry must prove that use in animal agriculture is not the cause.

This is the doctrine of -- and excuse my Latin -- res ipsa loquitur where the agency is stating that it is so obvious that food animals are at fault, that it is up to the industry to prove they are innocent.

The AVC asks for a description of how the agency would examine would causes of this resistance from both animal and human use.

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Along this line, I was troubled earlier today by the somewhat cavalier discussion of the mean of resistant human Campylobacter in Spain. According to my information, this country has a high prevalence of endemic Campylobacter in humans, has multiple generic an illicit versions of fluoroquinolones available to humans on an over-the-counter basis, and in some areas, has a sewer system far below that which we are accustomed to in the United States.

Does this mean that animal use has no bearing on human Campylobacter isolates in this country? No, however, discussing this resistance level in conjunction with animal use, with no discussion of possible human contributions, is misleading.

For animal data, the source of isolates must be carefully considered. The agency must commit to identify point sources contributing to a change in susceptibility detected in a nationwide monitoring program, and addressing control efforts at these point sources rather than utilizing a blanket approach, and we have discussed that today.

We are not convinced that routine on-farm monitoring would yield the most useful information on a routine basis. However, this may be useful if problems are identified with a specific drug-pathogen combination.

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It appears that the agency depends on sponsors to foot the bill for this program. Given the small size of the veterinary market and the extensive financial commitments required to fulfill obligations imposed by these higher categories and exposures, this will directly affect decisions by companies to pursue new animal drug approvals. Other concerns include drugs for which patent protection is expired, that now compete with numerous generic forms. The financial requirements of being placed in a high human importance category as currently established may lead to the demise of these compounds due to no company wanting to fund programs for the benefit of their competitors.

To some, the loss of new and currently approved products appear to be laudable outcomes of the framework document, however, to those directly responsible for animal health, and who do not just see animals as numbers on computer screens, it is a frightening proposition.

The AVC implores the agency to proceed with the realization that the goals of this document will not come without a cost to the veterinarian's ability to address disease.

The ultimate result of this framework document is best illustrated by combining the following excerpts. The agency notes that the ability to set scientifically based

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resistance and monitoring thresholds depends on at least two factors. One is the ability to demonstrate that a particular resistance threshold is adequately protective of the public health, and two, the ability to detect when the resistance of monitoring thresholds are reached. In the absence of either factor, the agency presumably would not be able to approve new uses of antimicrobials in food producing animals when such approval is dependent upon setting and monitoring such thresholds.

Another excerpt is that while the agency believes that some level of resistance transfer from animals to humans due to use of a Category II drug -- this is reference to Category II -- in animals may be shown as safe, it does not have data and information currently that would enable it to establish such levels.

By combining these statements with the stated intention of applying these principles to future and existing approvals, the agency is now effectively linking the existence of all food animal approvals to the creation of thresholds for which it states it does not have data or information to establish.

The current document is based on evaluating the potential impact of antimicrobial use in food animals, on therapeutic

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efficacy, and human medicine. How has the agency performed recently in this area?

In order to evaluate the potential human health impact of an antimicrobial use in veterinary medicine, the agency must follow the principles of a risk assessment. We have heard enough about those today, that I will try not to say that word again.

The Center for Veterinary Medicine was unable to reach a consensus resulting in a risk assessment for recent drug approval. This attempt risk assessment was conducted only within the Center. We would ask that the Center propose a process to come to a consensus on the contentious issues in the framework document with the additional participation of outside parties.

The proposed framework document is a excellent document for the purpose for defining areas where little information is available. As a basis of policy, it could -- I emphasize could -- serve to severely impact the ability of veterinarians to fulfill their obligations to food animals. This impact would be the cost if -- I emphasize if -- the agency errs significantly on the side of caution in multiple areas where the agency will be forced to make decisions based on limited data.

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The AVC looks forward to further cooperation between the Center for Veterinary Medicine and AVC members as we work together to protect human and animal health.

We thank you for the opportunity to comment.

I would like to close with a comment on the earlier statement the guidelines didn't work in human medicine, and good luck on getting them to work in veterinary medicine.

It just so happens that I am the guy that is the director of our attempt to create for veterinary medicine.

Our web-based database will be designed to allow the veterinarian to rapidly access dose regimen information based on empirical therapy, as well as for therapy with the benefit of culture and susceptibility testing.

We intend to be quick, be brilliant, and be gone, basically, what a good speaker does and I am fixing to do.

