FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

9:05 a.m.

Thursday, January 9, 2003

Grand Ballroom
Marriott Washingtonian Center
9751 Washingtonian Boulevard
Gaithersburg, Maryland

ATTENDEES

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JOHN POWERS, M.D.
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ATTENDEES (Continued)

ALSO PRESENT:

TOM BURKGREN, D.V.M., M.B.A.
American Association of Swine Veterinarians

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C O N T E N T S

P R O C E E D I N G S

(9:05 a.m.)

DR. LEGGETT: I'd like to welcome you to the Anti-Infective Drugs Advisory Committee meeting regarding the ranking of antimicrobial drugs according to their human importance in human medicine. I guess that's human importance or importance.

Let's start off by going around the table and having everyone here tell us who they are and where they're from. Dr. Brown, would you like to start off?

DR. BROWN: Ken Brown. I'm retired from industry and I teach at the University of Pennsylvania.

DR. PORETZ: Don Poretz. I'm a practitioner in infectious diseases in Fairfax, Virginia.

DR. WALD: Ellen Wald, infectious diseases, Children's Hospital of Pittsburgh.

DR. BRADLEY: John Bradley, pediatric infectious diseases, Children's Hospital, San Diego.

DR. RUPP: Good morning. Mark Rupp, infectious diseases, University of Nebraska.

DR. ELASHOFF: Janet Elashoff, biostatistics, Cedars-Sinai and UCLA.

DR. EBERT: Steve Ebert, an infectious disease pharmacist at Meriter Hospital, clinical professor of pharmacy, University of Wisconsin.

DR. PATTERSON: Jan Patterson, medicine infectious diseases, University of Texas-San Antonio.

DR. LEGGETT: Jim Leggett, infectious diseases, Providence Portland Medical Center and Oregon Health Sciences University.

DR. TURNER: Tara Turner, Executive Secretary for the committee.

DR. O'FALLON: Judith O'Fallon, Cancer Center Statistics, Mayo Clinic.

DR. RELLER: Barth Reller, adult infectious diseases, meta-microbiology at Duke University Medical Center.

DR. MAXWELL: Celia Maxwell, adult infectious diseases, Howard University.

DR. BELL: David Bell, National Center for Infectious Diseases, Centers for Disease Control and Prevention in Atlanta.

DR. BARTHOLOMEW: Mary Bartholomew, biometrics team, Center for Veterinary Medicine, FDA.

DR. TOLLEFSON: Linda Tollefson, Center for Veterinary Medicine, FDA.

DR. MULINDE: Jean Mulinde, medical team leader, Division of Anti-Infective Drug Products, FDA.

DR. ALBRECHT: Renata Albrecht, Director, Division of Special Pathogen and Immunologic Drug Products,

FDA.

DR. POWERS: John Powers, lead medical officer, antimicrobial drug development and resistance initiatives, in the Office of Drug Evaluation IV at FDA.

DR. GOLDBERGER: And Mark Goldberger, the Office of Drug Evaluation IV, FDA.

DR. LEGGETT: Thank you.

Tara.

DR. TURNER: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All special government employees and federal guests have been screened for their financial interests as they may apply to the general topics at hand. The following participants have reported no current financial interests with regards to pharmaceutical companies: Drs. James Leggett, Jr., David Bell, Barth Reller, and Judith O'Fallon. Dr. Mark Rupp reported a financial interest in a pharmaceutical company covered under CFR 2640.202(b), de

minimus exemption.

The following participants have reported interests in pharmaceutical companies and the Food and Drug Administration has granted general matters waivers to the following SGEs, which permits them to participate in today's discussions: Drs. Ellen Wald, Alan Cross, Steven Ebert, Celia Maxwell, Jan Patterson, John Bradley, Donald Poretz, and Janet Elashoff.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each member and consultant. FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

With respect to FDA's invited guest speakers, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments. Dr. Michael Apley is a scientific adviser to Schering, Intervet, Farnam, and Novartis. He lectures for Novartis, Intervet, Pharmacia, Pfizer, and Merial. Dr. Apley is a member of the Beef Cattle Advisory

Boards for Elanco, Ft. Dodge, and Intervet, and has received funds from Pharmacia, Pfizer, and Elanco for drug-related research.

In addition, we would like to disclose that Dr. Kenneth Brown is participating in this meeting as an acting industry representative acting on behalf of regulated industry. Dr. Brown owns stock in Merck and has stock options in the firm. As of July 2002, his 401(k) owns shares in Genentech, Johnson & Johnson, and Pfizer. During the summer Dr. Brown has been visiting scientist at Gordon College. The college has a contract with Merck that is currently inactive. He is a consultant to Wyeth and works at Merck two days a month. Dr. Brown has been an expert witness for Merck.

In the event the discussions involve any other products or firms not already on the agenda, for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. LEGGETT: Thank you. Dr. Goldberger, would

you like to give us some opening comments?

DR. GOLDBERGER: I'd like to welcome everybody here to the second day of this advisory committee, to what should be an interesting and important day.

Some of us within the Center for Drugs have been helping the folks in the Center for Veterinary Medicine over the last few years with their efforts to provide better information about approaches to the development of antimicrobial drugs for veterinary use. What we were asked to do was to provide information that would sort of provide a basis for looking at the importance of antimicrobial drugs in human medicine.

I want to make just a couple of observations about this.

One is, this is really not explicitly a part of our normal regulatory process when we approve new antimicrobials for human use. That is not to say that we don't try to get a sense of what their added value is, particularly if there is, as an example, an unexpected toxicity or safety signal. But there is no requirement that a drug -- for instance, a new antimicrobial -- offer added value or be particularly important. It simply needs to be safe and effective. So this is a function that we've done to help the folks at CVM, but it's not a normal part of our day-to-day process.

Second thing that's important to note, and we made this clear from the outset, that we were doing this totally from the perspective of their importance in human medicine and the potential importance in treating patients. We recognize that ultimately -- and this is underway now -- this type of approach and the information that we've provided needs to be integrated into a larger approach to provide guidance about how to proceed, and that obviously a number of other factors need to be taken into account.

But what we were asked to do, and the information that we provided, really focused on the issue of what is the importance of antimicrobial drugs in human medicine, and what kind of elements go into making that determination. The questions that we'll be talking about this afternoon really are to allow you guys to give us some additional advice in that area.

We are very pleased that there will be representatives from both the producer and the veterinary communities who will be giving talks as part of this meeting, both planned talks and additional talks in the open public hearing. Although, as I indicated, our goal was really from the CDER perspective to focus on the importance in human medicine, we realize that it's extremely important that people on the committee have a broader understanding of what this overall process is, and

these talks, as well as the talks by the folks from the Center for Veterinary Medicine, as well as John Powers, will hopefully provide that broad perspective which may also be important should additional scientific questions have to come before this committee, or perhaps a meeting of this committee and the CVM committee to outline and deal with some of the other scientific issues that come up in making this type of advice available to the veterinary community.

I think I'll stop at that point.

DR. LEGGETT: Thank you. Dr. Tollefson, would you like to start us off with an overview?

DR. TOLLEFSON: Good morning. I want to express my appreciation and thanks to the advisory committee for taking the time to provide us with your expertise and just good advice on trying to deal with this issue. We really do appreciate your input on the issue of ranking drugs for importance in human medical therapy.

Ranking the drugs is a very important component of a new draft guidance from the Center for Veterinary Medicine that provides a pathway to evaluate the safety of animal antimicrobial drugs with respect to their ability to cause resistance and thereby decrease the risk that resistant pathogens will affect humans by contaminating the food supply.

I want to cover several parts, and I want to do a brief background of the issue on the scope of the new guidance for industry, which I just mentioned, spend some time on the components of the qualitative antimicrobial resistance risk analysis, which is a key part of the guidance. This is going to be rather confusing. We recognize that you are busy people, you have limited time. We did not expect you to go through the guidance in detail. We've been through it, of course, several times and it still can be confusing to us.

So what we've decided to do is have Dr. Mary Bartholomew at the Center walk you through the guidance using a hypothetical example, and we're hopeful that this will clear up some of the mechanics of the guidance in more detail.

The overall human food safety evaluation of antimicrobial new animal drugs includes consideration of several things, not just the resistance issue. The residues of animal drugs in food, the effects of the animal drug residues on human intestinal microflora, and then the microbiological effects of animal drugs on bacteria of human health concern, the antimicrobial resistance issue.

This last point is relatively new. It was not considered for all classes of antimicrobials until approximately late 1998. At that time we changed our

policy to include in the pre-approval evaluation process the potential human health effects resulting from the emergence of bacterial resistance due to that use of the antimicrobial in animals, in food animals specifically.