Four veterinary organizations and one producer organization fund our project. In 1988, as a young veterinarian, I was introduced to Ciprofloxacin by a local physician when I was handed a handful of Cipro samples for a fever of unknown origin. I, along with the veterinary profession, remain committed to doing better than that.

Thank you.

DR. STERNER: Thank you, Michael.

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Questions from the panel members? Dr. Angulo.

DR. ANGULO: Mike, I am encouraged because I didn't hear the word that you were opposed to the framework. By you not saying you are not opposed to the framework, can I assume that you endorse the framework?

DR. APLEY: You know, Fred, the only thing I can say is if you wouldn't have asked something, I would have gone away crushed, because I was hoping to get Fred wound up.

I don't if it's support as much as it is a reality. Myself, and I think I speak clearly for the AVC, we are very anxious to come to some conclusions on this subject, and we are anxious to get us working together like Dr. Bell stated earlier.

Our biggest concern is what I tried to cover through this whole prolonged yak here was we are very concerned that our ability to adequately express health concerns in animals, including food animals, be preserved, and as a veterinary organization, our interest is actively reviewing this document and seeing how it would impact us.

I think there has to be some type of organized way to approach it. That, I would agree with. I think there are a lot of ways we could make the framework better.

DR. STERNER: Dr. Bell.

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DR. BELL: Mike, I want to thank you for your thoughtful comments, and I just have a question. It really didn't sound to me, Fred, like he was supporting the framework.

DR. APLEY: Fred is an optimist.

DR. BELL: Well, me, too, actually. My question is are there a list of specific suggestions that you could make, either now or in the future, specific modifications in this framework that would enable you to take a more positive role in it?

DR. APLEY: I think we could boil this down and have some other suggestions, yes. I took a part out because I thought it sounded a little too flippant.

Dr. Sterner will fully understand this. I spend a lot of time in a truck and with dirty boots and grew up in a veterinary practice, and you have to understand the veterinarian does not like to wake up in the morning and the first thing you hear is, "We are from the government, and we are here to help you."

If the question is do we trust the agency, the answer is, well, conditional. I don't mean that to be insulting, but we are going to approach this with a very jaded eye, but we do want to see progress. So, I would be glad to put together a list.

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I think we gave several constructive things in there, interactions we would like to see, and areas of the document we sure want to be transparent.

DR. STERNER: Thank you for your candor, Michael. Coming from Michigan and the home of the Michigan militia, I am not sure that the answer would be quite the same about I am from the government, and I am here to help you.

Our next speaker does, in fact, come from Michigan. Dr. Robert Walker from Michigan State University who was referred to earlier, who heads up the Campylobacter International Committee, is next on our agenda.

For those of you whose rear ends are at a true endpoint, I will tell you that we have, by my count, just three more speakers, so the end is in sight, or the train is at the end of the tunnel, one of the two.

Dr. Walker, would you state your affiliations.

Dr. Robert Walker

DR. WALKER: I am a Professor of Microbiology at Michigan State University. I do perform pharmacodynamic studies for numerous pharmaceutical companies. My expenses to this meeting have been paid for by the Animal Health Institute.

I think it is unrealistic -- this is from my own perspective -- unrealistic to expect a pharmaceutical company to develop

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a class of antimicrobial agents that is not or will be not be used for human need or human use, human medicine.

I also think 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.

I therefore believe that it is necessary for us to use the drugs that we have or will develop more intelligently, both in human and in veterinary medicine.

[Slide.]

So, because I only have a couple minutes, I will bypass the goal that FDA has put out, and you all can read that.

[Slide.]

From my reading these documents or this document, these are the methods that I felt that they were going to use to implement these goals. One was to quantitate the antimicrobial drug resistant enteric bacteria formed in the animal's intestinal tract following exposure to the antimicrobial new animal drug, which this was their definition of resistance.

[Slide.]

The second is determine changes in the number of enteric bacteria in the animal's intestinal tract that causes human illness. This is the pathogen load. They go on to say that

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enteric bacteria in animals represent a special risk for causing human illness and for including resistance in bacteria in humans because they are the bacteria most likely to contaminate a food product and then be ingested.

I would like to address the second issue first, which is determine the changes in the number of enteric bacteria in the animal's intestinal tract that causes human illness. Determine the changes in the number of enteric bacteria in the animal's intestinal tract that causes human illness.

Wow. As a microbiologist, how would I do that? If you go to the next overhead.

[Slide.]

If you look at the work done by Herdt and his graduate students, the mean concentration of total viable bacteria, aerobes and anaerobes per 5 cm segment of intestinal tract in healthy calves, you can see that 10^6, 10^6, about 10^6, clear up here at 10^9, this is a very conservative estimate, and this aerobes and anaerobes.

Are anaerobes involved in human health? I don't think that we have an answer to that question yet because we really haven't looked into it.

[Slide.]

If we look at just the coliforms, 10^5, we are going to see

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how the use of antibiotics changes this. To give you an idea of the complexity of this question, go to the next one, please.

[Slide.]

This is some work done by Moore and Holdeman back in 1976, and what I have listed here are the rankings of the bacteria found in the gastrointestinal tract of humans, this work has not been in animals for logical reasons, we don't have the money to do it, but if you look at the ranking and the percent of isolation, and these are all of the bacteria that they have isolated.

I am not going to read them to you for the lack of time. If you could go to the next one.

[Slide.]

You get clear down here to 56 or somewhere, 52, or 72, somewhere in this area, and this is where E. coli ranks. So, E. coli is not very prominent in terms of the gastrointestinal tract, at least in humans, and so where is it in animals? We don't know.

If we are looking at enteric pathogens or pathogens that could be transmitted by food, do anaerobes play a role in this? Again, this is an issue we don't know. This is just something that the FDA has proposed to include in their

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database.

[Slide.]

Say we are going to look just a E. coli or pathogens. This slide is a very complex slide, and I wanted it to be this way, just to emphasize a point. What we have here are 52 different canine or different dogs, fecal samples from 52 different dogs, all raised in the same environment, and what we did was we looked at five E. coli, we streaked the plates for isolation, picked five individual colonies from each one of those dogs, and looked at it for virulence factors where there was attaching interfacing gene or shiga-like toxin gene, hemolysins, and also the somatic antigens, and you can see from looking at this that there is a tremendous complex environment here.

Now, are these organisms potentially human pathogens? Well, they have the attaching interfacing gene, they produce a shigatoxin, at least some of them do, so they are potentially human pathogens, although this is a canine, and we don't ingest canine feces, not even in the home environment, so this is a kind of a moot issue.

[Slide.]

This is some work done by Dr. Holland where he looked at the distribution of the attaching interfacing gene and the

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shigatoxin and E. coli among serogroups in relationship with attaching interfacing lesions in calves, and you can see the different serotypes that are present here. Here is 0157. It is only one of the many that was there, and it didn't have an attaching interfacing lesion, but you can see the complexity of this, and are these potential human pathogens that haven't manifested themselves yet?

Go back 15 years. Take a mindset back 15 years, and tell me all you know about E. coli 0157:H7. Very, very little, and so next year maybe it's going to be one of these other attaching interfacing E. coli that becomes a pathogen, but we are not looking at it, because we are only looking at 0157:H7.

[Slide.]

Evaluate the quantity of antimicrobial drug resistant enteric bacteria formed in the animals' intestinal tract following exposure to the new animal drug.

[Slide.]

This is a slide where we looked at a fecal sample from a cow, streaked it for isolation, picked 25 colonies, assayed each one of them individually for their susceptibility to ampicillin, enterofloxacin, or gentamicin, and you can see that there is quite a bit of flexibility or diversity in

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terms of their susceptibility to these drugs, and these are E. coli isolated from the same animal at the same time.

[Slide.]

This is again a study by Dr. Holland where he looked at those attaching interfacing resistance patterns, and again you go back and you look at these serogroups that have these different numbers and their susceptibility profiles. What are we going to use for the baseline?

[Slide.]

So, I think what we need to do, we need to look at a fairly extensive national monitoring system, I think, where maybe we involve the farm, the laboratory, and the abattoirs, the different food animals that are involved.

[Slide.]

We need to look at, like Dr. Thornsberry said, from a variety of samples, enteric, respiratory, milk samples.

[Slide.]

We need to look at a variety of organisms, E. coli, not just E. coli 0157:H7, but let's look at E. coli as a whole and see what it is looking like. Salmonella, there is not going to be very many of those, so it is not going to be an extensive database. Campylobacter, it could be extensive. Proteus, one of the things that we found is that Proteus is

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a very sensitive indicator of susceptibility to fluoroquinolones.

[Slide.]