Just to make sure that everybody is on the same page in terms of the hazard or the risk, what we're dealing with is the issue that antibiotic-resistant food-borne pathogens may be present in or on animals. By "in" we're referring to the enteric system, so it's really on animals as a result of drug use in animals. Then those resistant pathogens may contaminate carcasses at the slaughter plant and be transmitted to humans through consumption of contaminated food and also handling of contaminated food and cross-contamination issues.

Then when these resistant bacteria cause an illness that needs treatment, medical therapy may be compromised if the pathogenic bacteria are resistant to the drug or drugs used for treatment.

We've been working on various aspects of our strategy to address the issue of antimicrobial resistance for the last four years. It's multi-faceted. It includes this revised pre-approval assessment. That's the focus of the new guidance to industry. We've also spent a great deal of effort on improved surveillance activities, looking at development of resistance and changes in resistance.

We've supported judicious use principles for food animal veterinarians, and we've also undertaken expanded research activities. Also we're part of the federal public health action plan to combat antimicrobial resistance and many of these activities fall under the scope of that broader issue.

What the committee has been asked to consider is one component of this revised pre-approval assessment, the ranking of the drugs based on importance in human medical therapy. The pre-marketing approval assessment takes the form of a draft guidance for industry, a copy of which we provided to you. The status of that is such that we are now addressing comments received on the document, as well as this ranking, which is an important part of the document, both written comments and comments that we received at a public meeting in October, where we went through the guidance in a lot of detail.

We plan to revise the guidance based on these comments as well as the discussion with you today. Guidance for industry, unlike a regulation, is much more easily changed to reflect new science, additional comments, and so on. So even when the guidance is finalized we consider it an ongoing work in progress and we can make changes based on new information.

Now, the focus of the guidance is primarily on

human exposure to antimicrobial-resistant bacteria, or resistance determinants through ingestion of animal-derived food. We recognize that the emergence, spread, and persistence of antimicrobial resistance is complex and involves many pathways. We believe that the food-borne pathway is the most significant and most directly linked to antimicrobial drug use in animals, but that isn't to say that it's not the only pathway.

The guidance is applicable to both therapeutic and non-therapeutic antimicrobial drugs intended for use in food-producing animals. Drugs in food animals are used to treat disease, prevent and control disease, and then also can enhance performance, growth, feed efficiencies.

The components of the risk analysis consist of a hazard identification, a qualitative antimicrobial resistance risk assessment, and then risk management strategies to deal with any potential risk to humans. The identification of the hazard is the first step of the process and it's really outside and separate from the qualitative antimicrobial resistance risk assessment. The hazard here is defined as human illness that is caused by a specified antimicrobial resistant bacteria, is attributable to a specified animal-derived food commodity, and is treated with a human antimicrobial drug of interest.

The three main elements of a qualitative risk

assessment are the likelihood of whether use of the drug in food-producing animals will first cause bacteria to become resistant, that humans will be actually exposed to the resistant bacteria, and that exposure will have a human health impact. We've elected to do a qualitative risk assessment because we anticipate that limited information will be available when a new drug is brought forward to us to be approved. If more quantitative data are available, they would certainly be used and would take precedence over the qualitative risk assessment.

Now, the release assessment describes the probability that factors related to the animal drug and its use in animals will result in emergence of resistant bacteria or resistant determinants in the animal.

Then the exposure assessment describes the likelihood of human exposure to the resistance determinant of human health significance that arises in a food-producing animal as a consequence of the use of the drug in that animal.

The exposure assessment also provides a qualitative estimate of the probability of this exposure occurring, and Dr. Bartholomew will illustrate that, as well as the components of this qualitative antimicrobial resistance risk assessment in more detail using an example.

The components of the qualitative risk

assessment then consist of the release, the exposure, and the consequence, which is Appendix A in your document. The consequence is the ranking of the drugs based on human medical importance. It's entirely the same thing; it's equivalent. So therefore, it accounts for one-third of the estimation of risk, but it's very important to point out that it does not equate to risk and does not equate to a categorization of drugs that I'll describe a little bit later. In other words, because it's high-consequence, it doesn't necessarily mean that it's going to come out as a category 1 drug which carries the most restrictions on use.

We asked the Center for Drug Evaluation and Research to rank all drugs, not just those used in food-borne disease treatment. We recognize first that many human drugs are used to treat enteric disease. And of course, we wanted to base the ranking on the best available science, which demands that we consider cross-resistance between classes as well as within classes, also factors related to drug efficacy. Dr. John Powers will describe this in more detail in his presentation, which will go through the factors. There are 10 factors that were used to come up with the ranking of the drugs.

Then we'll be asking for your comments on these factors and whether there should be more weight placed on certain factors. For example, that which concerns the

treatment of food-borne disease. Or, are there a subset of factors that should drive the ranking because they more clearly concern a connection to the use of the drugs in animals?

The next component of the guidance is a risk estimation which then integrates the release, exposure, and consequence assessments. This qualitatively, because it's based on a qualitative risk assessment, characterizes the potential for human health to be adversely impacted by the emergence of resistance associated with the drug used in animals, in food-producing animals.

The risk estimation is the point which leads to the ranking of drugs according to risk. Sorry, I didn't mean to use the word "ranking" because that's very confusing. It leads to the placement of drugs according to the risk to humans, and in turn these risk-based categories are associated with certain risk management strategies that we can take to control the risk. These parts of the process are where the veterinary medical aspects of the drug are considered mostly. There are other areas too.

Now, the risk management categories are very simple. There are three of them. Category 1 equates to a high risk estimate and we intend to approve the drugs only on strictly limited use conditions. I'll describe those in a little bit. Category 2 then is medium, and it's

intermediate restriction, and category 3 would be the least restriction on drug use. This may be the case where drugs could be used, possibly with no restriction or on a large number of animals for non-therapeutic purposes.

Now, we attempted to draft the guidance document so that all veterinary antimicrobials would be potentially approvable in food animals by using risk management strategies. We do not intend to dampen the development of veterinary antimicrobials, but rather develop a more reliable and predictable process for approval.

The risk management strategies are somewhat self-evident. One would be limitations on marketing. For certain antimicrobial drugs, we feel that veterinary involvement is important for ensuring safe use. The categories available to us are prescription, over-the-counter, or something that we term a veterinary feed directive, which for your purposes should be considered as a prescription product.

The extent of use and conditions of use of antimicrobial drugs influences the selection pressures for resistance development. So restricting use can be a risk management tool to determine the safe conditions of use of the drug for a food-animal drug. Specific drug use limitations are found in table 4 of the guidance document.

Basically they concern restricting both the duration of use and the method of administration.

The possible risk management steps are summarized in table 5 in the document, and they're stratified by the category of concern. Category 1 would only carry prescription marketing status. Category 2 would also only carry prescription status. However, in category 2 use of the drug in animal feed could be allowed, depending on the other parts of the evaluation.

We have the ability in veterinary medicine to restrict extra-label use or off-label use. And the extent of use I just describe, and those are described as categories again of low, medium and high. Unfortunately, we couldn't get away from that.

Post-approval monitoring refers to the surveillance system. It's called the National Antimicrobial Resistance Monitoring System that is a three-armed system of animals at slaughter plants, which is run by the U.S. Department of Agriculture; humans ill with food-borne disease, which is done by the Centers for Disease Control and Prevention, the National Center for Infectious Diseases; and then retail meat, which is done at the Center for Veterinary Medicine. Then, of course, advisory committee review is another option that we always have.

To summarize, we feel the draft guidance outlines a risk-based approach for evaluating these antimicrobial resistance concerns. Ranking of the drugs according to human medical importance represents approximately one-third of the qualitative risk assessment process. Our goal is to provide for the safe use of antimicrobials in food-producing animals, while ensuring that significant human antimicrobial therapies are not compromised or lost due to the use of these drugs in food animals.

The risk to humans, then, is managed through application of drug use limitations and restrictions to maximize the availability of antimicrobials for animal therapy. That's our theoretical approach. That's how we wrote the guidance to accomplish that goal.

We very much look forward to continuing working with CDER and the public and the industry and other valued stakeholders to successfully address this very complex health problem. I thank you very much for your attention.

DR. LEGGETT: Thank you. Are there any questions for Dr. Tollefson?

(No response.)

DR. LEGGETT: Very good. Thank you.

The next speaker will be Dr. Mary Bartholomew, who will give us an explanation of antimicrobial risk

assessment.