What we found when we looked at E. coli, in 1991 to 1996, there really wasn't much of a change in their susceptibility to the fluorinated quinolones, but the Proteus mirabilis, there was a tremendous change. Here, the MIC nidi is equal to or less than 0.08 -- this is 1991 data -- in 1996, 98 percent of them are right at the breakpoint. They are still classified as susceptible, but they are right at the breakpoint. I think an extensive monitoring system would have picked these up long ago saying that this trend is occurring.

[Slide.]

If you look at trends, this is a trend from Lorian's, when we are looking at setting these threshold, Ciprofloxacin, where do we sound the alarm here in this decrease in susceptibility? You can look at any one of these drugs and see that there is really not a dramatic change in them, so where do you call it, where do you sound the alarm? Has FDA really identified that point?

Look at the next one. Perhaps the thing to do -- this is the last one --

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[Slide.]

I think what we need to do is we need to look at looking at MICs and changes in MICs in relation to time, not resistance or susceptibility, but changes in the MIC, and just to emphasize that example, here we have Ciprofloxacin, tested in '98. There should be '98 there, that's a typo error. But if we look at Proteus, we can see that they are beginning to creep up.

This should be an indication that there is something going on here, and this is where I think education can come in.

So, from my perspective, I would encourage the committee to think very, very carefully about the decision that you are about to make, very, very carefully about the path that you are about to go down, because it can adversely affect the use of anti-infectives in veterinary medicine.

Thank you.

DR. STERNER: Thank you, Dr. Walker.

Next, we have Larry Glickman from Purdue University on the agenda, and, Larry, your title is not there, but I assume you will explain that to us in short order.

DR. GLICKMAN: My title is not what?

DR. STERNER: It is not titled. It says you are from Purdue, that's it.

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DR. GLICKMAN: That's enough.

Dr. Larry Glickman

DR. GLICKMAN: I am on the faculty at Purdue University. I have no financial interest in the pharmaceutical industry. My travel expenses to this meeting have been paid by the Animal Health Institute, however, the comments I am about to make have not been reviewed or even shared with the Animal Health Institute.

I appreciate the opportunity to comment on the proposed framework document that sets out a conceptual risk-based framework for evaluating the microbial safety of antimicrobial drugs.

One question asked by the FDA at this time is whether the concepts set out in the document, if implemented, will accomplish the agency's goal of protecting the public health by ensuring that significant human antimicrobial therapies are not lost due to use of antimicrobials in food producing animals, while still providing for the safe use of antimicrobials in the food producing animals.

The agency also requested input on important areas of scientific complexity identified in this document. This, in fact, is indeed a very complex issue that has been recognized and debated for some time by the regulatory and

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scientific communities.

It sort of reminded me as I was sitting back there of a quote about complexity from H.L. Mencken, who said, "For every complex problem, there is a solution that is simple, direct, and wrong." I hope the framework document is not that solution.

Now, no one individual possesses all the expertise to address the questions raised in their entirety. As an epidemiologist, I would like to comment on six key points or principles put forth in this framework document, which I admit is not simple.

The first and perhaps most important point I want to make is that insufficient information and knowledge currently exist to establish definitively scientifically-based protocols for monitoring and regulating the impact that veterinary antimicrobials have on human health when used in food producing animals.

I fully agree with the recent report, The Use of Drugs in Food Animals: Benefits and Risks, that was published by the National Research Council, Institute of Medicine, and I know it has been said several times, but I think their quote from that document is well worth repeating.

It says, "Until more accurate data on animal antibiotic use,

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patterns and rates of resistance transfer to humans, and occurrences of actual disease emerge, and mechanisms of resistance are available, actions aimed at regulating antibiotics cannot be implemented through a science-driven, well-validated, and justified process."

This indicates to me that the highest priority now for regulatory agencies should be to establish and strengthen programs, to collect the scientific facts that are needed for adequate risk assessments, that is, establish the scientific knowledge base which will lay the foundation for future regulations regarding use of antibiotics in food producing animals.

In addition, a greater effort should be placed on educational programs directed at veterinarians and food producers to promote judicious therapeutic antimicrobial use in food producing animals. I think this should be a tremendous effort.

Point 2. The FDA in its framework document developed concepts for evaluating, "complex issues related to the use of antimicrobial drugs in food producing animals."

Given the complexity of these issues and the lack of a scientific database for drafting regulations at this time, an interdisciplinary task force representing the disciplines

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of veterinary medicine, human medicine, epidemiology, biostatistics, economics, and microbiology should be established for several purposes, and this could be referred to this blue ribbon committee which another speaker mentioned.