DR. BARTHOLOMEW: Good morning. I too would like to take this opportunity to thank the committee for their time, and I'd also like to thank Carol Andrus and Bill Flynn for their work on condensing this presentation from three presentations that we made at our public meeting in October.

Now that Dr. Tollefson has provided you with a general overview of the risk assessment process, I'd like to take the opportunity to run an example of a hypothetical drug through the risk assessment process in hopes of helping us understand the process.

First, as outlined in the draft guidance, the risk analysis process is intended to organize and integrate an array of relevant information and to provide guidance as to how this information may be used to manage risk. As mentioned earlier in Dr. Tollefson's discussion of the qualitative risk assessment process, it's composed of the hazard identification process, the qualitative antimicrobial resistance risk assessment, which has three parts, release assessment, exposure assessment, consequence assessment, and the integration of the three parts in the risk estimation process. Also the risk management steps.

Prior to initiating the risk assessment, we must identify the hazard and the conditions that influence

the occurrence of the hazard. By definition, the hazard is human illness that is caused by a specified antimicrobial resistant bacteria, is attributable to a specified animal-derived food commodity, and is treated with the human antimicrobial drug of interest.

As stated in the guidance, we recommend that the hazard identification step of the risk assessment include drug product information, and that would consist of information for the example such as miraclemycin is the name of the drug. Its trade name is Miracin. It's in the class, second generation, curalloside, with a CAS number of 2002.

Its use information, we're going to talk about dosage regimen. It's intended to be administered as an oral solution in drinking water for 5 days. It's going to be given for the treatment of swine respiratory disease, and the target species, of course, then would be swine.

In addition to the drug-specific information, we need information about bacteria, resistance determinants information, including antimicrobial susceptibility testing methodology, as well as any data gaps or emerging science related to the particular drug-bug combination.

The release assessment describes the probability that factors related to the antimicrobial new animal drug and its use in animals will result in the

emergence of resistant bacteria or resistance determinants in the animal. That was defined before as the probability that resistant bacteria or resistance determinants are present in the target animal as a consequence of the antimicrobial new animal drug use. That probability would be expressed, since this is qualitative risk assessment, as low, medium or high.

The boundaries of the release assessment span from the point the new antimicrobial drug is administered to the food-producing animal to the point the animal is presented for slaughter or animal-derived food is collected.

For the purposes of this risk assessment, a number of relevant factors are suggested for consideration. They're listed here on the slide. Some of them overlap with those in the hazard identification set. They are: product and drug substance description, mechanism and type of action, spectrum of activity, PK/PD, resistance selection pressures, prevalence of resistance, resistance mechanisms, resistance transfer, other relevant information.

So the sponsors may consult with FDA -- in fact, we encourage them to do so -- to determine the specific factors that are most relevant to the new animal drug in question. The sponsor or FDA may consider

additional factors to take into account any specific considerations pertinent to the drug and its proposed conditions of use.

The relative significance of any one of these particular factors among all factors pertinent to the release assessment may vary, depending on the specific new animal drug under consideration. Therefore, certain factors may carry greater weight than other factors when determining the overall release assessment ranking.

So we turn to our example of Miracin. In the interest of time, I will not provide an in-depth explanation related to each of these criteria for this particular example. Rather, this background information will be handed out after my talk to the committee, and it was presented in our October meeting so that you can visit our web site and see the slides from the presentation in which this was done in a series of several slides with more explanation.

I will move directly to the outcome comments and conclusions for each of these criteria.

Miracin is a bactericidal drug with some activity against Gram-positives. Campylobacter exhibit low MICs. The PK/PD parameters are favorable for minimizing resistance release. It has rapid absorption and high distribution to the tissues, and the serum concentration

greater than the MIC for 6 hours makes for minimizing resistance release. And the in vivo post-antibiotic effect is about 3-and-a-half hours.

The transfer of resistance is infrequent. There's a low baseline resistance and a low mutation rate.

The FDA recommends that the sponsor use the conclusions obtained from assessing all relevant factors to derive an overall qualitative ranking for the release assessment, and in this particular case, the release assessment conclusion for Miracin would be that there is a low probability of release.

Let me turn to the third component of the assessment. Well, let me say a few more words about that.

The overall conclusions are expressed as low, medium and high, and as we mentioned, this is just one of the three. So it's intended to estimate the probability that resistant bacteria or resistance determinants will occur in animals as a consequence of the proposed drug use in animals.

It's also important to note that if sufficient information regarding a factor is not available or has not been generated for the assessment, the most conservative significance of the particular factor may be assumed. That is, the factor would be assumed to have a high likelihood of contributing to resistance emergence. And that's one of

these factors. So if a number of those would turn out to -- would be unknown, we would assume high likelihood, and that would tend to bump up the overall release assessment probability.

The next component is the exposure assessment. The exposure assessment describes the likelihood of human exposure to the hazardous agent through particular exposure pathways. And again, the strict definition from the guidance document was that the exposure assessment is the probability for humans to ingest the resistant bacteria or resistance determinants in question from the particular relevant food commodity.

The exposure assessment describes the likelihood of exposure to the hazardous agent through particular exposure pathways, and at this time assessing human exposure to the hazardous agent is focused on food-related pathways. FDA believes that human exposure through the ingestion of resistant bacteria from animal-derived foods represents the most significant demonstrable pathway for human exposure to resistant bacteria or resistance determinants as a consequence of drug use in the food-producing animals. As we say, it's the most significant.

The probability for exposure is also qualitatively determined to be low, medium, or high.

The exposure assessment may be accomplished by

integrating information that characterizes the probability for humans to be exposed to given bacteria via a particular food commodity. We're not talking about resistance at this point. This is just being exposed to the bacteria. Then the probability that the bacteria of interest to which the humans are exposed are resistant to a particular antimicrobial drug or possess associated resistance determinants.

Returning to our example, the probability for humans to be exposed to a given bacteria via a particular food commodity is independent of drug use, and may be estimated by considerations of per capita consumption of the food commodity. And this example was pork. Now, this information is available from several sources.

The probability of contamination of the pork by bacteria of interest, and in this case we're looking at the example of Campylobacter.

While it's acknowledged that other factors such as food preparation practices can affect exposure, the above two considerations can provide a qualitative indication of the magnitude of the probability of human exposure. Survey data of both food commodity contamination and per capita consumption may be submitted to support a qualitative ranking of probability of human exposure to the given bacteria via a particular food commodity, and

examples of such sources of data are shown on the slide.

Appendix B of the guidance document contains examples of how such information may be integrated, and we'll run through that for the example.

According to current consumption data from the USDA Economic Research Service, we see that 47.7 pounds of pork are consumed per capita per year, which will give a qualitative ranking of high. From Food Safety and Inspection Service data, we also note that there's a 32 percent prevalence of Campylobacter contamination of market hogs, which results in a high ranking relative to other contamination levels.

Next, the consumption and contamination rankings are merged to derive the qualitative ranking for the probability that a human is exposed to Campylobacter on pork. Looking at our table of outcomes, the per capita consumption being high and the probability of food commodity consumption being high, then we see that the overall ranking results in a high probability of human exposure to the given bacteria. Now, this is not completion of exposure assessment because we haven't discussed resistance to this point.

So finally, overall exposure assessment ranking is derived by integrating the ranking for the probability of human exposure through food to the bacteria in question

-- high from the previous slide -- with the probability that the bacteria will be resistant to the antimicrobial drug in question, which we saw was high from the previous slide, and with the probability that the bacteria will be resistant to the antimicrobial drug in question. That comes from our release assessment, and that was low.

So looking at our table of possible outcomes, we see that a high probability of human exposure to a given bacteria and a low probability of the bacteria of interest being resistant will result in a medium overall exposure ranking. So that completes the second of our third components.

Now we move on to the consequence assessment. Now, in the third component, we note that the consequence was the probability that human exposure to resistant bacteria determinants results in an adverse human health consequence. That was based on the medical importance of the antimicrobial drug under review, and is also ranked low, medium or high.

Returning to our example, then, we find that in Appendix A the antimicrobial drug ranking developed by CDER determined that Miracin is high, of great importance in treating of human disease. However, I'll reiterate what Dr. Tollefson mentioned. This does not equate to a high potential risk to humans or to a category 1 drug. This is

not the completed risk estimation, as the two other assessments, the release and the exposure, have not yet been integrated.

We will move forward then to this process of integrating the release, the exposure, and the consequence assessment, and that will provide a result as high, medium, low risk for human health to be adversely impacted by emergence of antimicrobial resistance associated with the use of the drug in animals.