The purpose would be (a) to define the multiple endpoints that should be used to determine safety of antimicrobial use in animals.

Two. Conceptualize the appropriate monitoring systems to measure these endpoints in a cost effective manner.

Three. Once regulations are enacted, this committee could serve to constantly evaluate their impact on the endpoints selected, and recommend changes to the monitoring systems.

In effect, the regulatory and scientific process concerning the safety of antimicrobials should be a dynamic one until such time as the measures of safety can be validated using human health as the gold standard.

Point 3. The multiple and complex human health and safety issues raised by FDA, the CDC, and other federal agencies concerning the use of antimicrobials in food producing animals cannot and should not be addressed by imposing post-approval monitoring requirements at this time on a product-specific basis. This would be neither cost

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effective nor in the best interests of public health.

Rather, systematic and uniform monitoring systems should be designed that assess appropriate safety endpoints in such a manner that any antimicrobial on the market can be identified if it significantly increases the pathogen load or the resistance threshold, two outcomes suggested in the framework document.

Furthermore, if changes in pathogen load or resistant thresholds are used to assess safety of antimicrobials, a significant change should be based not only on statistical principles, but also use measures of biological significance that have been validated.

For example, even a very small increase in pathogen load or resistance threshold can achieve statistical significance with a large enough sample size, however, such a small increase may have little or not biological relevance to public health.

Point 4. Existing programs, such as NARMS, established in 1996 as a joint effort by FDA, USDA, and CDC, should form the basis for monitoring fluxes in antimicrobial resistance associated with antibiotic use in food producing animals rather than establishing new and costly systems for this purpose.

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However, monitoring systems, such as NARMS, are designed primarily to detect changes in antimicrobial resistance of pathogens or indicator microorganisms over time rather than to identify the specific reasons for these changes.

Even if the increased use of a specific antibiotic in food producing animals is associated temporally with increased antimicrobial resistance of potential human pathogens, there is no scientific way to prove that the two phenomena are related using only NARMS data.

Therefore, additional investigation is required to not only this specific question, but also to identify other risk factors related to farm management, inappropriate antibiotic use, et cetera, that contribute to increased antibiotic resistance over time.

One mechanism to do this is to use NARMS data to identify changing antibiotic resistance patterns that merit further investigation. For example, farms that were the source of antibiotic resistant microorganisms of concern -- we call these case farms -- could be compared with farms that were the source of the same type of microorganisms, but that showed no increased antibiotic resistance, which I call control farms, using standard case control epidemiologic methods.

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This can involve farm business by individuals who are blinded to the case control status of the farms to collect management information, as well as blood or microbial samples from animals in the environment.

This approach would measure the risk of antibiotic resistance occurring in animals associated with the use of specific antibiotics on the farm. However, it would also identify other farm level management factors that contribute to this resistance, including inappropriate use of antibiotics.

Such findings would be extremely useful in determining the relative importance of these factors in the development of antimicrobial resistance, and would be valuable to the regulatory process and in establishing educational programs of farmers and veterinarians to prevent resistance.

In fact, FDA alludes to such studies in the framework document on page 20 by stating that if NARMS data indicated that unacceptable resistance was emerging, FDA could reevaluate ongoing post-approval studies, order other studies to be conducted, or institute other appropriate actions.

Point 5. The framework document, on page 17, states, "FDA believes that on-farm studies to monitor antimicrobial

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resistance prevalence by the sponsor would be necessary to ensure that resistance thresholds are not exceeded after approval." Furthermore, data generated through these studies in addition to other scientific data would provide an early critical warning system for detecting and evaluating the emergence of resistance under field conditions.

For the reasons stated above, it does not seem reasonable or cost effective for reach manufacturer to monitor a geographically representative sample of swine, poultry, and cattle farms in the U.S. to determine the prevalence of antimicrobial resistance.

This is better achieved by using or expanding the existing NARMS system coupled with the follow-up studies I described. It is not in the public's best interests to establish a broad national on-farm program in a drug-specific manner as FDA believes or at least as they state on page 17 of the framework document.

Such programs would significantly increase the cost associated with drug development and potentially diminish the availability of new antimicrobials for therapeutic use by veterinarians.