How is this integration done? The risk estimation is low if all three are low, or if two are low and one is medium. It's high if all three are high, or there are two highs and one medium. And otherwise it's medium. The thinking behind this integration scheme is that the presence of one medium along with two lows would not raise the estimate to a medium. Similarly, the presence of one medium along with the two high assessments would not decrease the risk to medium.

These three rankings relate to the level of concern for human health impact potential of the new drug. Each level of concern corresponds to a category of risk management steps. Category 1 management options or steps are applicable to situations where the risk estimation result is high. Conversely, category 3 management steps are applicable when the risk estimation result is low. Dr.

Tollefson showed the table of risk management steps in her talk and we will display it again shortly in context of the example.

Recalling again in our example for the release assessment, we had a low. For the exposure assessment, we had a medium. For the consequence assessment, we had a high. From the general rule for integrating the three assessments, we note that the risk estimate is medium, which is associated with category 2 risk management steps.

Category 2 risk management option or steps permit therapeutic application to selected groups of pens or animals for short durations.

Returning to the example, Miracin oral solution for swine, we note that the sponsor is proposing that the drug be used by prescription only, administered as a therapy to select groups of pens or animals, and that it be limited to 5 days of administration. In this instance the use conditions for the proposed drug are those of a therapeutic drug rather than those of a non-therapeutic drug. Also, note that the proposed use is consistent with conditions of use deemed appropriate for category 2 drugs on the previous table, the risk management steps.

Therefore, based on the risk assessment and the drug application as a whole, FDA concludes that the antimicrobial new animal drug Miracin is safe. That is,

there is a reasonable certainty of no harm when the drug is approved under the defined use conditions.

That completes the explanation for the example. Are there any questions?

DR. LEGGETT: Do you have a question, Steve? Otherwise, I have a few.

Thank you for the example. It has a great name, too.

On your slide on page 3 of the example, the release assessment of Miracin, are all of these data currently provided for new drugs when they are brought before the FDA? In other words, is this data available for drugs now?

DR. BARTHOLOMEW: If there are data gaps, as we mentioned, what we would tend to do would be to make the assumption that that factor corresponds to increasing the probability for release.

DR. LEGGETT: I realize that. I'm down to nuts and bolts. Do you know the mechanism of activity, the spectrum, the kinetics, the dynamics, the resistance when the drug is brought before the FDA? Or is this all theoretical?

DR. BARTHOLOMEW: A lot of the development work is brought forward and has this information in the submission. A lot of the times, yes.

DR. LEGGETT: My second question is, on the slide on page 5, you were talking about exposure assessment. It sort of made me think, are there data available to test this sort of qualitative mathematical model already? In other words, are there data from outbreaks, epidemics, that sort of thing, that are available to sort of look at how -- it's a quasi-mathematical model of the various risks.

DR. BARTHOLOMEW: For the major food-borne pathogens, Foodnet has a lot of epidemiologic data about exposure to the bacteria.

Now, about the exposure to the resistance, of course if you were looking at a new animal drug that's not been out there, then there will not be information about resistance, about that particular --

DR. LEGGETT: Right. I'm getting at the model testing. You've sort of got X times Y percentage times Z percentage in terms of figuring out just whether somebody eats it. Are there any data for drugs currently available for outbreaks that have occurred of animal-associated illness in humans? Do we know if low, medium and high are logs apart in terms of the risk, or just how good are these assessments? Or are we sort of floating free?

DR. BARTHOLOMEW I'll try to answer that and then I'll see whether somebody else from the panel wants

to.

But we have information from the Economic Research Service on how much of all the different food-animal products are consumed. We have FSIS data on what the levels of contamination are. Those permit us to look at broad bands and say that some of them cluster above a certain percent, so that's a high rate of contamination. And some cluster low. So yes, it's based on real information from FSIS about contamination levels.

DR. LEGGETT: And my final question is about the risk assessment. Say it's pork for Campylobacter. How do you compare a pork chop with ground pork? I mean, even though the rate of contamination of the animal may be the same, the transmission to people may be different, much like the E. coli 0157 would be for steak versus hamburger.

DR. BARTHOLOMEW: Right, and a lot of the products are looked at in terms of ground product and whole product. I think that our approach probably would be to be more conservative. If one product were highly contaminated, I mean that would be a route of exposure that we would go with the more conservative process.

DR. LEGGETT: Steve.

DR. EBERT: Probably just a comment. It appears from the assessment that you've done that the release assessment is actually being used twice in the

analysis. You're using the release assessment by itself and then you're also modifying the exposure assessment based on the release assessment. Is that an accurate statement?

You initially said that the exposure was high, but then when you take into account the release, that got downgraded to medium so that the ultimate result was medium. So you're really using that in two different ways.

DR. BARTHOLOMEW: That's accurate in terms of we need to decide during the exposure what the rate or the prevalence of resistance in that exposure is. And it may be that there are some data -- for instance, we frequently get proposals to add to existing claims. And then there might be some information out there, but if not, you just use the information straight out of the release assessment. You might, in fact, have more information to bring to bear on that.

DR. EBERT: The reason that's of concern to me is, at least from my initial reaction, of the three it seems as though the release assessment is the most subjective in its analysis. For example, some of the things that are included in there, the drug has a time above MIC of 6 hours. It has a PAE of 3 hours. What does that really mean? Is there any real clear-cut relationships between some of these measures and the

likelihood of resistance? Maybe that will be discussed later in the day.

DR. LEGGETT: Ellen.

DR. WALD: This is a small point, but the word "release" just seems like a funny word for this assessment because at least it doesn't relate to anything that I can think about, whereas the other terms are sort of meaningful. Could you think about changing that to like probability of emerging resistance or something where the description would be relevant to what you're talking about? It would have helped me understand the documents.

DR. LEGGETT: Mutant escape.

(Laughter.)

DR. BARTHOLOMEW: I'll take that comment forward. However, that term comes out of an OIE, Office of International Epizoides, paper in which a formulation for risk assessment for resistance determinants was proposed, and that's where the term arose. I guess we can take that under consideration.

DR. LEGGETT: Go ahead, John.

DR. BRADLEY: The model looks very nice, and as a pediatrician there are lots of data on day care centers' spread of resistant organisms, and I sort of see a feed lot to be analogous to a day care center.

(Laughter.)

DR. BRADLEY: There are lots of new colonization studies which show introduction of a resistant organism into a day care center and how quickly it spreads. In addition, in the release assessment, once you eradicate a certain set of organisms with an antibiotic, there's a chance that you can get colonized with resistant organisms of a different type because you lack colonization interference at that time.

So my question is, are there data in feed lots or herds or flocks -- I have no idea -- on how rapidly a resistant organism can spread under conditions of antibiotic therapy.

DR. BARTHOLOMEW: I'll defer to some other people on that -- we have some veterinarians and veterinary epidemiologists in the audience -- about the studies for the prevalence of rate of spread in herds.

DR. LEGGETT: Hopefully we'll remember to bring that up later in the discussions.

DR. BARTHOLOMEW: That's fine.

DR. LEGGETT: Yes, Mark.

DR. RUPP: I don't know if this is the appropriate time to bring this up. I suspect there will be a lot more discussion on this. But, for instance, in the document you provided us, in Appendix B, where you're trying to figure out the risk of exposure based upon the

prevalence of this antibiotic being in animals, and you've cited some data where you go and sample ground chicken or ground turkey. It seems like you've got some really high percentages there, 40, 50 percent levels, that you've only graded as sort of a medium risk. I'm wondering how you break that down, low, high and medium, based upon the prevalence of bacteria found in these food items. 40 percent prevalence seems real high to me.

DR. LEGGETT: That's the table B-2 where we broke it down to less than 5, 5 to 25, and greater than 25 percent in terms of the prevalence.

DR. BARTHOLOMEW: Right. Well, I think that we just looked and sort of saw a clustering and made what was out there. It's relative to what the other products had. If they only range from 0 to 15 percent, then 15 percent is going to be high relative to others. If they range from 25 to 75, then 75 is going to be high relative to others. It's not an absolute.

DR. RUPP: Right, so it's a relative scale, but it would seem to me that again if 40 percent of your broilers have Salmonella in it, you have a very high risk of exposure, even though 40 percent is only in the middle of that rank, or what-have-you.

And then another question would be, in the tables that you've shown you proposed certain policies

based upon your assessment, and I guess my biggest concern is use of antibiotics in animal feed. And for instance, in a medium-risk situation like this product, it would be allowed to be used in animal feed, it sounds like. How did you decide where you were going to draw those lines of, gee, you're going to restrict it only to therapeutic use versus non-therapeutic use in animals?

DR. BARTHOLOMEW: In this whole process the upper end and the lower end are the easier things to discern. Then when you get toward the middle, yes, there's an issue about where you make your cutoffs. I'm trying to go back to that risk management slide. I guess the rationale was -- and somebody can correct me if I'm wrong -- that Rx or a veterinary feed directive -- this is still on your prescription of a veterinarian. So that's medium. It's still being controlled there by a veterinary feed directive. So it would take the input of a veterinarian to make that decision.

DR. RUPP: So as a feed directive you're still using this drug therapeutically, not as a growth-enhancer?

DR. TOLLEFSON: That's correct.

DR. LEGGETT: Any further questions at this point?

(No response.)

DR. LEGGETT: Great. Thank you very much.

DR. BARTHOLOMEW: Thank you.

DR. LEGGETT: The next speaker is Dr. Richard Carnevale, who will talk to us about the ranking of antimicrobial drugs relative to their use in animals.

DR. CARNEVALE: Thank you, Dr. Leggett. I appreciate that pronunciation.

DR. LEGGETT: My wife's Italian.

(Laughter.)

DR. CARNEVALE: It is indeed a pleasure for me to be here, and first let me say I appreciate the invitation from Dr. Tollefson and Dr. Powers of CVM and CDER to come and present to you today the AHI, the Animal Health Institute's concerns about this categorization issue.

Before I begin, though, I'm happy to see someone in the audience -- Dr. Brown from the committee is at the University of Pennsylvania. I'm a proud graduate of the University of Pennsylvania veterinary school on Spruce Street. However, I will not reveal when I did graduate from that school because it's too many years ago.

In any case, what I'd like to do is talk a little bit about why we're here. We, of course, are the representative of the major animal health companies in the U.S. We are a small PhRMA, the Pharmaceutical Research and Manufacturers Association, and we're quite a bit smaller

than them.

We are pleased that CDER and CVM have asked this committee to take a look at the categorization issue. We think the advice of this committee is going to be very important and very critical to the practice of veterinary medicine and animal production in the future with regard to the use of important therapeutic products.

The FDA regulatory approach will affect new and existing antimicrobial drugs for food animals. This document will apply retroactively to existing products as well, so this risk assessment process that is underway will be applied to existing products on the market, which of course have been on the market for many years in some cases for a range of uses.

Infectious bacterial, fungal, viral diseases are very big problems in food animal production, as you can expect. And antimicrobials are a vital product line with many of our members. Antimicrobials, anthelmintics are probably the two biggest pharmaceutical products and feed additive products that our companies manufacture.

Of course, we are members of the larger human health companies, and being members of those larger companies they are greatly concerned about the resistance development not only with animals, but of course how it might affect human health. Of course, this issue has been

around for many, many years. Probably in the late 1970s the concern first came up with regard to the use of antibiotics in feed particularly, and now it's extended also to the use of therapeutic antibiotics, which this document would mainly apply to, although as I said it does apply in a more broad fashion to existing feed use antimicrobials as well.

As with human medicine, availability of a wide variety of products in veterinary medicine is very important. A range of products reduces resistance pressure on the few compounds that may be available, and timely and effective treatment of animal diseases does improve not only human health but food safety as well. There is some research that is underway that actually indicates that by not treating many animal diseases, you can have an increase in pathogens in the food supply. I think evidence in Europe is coming out that there is increased animal disease over there and possibly a concomitant increase in food safety problems.

The FD&C Act applies the same standards to antimicrobials as with human products. There is a very rigorous approval process that is required. There is an additional burden over and above safety and efficacy to the patient that residues that are left in the animal, any drug residues that might remain in the food when an animal goes

to slaughter is safe. And of course, that's been a process that's been underway for many years.

Resistance concerns are a bit newer, and as Dr. Tollefson mentioned, the concerns that CVM has for resistance will now apply to a whole range of products that are on the market. Originally the concerns were with feed use, continuous use feed use antimicrobials, and there were some standards applied in the 1980s for those. But this document will now apply a risk assessment process and additional standards to all antimicrobials.

We certainly support a strong FDA and rigorous standards. I mean, without a strong FDA I think that the consumers don't have the assurance that these products are safe. But, of course, industry must rely on science, and we hope that the agency operates on a basis of science and not on supposition or emotion. Unfortunately, this issue, antimicrobials in animals, has been driven to a large extent -- not necessarily the agency, but certainly in the media and other places -- by an emotional reaction to the concerns that some people think animal drugs contribute to human health.

We rely on a predictable process. We want strong standards, but they need to be reasonable standards so that we can invest in new products. Without an assurance that the agency is operating in a predictable,

transparent fashion, the industry is going to be hard-pressed to invest new monies into new products that may, in fact, benefit resistance in the long run.

Now, this qualitative risk assessment process has been described to you this morning, and it's really to determine the risk to human health. I want to talk this morning just talk about the categorization issue. I know there are a lot of questions that came up with regard to the release and consequence assessment, but maybe others can speak to that. I'd really like to focus on the categorization issue.

As Dr. Tollefson and Mary Beth Bartholomew mentioned, food-borne zoonotic infections are considered the most likely route of transmission driving this risk-assessment process, and we certainly agree with that. However, we are concerned that there is a reference to commensal organisms, commensal enteric bacteria in the animal, transferring resistance to non-commensal bacteria, which is driving a lot of the concern about the impact on human health. I will be addressing that later.

Most of the drugs in Appendix A are ranked as of high importance based on meeting one or more of 10 different criteria, as has been discussed with you. We feel that most of the criteria don't have a lot to do with how drugs are used in animals or the infections

veterinarians are treating. For example, macrolides are rated as high because of their usefulness in treating Legionella, but Legionella to my knowledge is not a zoonotic pathogen. I'm hard-pressed to find a connection between animal use and Legionella.

So that's the concern we have, and it was mentioned that the categorization was done irrespective of its connection with animals. I hope to present some information to you to put that in context.

If, in fact, this risk assessment process goes forward and many drugs are categorized in the high risk category, as has been described to you, because of concerns for its importance to human health, which will drive a lot of that final ranking, then this could really mean very few if no new animal drug approvals, and we think that's going to be a detriment to veterinary medicine.

What is our concern? Well, the underlying assumption by the agency appears to be that there is resistance gene transfer between commensals and non-enteric bacteria. Certainly we have no argument, or little argument with the fact that food-borne transmission of zoonotic pathogens such as Salmonella and Campylobacter and possibly E. coli are a concern, but this commensal to non-commensal transfer we find difficult to understand because we know of no documented in vivo evidence. There certainly

have been in vitro studies showing that you can transfer resistance genes, but in vivo we don't know of any.

In fact, there are two studies that I would reference here, one that attempted to colonize humans with Enterococcus faecium, and that a was very transient colonization, about 2 weeks in duration, and they fed very high doses of Enterococcus faecium, somewhere in the range of 10 to the fifth to 10 to the sixth organisms, and they really did not get permanent colonization of that.

Also there's a study in the literature that shows the reverse, taking human pathogens and trying to colonize animals was not successful. So it's questionable whether there is actually in vivo resistance transfer.

We do believe that the majority of infections that are critical for antimicrobial treatments in humans aren't going to be jeopardized by animal use, and we want to put this in context. The ranking of importance, therefore, should factor in whether there is real evidence of an animal connection and not just theoretical evidence. We can't operate on theory. We need to operate on evidence.

The Appendix A ranking, therefore, is double jeopardy for our companies. One, it is the sole criteria for the consequence assessment portion. If the drug is considered important in human medicine, it will drive the

approval for new products. It also will drive the evaluation of currently approved antibiotics. So both existing products and new approvals will be jeopardized by how Appendix A finally comes out.

I'd like to present three pieces of information. I don't want to call them evidence because they're really opinion surveys, if you will, in some cases. But there are three pieces of evidence that I hope puts this whole issue of animal use of antibiotics and human health in context.

The first is a study published in the Journal of Antimicrobial Chemotherapy in 2000 by Bywater and Casewell, assessment of the impact of antibiotic resistance. What they did is they went out and surveyed practicing physicians and microbiologists in the UK and other countries, some in the U.S., on major human antibiotic resistance problems. They developed a seminar. They designed a list of organisms or developed a list of organisms that they thought were the major contributors to resistance. And then they sent this questionnaire out to a number of experts in the field. They originally tried to get 25 or 26 experts. They ended up getting 16 replies.

They asked what was the burden of ill health resulting from this bacterial species in a ranking of 1, negligible, to 5, major. What is the impact of resistance

on treatment choices? Again, 1, rare, to 5, resistance is common. And what they thought the contribution of animal sources to human resistance for all the particular species they were looking at, 0 being of no consequence and 5 being the main source.