Finally, the last point. At a recent national conference on

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emerging food-borne pathogens, entitled "Implications and Control," sponsored in part by combined FDA, USDA, and CDC, it was noted that, and I quote, "Infectious diseases transmitted by foods have become a major public health concern in recent years. Response by both the food industry and public health and food safety regulatory agencies to new microbiologic health threats and reemerging pathogens in food have been primarily reactive. The multiplicity of factors and complex interactions involved in the emergence and reemergence of microbial food-borne hazards, and the need for multifaceted integrated approach to protecting the population prompted this national conference."

In the closing address to the conference, it was concluded -- and I quote -- "Concerted controlled efforts by public and private sectors are needed."

The FDA framework document should be viewed as the first step in this process. A coordinated team effort involving both the public and private sectors is now needed to develop a strategy to bridge the human and animal health issues related to the use of antimicrobials in food producing animals.

Such an effort will required considerable time since an adequate knowledge base for a scientific risk assessment

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does not currently exist. It must not be approached in an adversarial manner since too much is at stake.

Premature promulgation of regulations without a sufficient knowledge base at this time might only serve to retard development of long-range solutions that best serve the public's health and farm animal welfare.

Thank you.

DR. STERNER: Panel members, questions of Dr. Glickman?

[No response.]

DR. STERNER: Thank you.

Dr. Jim Cullor from the University of California, who is the director of the University of California at Davis Veterinary Medical Teaching and Research Center, is our next speaker, running rapidly to the lectern.

Dr. James S. Cullor

DR. CULLOR: I appreciate being here. My travel expenses are being paid by the Animal Health Institute. I am the director of the VMTRC. From time to time our faculty and our Center, through the contract and grant process, receives money from private industry including my laboratory, although it is mainly vaccines and not pharmaceuticals.

[Slide.]

I am here today to talk about the framework document as a

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representative of and the director of the Dairy Food Safety Laboratory.

[Slide.]

What we are being asked by all these discussion we have talked here today is really how do we do daily management of the production unit for animal health and well-being, public health, environmental health, and medical ecology, and still manage the financial well-being of the dairy. That, in fact, is what we are doing at the VMTRC with our students through programs like Dr. [Sisco's], TQM, breakthrough management, and infectious disease control, and so on, and so forth.

[Slide.]

We have had several reviews today, and this one I think we need to go back and look at. The probability of disease transmission from animals to man is really influenced by the length of incubation period in the animal, the length of time the animal is infective, the pathogen load contained in the animal product or placed into the environment, the stability of the agent in the environment, the population density of animals and man, animal husbandry practices, maintenance, production, and control of wild rodents and insects, virulence of the microbe, and the route of

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transmission.

[Slide.]

In all of this, the compounds we are talking about, these anti-infective or antimicrobial agents, really have a positive impact in two main areas. By shortening the length of time the animal is infective and reducing the pathogen load contained in the animal product, or placed into the environment.

At the American Academy of Veterinary Pharmacologists and Toxicologists last year, we presented a model where we looked at, on one end of the spectrum, absolute, unrestricted use of all antibiotics where you could violate any orifice you wanted to, with any antibiotic you wanted to, and given enough time you would get enough drug resistance that the pathogens would overwhelm the pasteurization and our meat processing, and we would have an increased risk to the human population.

That same model shows, on the other end of the spectrum, if you completely remove antibiotics from the food animal production system, the pathogen loads again will reach critical mass where they will get past all of the pasteurization and other types of procedures, and again present a problem to the human population.

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In that model, then, the middle ground is where you combine management practices, antimicrobial therapy, good methods of animal husbandry, and so on, and so forth. That is where the human population is at the least risk of being infected by these pathogens.

I submit to you that if you go to Vietnam today, you can see one end of that spectrum. You can go see the result of the human population for the lack of antibiotics, and the model accurately predicts what happens.

I am afraid that if we continue this framework as it is, that we will have that type of an environment and really a problem for our food animal production industry.

We have talked about and heard a lot about Salmonella, E. coli, and Campy, but I submit that the list will grow and grow each year until we get these plus Yersinia and others, and so that --

[Slide.]

We get often as veterinarians, we get the comment, "Well, why don't you just go clean up the dairy" or "Why don't you just go clean up the farm, and we wouldn't have all this trouble."

I submit to you that every day in the hospitals around this country, they have problems with cleaning them up, and when

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we work in an environment where these are the criteria for eradicating a pathogen, it has to be a single host species with no external reservoir species. That is not the case with Salmonella, E. coli, or any of the others.