The bacteria in the survey are listed here, things like methicillin-resistant staph, Mycobacterium tuberculosis, on down to some of the food-borne pathogens such as Salmonella and E. coli.

So what they first came up with is the contribution of individual species to the total resistance problems in humans. I don't think it would surprise any of these committee members to note that MRSA is sort of the leading candidate for resistance problems in humans. And on down the list we have Pseudomonas aeruginosa, Klebsiella. And then down towards the right-hand side of this scale we have non-typhi Salmonella, Campylobacter, E. coli 0157 of a lower importance to the contribution of resistance.

Then when you overlay this on their estimation of what animal source might be contributing to these, as you can see, down in the areas of Enterobacter, Salmonella clearly, Salmonella non-typhi, Campylobacter, there is some contribution that clearly was felt to be due to animal sources, but overall a fairly low percentage of

contribution.

So the analysis of this questionnaire, certainly this was to my knowledge the first time that the relative impact of individual organisms was quantified. Clearly MRSA is the biggest problem. The opinion of these experts was that animal sources were resulting in less than 5 percent of the total human resistance problems, and furthermore, the enterococcus, the growth promoter link, which has been the big issue particularly in Europe over the last 5 or 10 years, was less than 1 percent contributing to antibiotic resistance problems in humans. So for what it's worth, that's one study that was published.

I'd like to cite another source of information, a 1999 European Union Scientific Steering Committee. These sets of slides come to me by way of Dr. Herman Goosen, who is a physician in the Netherlands, who was part of the steering committee in Europe. I'll briefly run over this just to give you a context for what the steering committee looked at.

They were charged with evaluating the current position regarding the prevalence of resistance. They examined the implications of human and animal health, and they looked at factors contributing to the present situation. They also looked at ways they could influence

or control resistance. They made recommendations, and they advised on monitoring of the outcome of measures and considered the implication of the advice.

They looked at a range of bacteria. Mainly they focused on the enteric food-borne bacteria, enterococci, E. coli, Salmonella, Campylobacter, the common food-borne organisms. They also looked at other bacteria. They also looked at a range of uses for animal drugs in food-producing animals, such as the growth promoter, performance-enhancing use, the prophylactic use, drugs that are used to prevent or control disease that might occur, or that are occurring. And then finally the true therapeutic use when animals are clinically ill and there's a need for high-dose, short-term treatment.

They looked at a range of antibacterial feed additives of concern, and I think the important thing in this slide is that there are many, many of these drugs that are used in the feed of animals that really don't have any analog to human health. Clearly there are some. A number of these drugs were removed from the market in Europe, not on the basis of good science but on the basis that they were concerned about the potential effects in animals, but in fact many of the drugs that are used in animal feed don't have a clear connection to any real human health care product.

The important part of their discussion also looked at infections in humans, and they looked at the same kinds of bacteria that the Bywater-Casewell study examined -- staphylococcus, Citrobacter, Pseudomonas, staph, strep, Salmonella -- and they looked at evidence for a link with antibiotic use in animals. The important thing with this slide, which agrees with the previous survey, is that at least for vancomycin and enterococci they saw some link. Clearly for Salmonella and Campylobacter with the fluoroquinolones there was potential link. But for most of the other bacteria there was really little evidence that there was a connection between animal use and human health.

The same thing with hospital-acquired infections. Clear evidence for antibiotic use and resistance problems with these bacteria, but again, enterococcus, vancomycin possibly was the only one that might be linked with a human health problem.

To round it out, the human community-acquired infections, the same kind of situation where Salmonella and Campylobacter, maybe fluoroquinolones had some connection, but not too much of a connection with the others.

The third piece of information I'd like to provide to you comes to me by way of Dr. Ron Jones, who runs the SENTRY program. Many of you, I'm sure, are familiar with it. This is a program that was established

in 1997, funded by SmithKline Glaxo. It looks at antibiotic resistance patterns around the world from a number of pathogens. It's a very large database, collects thousands of clinical isolates in a statistically designed fashion, and it has international networks of sentinel hospitals which supply isolates to the SENTRY program for both nosocomial and community-acquired infections.

This is a chart Dr. Jones developed in consultation with us. He looked at the risk of animal pathogens occurring in human medicine and he looked at them by pathogen, by infection type, and he first classified them in three categories. One, respiratory tract infections, both community-acquired and hospital, skin and soft tissue infections, and urinary tract infections.

In his estimation these are the main contributors to respiratory tract infections in humans, and he believes that 75 percent of all prescribed antibiotics go for those particular infections. Skin and soft tissue infections, Staph. aureus, Pseudomonas, E. coli, and enterococcus are contributors to those problems, and urinary tract infections, E. coli and enterococcus.

In his estimation the animal-related risk, none of these respiratory tract pathogens have any animal-related risk or any evidence that we know of that there's a connection between animal use and these pathogens. Only

with regard to enterococci with these other infections is there a possible connection, and that's not clear what the connection is. But clearly enterococcus has been linked to some degree with animal use. But clearly the majority of these infections in his estimation don't have a lot to do with animal use.

I also included a paper -- I hope that it was made available to the committee -- called "Contemporary Patterns of Antibiotic Resistance in Humans" that Dr. Jones prepared this fall for us. I think that should be in your package.

The references supporting that previous slide are listed here. You have those. If you want to look up those references, they are all SENTRY program references.

So what does this all mean and why did I present all this data? Well, we certainly believe that antibiotics are important to human health and food safety and we don't want to do anything that would limit the ability of veterinarians to continue to be able to treat our food supply. It is very important obviously to human health that our food supply remains safe.

Veterinarians do need a wide variety of products, as do physicians, to combat bacterial disease and reduce selection pressures on existing antibacterials.

We don't believe -- it is our opinion that the

vast majority of antimicrobial use in food animals will have much consequence to human health, and we certainly support the FDA assessing that and trying to do that in a realistic and as scientifically accurate as possible.

We need to stimulate research and development so that safer and more effective antimicrobials can be put on the market. Therefore, we need a rational approach to assessing the risk.

Current ranking criteria in Appendix A, we believe, will tend to over-estimate the risk to human health, and we think that the current way drugs are ranked and categorized is important to human health. It will certainly push many, many animal drugs, as you heard before, into the high- or medium-risk category, which will in fact prevent many of those drugs from being approved or will greatly restrict their uses.

So we believe that absent evidence of an actual connection between antimicrobial use in animals and non-enteric human disease, as I've talked about here, only those antimicrobials that are really important for treating food-borne disease should carry a high risk ranking. So we would appreciate this committee taking this information into consideration in their advising the agencies on how to proceed in developing this document.

I do appreciate your time this morning. I'll

try to answer any questions that you may have. Thank you.

DR. LEGGETT: Thank you.

Are there any questions? Dr. Maxwell.

DR. MAXWELL: I just have a question on your next-to-last slide, the one that says risk of animal pathogens occurring in human medicine. It lists E. coli as possibly having a related risk.

DR. CARNEVALE: You're talking about this slide?

DR. MAXWELL: Yes.

DR. CARNEVALE: Actually you probably can't see it on the slide. There's an asterisk right there, which says possible. The way he prepared this slide, it is a bit misleading. It looks like all these organisms have a possible link, but really what he has done is put an asterisk next to enterococci. I don't believe he feels that there is a connection between E. coli skin and soft tissue infections and animal use.

DR. MAXWELL: Okay.

DR. CARNEVALE: I know it's a little confusing on the slide, but if you look at the asterisk you'll see.

DR. LEGGETT: Dr. Wald.

DR. WALD: The chart entitled Antibacterial Feed Additives of Concern on page 13, is that a pretty comprehensive list of all the current antimicrobials that

would be found in feeds? And are those the same that might be used for growth promotion?

DR. CARNEVALE: I would say that is a relatively comprehensive list. I can't guarantee that every single one is on there, but it's relatively comprehensive, yes.

DR. WALD: I guess I'm asking, are there important ones that aren't on there?

DR. CARNEVALE: Well, offhand I don't see any.

DR. TOLLEFSON: I don't see any that aren't on there. I would point out that it includes Monensin. It includes some what we wouldn't consider an antimicrobial. They are used for growth promoting. Those are approved for use in growth promotion.

DR. CARNEVALE: Right. And things like Monensin and olaquindox and Salinomycin are mainly anticoccidial compounds. They're mainly used for coccidiosis, although they are technically classified as antimicrobials. They don't have any, to our knowledge, use in human medicine and don't have any cross-resistance selection pressure. But they are used in some cases for growth promotion. For example, Monensin is used for growth promotion in cattle.

DR. LEGGETT: Dr. Bell.

DR. BELL: With reference to the SENTRY

methodology, I'm trying to remember that methodology, but I am inclined to take issue with your statement that this is statistically designed. It's certainly not population-based. It relies on a group of sentinel hospitals that sort of agree to participate. And I believe that the isolates virtually always come from that hospital laboratory, which means that it's going to be mostly, if not almost all, hospitalized patients. So a lot of these pathogens cause community-acquired infections and I think would not be captured necessarily, and certainly not proportionately so in the SENTRY database.

DR. LEGGETT: Dr. Patterson.

DR. PATTERSON: As a clinician, of course, with the perspective of human health and someone who's been interested in both hospital and community antibiotic resistance for some time, I just had some observations from the presentation that I think could be misleading.

One is from the slides on page 6, where you make the case that there's no evidence of resistance gene transfer between animal organisms and human organisms. While that may be true that the particular gene hasn't been documented to be transferred, there are clearly a number of instances where there have been well-documented outbreaks of actual organisms going from food from animals to humans, not the least of which includes Salmonella and hemorrhagic

E. coli. So I think that is sort of missing a point.

Then on page 9, you have the slides there, those two graphs. You make the case that food-borne pathogens like Salmonella, hemorrhagic E. coli and Campylobacter -- resistance in these organisms are of lower importance in the overall picture of resistance. However, these are of the most importance in terms of food-borne concerns of resistance, which is what we're here to talk about today. I think in the context of that, that the potential impact for prevention in a setting where we can do something about resistance in food-borne pathogens makes them quite important for our discussion today.

Obviously, these other pathogens that you cite are primarily nosocomial, and we continue to work on infection control and antibiotic utilization programs in hospitals to control them, but in terms of food-borne pathogens, these are quite important for public health. I think it's somewhat irresponsible to state that they're not important.

Then on page 15, you have a slide indicating that E. coli/UTI being a primarily community-acquired infection, although it can be hospital-acquired also, that there is no link with animals in the slide, and that is in conflict with your slide on page 16, where in Ron Jones' opinion E. coli is linked with resistance in animals. I

think that that in fact is true, that the potential for emergence of resistance in E. coli with regard to urinary tract infections in humans is a concern, particularly now that there has been such an emergence of resistance in trim-sulfa, which was our previous drug of choice for UTI's, that the drug of choice now in most cases is fluoroquinolones, and we know that increase in fluoroquinolone use is, in fact, linked with increase in resistance. I think that is indeed a concern, and your slides there I think appear to be in conflict.

DR. LEGGETT: Dr. Bell.

DR. CARNEVALE: Can I address --

DR. LEGGETT: Yes, Dr. Carnevale.

DR. CARNEVALE: First of all, I didn't say that food-borne illness was not important. What we're trying to present here is in context with all the problems that occur in human medicine with regard to resistance and what the connection to animal use is. The current category or Appendix A categorization categorizes many drugs as very important to human medicine, but we fail to see a link between animal use.

Clearly food-borne pathogens, there is a link, zoonotic food-borne pathogens there is a link. There can be a link with animal use. That's the point I was trying to make, not that food-borne pathogens are not important.

Furthermore, I don't think Dr. Jones' opinion conflicts with the previous one. As I mentioned, if you look at the chart, and I'm sorry that it's a bit misleading but he did not believe that skin and soft tissue infections are due to E. coli or related animal use. Now the possible down there at the bottom is really starred, and he's got enterococci as possible.

DR. PATTERSON: Your slide on page 15, the top slide there says E. coli/UTI, fluoroquinolones, evidence for link with antibiotic use in animals, you have negative there in that column, and that appears to conflict. Yes, that slide right there.

DR. CARNEVALE: This is from the European Union. This is not my data. I didn't develop this. This is the European Union Steering Committee for Antibiotic Resistance that came up with this.

DR. PATTERSON: I'm just pointing out that it's in conflict with your slide on page 16.

DR. CARNEVALE: If it is, I apologize for that.

DR. LEGGETT: I think I'd just let it drop there.

Dr. Bell.

DR. BELL: Yes, I just wanted to bring up a couple of other things. For the E. coli, there actually is documentation of transfer of resistance determinants from

an antibiotic used in animal agriculture to strains causing urinary tract infections. This was in East Germany back in I think it was the 60s or 70s. There was a streptothricin class of antibiotics that were used only in animals, and it turned out that the resistance genes were spread and ended up in E. coli that actually was isolated from people with urinary tract infections. This class of drugs was only used in animals. So this is documented. It does happen.

It's certainly easy to understand because we're talking about gut flora, and you didn't, I don't believe, state the contrary, but I just wanted to add that this actually has been documented.

Also, many times bacteria that are pathogenic in humans are really only commensals in animals. Salmonella, for example, is not always, not necessarily pathogenic in animals, but can be in humans. The issue of enterococci, certainly they can be both commensals and pathogens in humans. I'm not sure if they're pathogens in animals. But it's noteworthy that we now have two documented cases in the United States of fully vancomycin-resistant Staph. aureus and the resistance gene, the resistance elements were transferred from enterococci that happened to be in a contiguous site.

DR. CARNEVALE: Vancomycin has never been used in animals. Not in the U.S.

DR. BELL: No, I understand, but yes, in parts of Europe. Vancomycin is not used in the U.S.

But the point I'm making is that a resistance determinant from enterococcus can transfer to Staph. aureus that is not necessarily in the gut. Now, in this particular case I'm not attributing the VRSA to any sort of animal drug use, but I'm just making the point that enterococci are present in gut flora in both animals and humans, and the vancomycin-resistant Staph. aureus that we've seen has acquired genetic material from enterococci. So the possibility has to be entertained that the drug-resistant element that is generated or spread through agricultural use could be transferred to humans and then transferred across to a Staphylococcus aureus in humans as well.

DR. CARNEVALE: Well, David, certainly no one is going to discount the possibility. But again, we need some real evidence for that happening in order for these companies to be regulated in appropriate fashion. You can't operate on the theoretical. Certainly these things are possible, but unless you have real evidence that there's a connection. If you raise theoretical concerns with every case, then you might as well not approve anything for animal use if there's a potential connection out there. So that's all we ask, is evidence.

DR. BELL: Obviously, this is a controversy that's been going on for decades.

And I think that my understanding of what the committee is being asked to address is, fortunately, a pretty narrow aspect here, which is the ranking of the antibiotics that are listed in terms of their importance in human medicine. I would just hold out that antibiotics that are viewed as critical in treating Staph. aureus, which is not normally food-borne infection, we do have to bear in mind that there is documented precedent for Staph. aureus to acquire resistance genes from bacteria that are essentially gut flora.

There are many factors that enter into this complicated FDA guidance that address the issues of how frequently, what would the connections be to the actual use on the farm, but the particular narrow aspect that we're looking at is should a drug for Staph. aureus be ranked very highly in this list that CDER gives to CVM.

We're going to have more discussion this afternoon.

DR. LEGGETT: Yes, let's go on to the next point. Dr. Bradley and then Dr. Rupp.

DR. BRADLEY: On page 6 of the handout, I just wanted to comment on the ranking of importance should factor in whether or not there's real evidence of an animal

connection. Dr. Tollefson's original presentation highlighted how complex this whole antibiotic resistance problem is, and it's very multi-factorial and certainly I don't think we're going to come up with a single solution to the problem today.

To say that there is no real evidence is not the same thing as to say that there's not a problem. In each situation I think if there's an investigation which shows that there's no problem then that certainly is the scientific evidence you're looking for. But until there's actually an investigation to look at, once an antibiotic is introduced into a herd, what is the actual risk that a resistance determinant will go into a human, I think one can't really say whether there's a problem or not.

So it appears as though we're dealing with a lack of information, and theoretical concerns about antibiotic resistance are very real, but I agree with you that we need further study in order to show whether those theoretical concerns are actually important or not.

DR. CARNEVALE: That's been the problem. It's been very, very hard to design such studies. That's been the difficulty.

DR. LEGGETT: Dr. Rupp.

DR. RUPP: I guess I would just voice agreement with the previous two comments, and I think that overall

your presentation seemed to try to place these organisms and conditions in a very static manner, particularly that last material on classifying things as hospital-acquired, community-acquired organisms put into these silos. I think it's a very, very dynamic process. We're seeing this all the time in human medicine, the crossover between community-acquired, hospital-acquired. I think there is good evidence to suggest that antibiotic resistance traits do transfer from pathogens to commensals. I think there is good evidence to suggest that these organisms, particularly food-borne organisms, get from animals into people and I think it's a major concern.