In order to eradicate a pathogen, it has to be identified to be present in only a small percent of the farms, ranches, dairies, or feed lots, and we know that it can be worldwide, not just in the U.S.

The pathogen of interest serves as a disease marker for detecting endemic herds, and we know that organisms like 0157 is not a marker for the endemic disease.

Appropriate assays are validated and can correctly identify the carrier animals. In fact, they do not exist, and not have been validated for such a purpose.

Effective means of intervening in the chain of infection after the carrier animals have been removed from the herd must be established, and that is where antimicrobials and vaccines and management practices can play a part.

We have to have substantial financing, many billions of dollars to do this, and we don't see that anywhere either in private industry or from the government, and a long-term resolve by everybody involved to implement all of the necessary measures for eradication, and we very seldom see

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that long-term resolve exist.

[Slide.]

I know this is a little difficult to see and almost impossible, but what I wanted to show is that we took -- one of the issues is the surveillance system, how can we track antimicrobial resistance and what is going to happen.

What we used was the USDA panel of organisms, and what we did then is we took that panel and we looked at heifers -- we call them springer heifers. They have been on the dairy. This is a closed herd that milks about 5,000 cows a year. They have five dairies. They feed their babies hospital milk, mastitis milk. It has been pasteurized. It has antibiotics in it. They were raised on that for at least 60 days in their early life.

Then, they are raised in the environment all the way through out of the dairy until they are pregnant and ready to calf. We go in and test those animals just before they calf, and these are Staph aureus isolates.

What we saw was that on this dairy -- we did it for 1995, 1996, and 1997, the same dairy where we know all the antibiotics used -- and what this assay showed was that in '95, 4 percent of the Staph aureus isolates were resistant to chloramphenicol, in '96, 12 percent, and in '97, zero

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percent.

We looked again at another one, streptomycin; in '95, 4 percent were resistant; '96, 4 percent resistant, in '97, none, and so on, and so forth. We had four different antibiotics out of that panel that showed this resistance, where, in fact, these animals weren't exposed to these antibiotics any other way than at birth or in the environment around.

We used this data as an early indicator. We are going to do the 1998 data now. This surveillance system can't be looked at, at any one year. It has to be looked at over a period of time, and you have heard that several times already today. Probably a minimum of three years is going to be needed to take a look at some of this information.

So, now we have been asked several times to comment on the framework and what we might do.

Part 1, the categorization. It makes sense, but it really needs to be better simplified, and you have heard over and over again if you get in number 1 category, you can't get out of there under this system.

So, I think we can reduce it maybe to three categories, and then be objective and really make this setting transparent; that an expert panel get together with CDC and CVM and

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really relook at these categories and see if we can't help them out a little bit.

Monitoring thresholds. It is a good idea, but we really don't know where to set them, and you have heard that over and over today.

For veterinary therapeutics, we have breakpoints established for maybe three or four drugs, but none are set for enterics, and we have got to look at that. Therefore, it is not going to be very easy for these products and for these zoonotics to be put together especially under a direct regulatory action.

So, let's set some targets and then use them for further study, let the NCCLS group sit in on this, and let them be responsible for setting these targets and then reviewing them, and not a government agency.

For therapeutic use in animals. Again, a full risk assessment needs to be done, and we have heard that over and over today, and we have heard it challenged over and over, but I think we have heard from our colleague from Canada of the fact this can be done, and if we don't know how to do it, let's take him out to dinner tonight and get some ideas.

We do support judicious use and education about use of antibiotics, and we should continue to do that, and this

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framework should reflect that position.

We need R & D on better slaughter, processing, storage, and preparation of our food products, cold sterilization with pulsed ultraviolet light, things like that can be done, and we have seen over and over that the HACCP program that is being implemented has been severely underestimated by this document and by some of the early speakers.

This is working. The statistics show it, and the prevalence data shows it, and we need to keep supporting it, and then build upon that. Resistance thresholds, really, this is more appropriate as a research study, not that I am from an academic environment or anything, but I think rather than a regulatory document, we need to support more research into this area, and really work from there and then set the thresholds.

Regarding the pre-approval and post-approval studies, basically, I support a good body of studies on the pre-approval side, including the Salmonella shedding studies and modifications that were proposed by Dr. Miller this morning.

We should support other good descriptive studies of treatment resistance, transfer of mechanisms, and so on, and so forth. We should support and enhance slaughterhouse

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under NARMS surveillance system. It is in its infancy right now, we have heard that, and it has its strengths and weaknesses and I think, as a group, we can together and really pull it together and make it a better system, and just like it was intended to be, and mature it as we go along.

Really, I support research and not regulatory studies for understanding on-farm animal epidemiology through a competitive grant system. We have a wealth of good university personnel, a lot of good scientists, a lot of good veterinary students and animal science students, and so on, and so forth, that can do a lot to improve this.

I think these suggestions represent really a simple, solvable proactive way that is science driven, and it does support public health. Remember, you are asking us to, on a daily basis, manage these dairies for animal health, public health, environmental health, medical ecology, and the financial well-being.

This framework document, although a good start, does not help us to do that, and we need to work on it, and I support the idea that we can modify this and make it a better document than it stands today.

Thank you.

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DR. STERNER: Thank you, Dr. Cullor.

Questions of panel members of Dr. Cullor?

[No response.]

DR. STERNER: We are at that stage, and I know you have all been anxiously awaiting with relief to your posterior, and that is our final speaker of the night.

Dr. Barbara Glenn, is that correct? I have no affiliation for you, but I assume again that you will explain that to us, and you have the final 10 minute period of the night.

Dr. Barbara Glenn

DR. GLENN: Mr. Chairman, it is my pleasure to be the last speaker this evening. My name is Barbara Glenn, and I am executive vice president for Scientific Liaison for the Federation of Animal Science Societies.

I have not received any financial support regarding my statement, and my expenses are paid by my employer.

FASS, or the Federation of Animal Science Societies, is a federation of three professional societies, and has a membership of about 11,000 scientists who are in academia, government, and industry. Our members do research, teaching, and information exchange to students, producers, consumers, and other members of the public.

Our three member societies are sponsors of three major

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scientific journals that are respected around the world in the animal, dairy, and poultry scientific community.

We are familiar with the proposed framework that you have released for review and comment. In general, we request that you allow the science and the facts to guide your deliberation and actions.

Some of the issues are old and have been raised for 20 or more years. With new antibiotics and possible new emerging strains of pathogens, some questions are new. We should learn from past experiences and carefully look at new situations while research should be directed to fill in the information gaps that exist, so as to factualize the decisionmaking process.

This is a topic of very serious concern and should not be taken lightly. To not act if some of the concerns turn out to be real is not ethical. Likewise, to take actions that are not warranted also can be inappropriately costly to both livestock producers and consumers.

Specifically, we believe the issue of implementing a valid monitoring process to assess the development of resistance in microbes to be much more complicated than might be thought. There are a number of questions that seem to be pertinent, and for which the answers are not obvious from

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your framework.

Some of these that come to mind are the following. First, how many samples are needed to provide assurance of real changes due to antibiotics versus random changes that occur over time? Are present baselines defined?

Secondly, what is the definition of resistance? Is it just any increase in dose required to inhibit organisms, or is it the total resistance to a previously effective antibiotic? Many new antibiotics have required an increased dose after initial introduction, but remain effective at the slightly higher dose levels on an indefinite basis. Would such be considered evidence sufficient to remove an antibiotic? If required dose increases, what level is considered resistance, 2X, 100X, et cetera?

Thirdly, where would microbes be sampled? Is it feasible to do adequate sampling on the farm? Who would do this, and what level of funding would be needed to have government employees doing this sampling? What does the farm information do if it does not relate to the level on the food? What are levels on farm or at the processing level more important to human health considerations?

We hope that the VMAC and your professional staff will discuss these and other related scientific issues, and

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provide us with answers prior to taking any actions that have a major impact on the health and well-being of animals. Further, we would hope that your deliberations would identify areas of critical information that are really needed to shore up the basis for such decisions.

In addition, we would hope to have your support for research funding to provide enough information to make all of us more comfortable with the important questions that are being raised.

Thank you very much.

DR. STERNER: Thank you, Dr. Glenn.

Questions from panel members?

[No response.]

DR. STERNER: You really drew the short straw when it comes to how much we could stand.

I want to personally thank you all for your kind indulgence. I think we might have set an all-time record for a continuous meeting. That is not my intent, but I think you all see the importance of this issue and the deliberations that will go on subsequent to our tomorrow morning's two scheduled speakers.

With that, we stand adjourned until tomorrow morning's reconvention.

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[Whereupon, at 7:45 p.m., the proceedings were recessed, to be resumed at 8:30 a.m., Tuesday, January 26, 1999.]