DR. LEGGETT: Dr. Carnevale, a couple of points. I think what you're hearing in sort of your statement that you wanted scientific evidence, the committee is sort of raising their hackles a little bit in that I think the sense is that the data that you tried to use didn't really seem to be all that scientifically neutral. It was sort of a pick and choose, as in sort of a survey in the JEC, and then the use of the SENTRY data, which is not population-based, as Dr. Bell.

And in the chart, for instance, on page 16, where Dr. Jones comes up with a list of skin and soft tissue infections where he put Staph. aureus first and Pseudomonas aeruginosa second. Come on. It's group A

strep that's 90 percent. Staph. aureus is maybe 10 percent, and all the other things don't even exist. And in that slide there's nothing about GI infections, which is the major cause, as you mentioned.

So it would be nice for us, I agree, to come up with some data. It would be also nice, in terms of coming up with our program, to get some input from both AHI and the CVM about what do we know about which pathogens are in animals that didn't move to people.

While we state that food-borne illness is the only transmission, we also -- off the top of my head right now, Rhodococcus equi from horses, we didn't know about it until we got AIDS. So there's lots of things that we don't know that we may find out.

I think the committee is taking the standpoint of if there's a risk, let's think about that as opposed to when the cat's already out of the bag, the horse out of the barn, or whatever the heck it is. So look at all the things we're doing about smallpox, which doesn't even exist in the world. So I think that's why you sense some of us bristling.

But I think your point is well taken that we should certainly think of those pathogens from animals that are of the main consequence to humans. I think everybody would agree with that point. It's just how do we come up

with refining that list of the things we really want to concentrate on.

If there are no further questions, I thank you very much for your presentation.

DR. CARNEVALE: Yes. Well, that was my point, thank you. And hopefully Dr. Apley can add some further context to this discussion after the break. Thank you.

DR. LEGGETT: Thank you.

So why don't we take a break a little bit early and come back at 11:00 o'clock.

(Recess.)

DR. LEGGETT: If we could please reconvene.

Our next speaker will be Dr. Mike Apley, who will talk to us about relating food, animal, and human antimicrobial use. Dr. Apley.

DR. APLEY: Thank you. Well, good morning. On behalf of the American Veterinary Medical Association, I would like to thank the committee for the opportunity to speak with you this morning.

And in the hope of stimulating some questions and discussion after my brief presentation, I'd like to give a little bit of my background. I've been a general practitioner in central Kansas, spent four years as a feed lot practitioner on the high plains, and since then I've been teaching antimicrobial clinical pharmacology and beef

production medicine at Iowa State University.

On the comments on day care and feed lots, as a father of a past child care child and now two in grade school, I've often commented on the similarities also, and I think we could get together and work out a mutual model type deal.

(Laughter.)

DR. APLEY: The difference is in the feed lot the outbreaks occur about two to three weeks after the stress of shipment, and in the day care it's just the stress of Easter, Christmas, and Thanksgiving, I think.

(Laughter.)

DR. APLEY: Another big difference is when they start to break, we round them up and re-vaccinate them. So I have often looked at that.

(Laughter.)

DR. APLEY: Another question was on looking at some of these pathogens, rate of transfer, spread, around for example a feed lot, there's been a lot of work done on that, especially for pathogens that affect our animals, the ones we're very, very concerned about treating. For example, in feed lots we look at some of the respiratory disease cases, et cetera. A lot of the ones that would involve the zoonotic pathogens such as Salmonella or indicator organisms such as E. coli have been like a cross-

sectional single time study with looking at prevalence more than actual spread within the operation.

There was an epidemiological investigation, getting to be 8 or 10 years ago now in the Pacific Northwest that dealt with Salmonella that was being found in some cattle in a feed lot, and they traced it back to our central, what we call the hospital facility. That was stopped by applying hygiene principles.

So to go back to our topic of choice this morning. The AVMA has presented written and public comments concerning the guidance for industry No. 152. This morning in the context of this discussion, we'll concentrate on the ranking process.

The AVMA does have a significant concern with the ranking of these drugs as it now stands. There are some reasons why the AVMA has some concerns, and one of them is that we do rely on preventive and therapeutic strategies to maintain the health of food animals. Within these strategies, antimicrobials are essential for addressing disease in food animals in order to relieve animal suffering and conserve livestock resources. In our oath veterinarians pledge to be responsible for both animal and human health, and we believe that healthy animals are the basis for a healthy food supply.

The point of my presentation here this morning

is that we feel we need to be very careful that we don't bias the decision process so heavily towards protecting any potential theoretical effects on human health that we remove vital tools for protecting human health through maintaining animal health. I think that would be a reasonable agreement for most in the room and what it comes down to as we start talking about some of the details and where the break is from a problem to no problem.

The antimicrobial ranking section of Guidance 152 is especially critical. The hazard identification that's mentioned in there, it's not near as critical, of course, as the consequence assessment, which has been very nicely discussed in previous presentations.

Guidance 152 does have multiple required input categories that must be categorized as being of low, medium, or high risk, and for many of the primary categories there's really no defined method to determine that degree of risk. An example is mechanism spectrum, pharmacokinetics, dynamics, resistance mechanisms, et cetera. The criteria for calling them low, medium or high is really not there, so you tend to go towards a more conservative approach. We feel that by some of the methods that are being used to put some of these antimicrobials in a high ranking might further bring about this potential to have an overly conservative approach.

Within each one of these, and going along that conservative approach, if the FDA determines there is inadequate information, then the most conservative assessment of high risk is assigned. Now, this next statement, I'm not implying that this was the CVM's intent in any way, but we do feel it is an outcome of some sections of the document that if we do not have the evidence to argue that, hey, this is low rather than medium, or medium rather than high, then we end up going to the more conservative or higher approach, which gets to the issue of proving there's not a problem or proving that there is.

We realize the concern that nothing be let slip through, that a potential problem not be missed, but on the other hand, we ask that the committee consider that by going too far to the side of saying there is a potential problem, let's really err on the side of conservative, that the potential adverse effect of that is to take away a valuable tool for use in veterinary medicine.

The context within which these drugs should be ranked is defined or we feel they should be ranked as defined in Guidance 152. For example, in the hazard definition "is attributable to a specified animal-derived food commodity," and again, in the risk definition "is attributable to a specified animal-derived food commodity."

There has been discussion today on just how hard it is to say exactly probably what attributable means. How many steps removed from a potential resistance genetic transfer do you need to be? That's really one of the issues.

So they're related. Food, animal, and human antimicrobial use in this document are related through a specified animal-derived food commodity. So we believe that the antimicrobial drug rankings in this guidance document should consider only those bacteria or resistance determinants that are food-borne.

In other words, antimicrobial drug rankings justified on the importance for treatment of other than food-borne bacterial disease or disease involving food-borne resistance determinants should not be included as part of the final outcome determination in this document.

Now, what we would ask for is justification, and I look back at this and that's probably a more combative word than I wanted to use, but justification of antimicrobial rankings based on the following disease organism combinations in a document intended to address resistance relationships through food-borne channels. Our goal in asking for this is to be able to evaluate and understand the reasons for each ranking and then to be able to comment on what the degree of evidence is or potential links that may exist as specified for reasons for ranking.

So these are examples of some of the ones that you can read in the slides, rather than me go through them, that were either mentioned at the public meeting or come out of Guidance 152. Again, we are not saying that you are incorrectly ranking these for importance in human medicine. That's not our intention at all, but rather we're asking what could be the potential outcome on the final classification of this guidance document by using these types of applications to come up with the ranking of the antimicrobial drug for use in the consequence assessment. So these are in your slides and ones that we'd be interested in discussing and seeing comments on. Are these related to a food-borne context?

As it stands right now, the guidance document does not provide specific disease justifications for the rankings of each drug. There are examples given in the document. We would be very interested in seeing these actually linked to the drugs so we could evaluate those, and there is a degree of subjectivity in them. I think that's why it's really important that the ability to comment on them be given.

An example of one of the antimicrobial situations we would have questions about, which was discussed at the public meeting, is the ranking of the natural penicillins is high. And what this would do is say

that in the first two sections of the document you were to have low and low, the consequence assessment ranking of penicillin G is high would move this up into the medium category and puts us into a whole other set of situations.

The AVMA recognizes and supports the need to preserve human health and our part in that. We also have an obligation to do everything we can to make sure we have the tools available to protect and address animal health. We feel that by taking this document to the direction that the consequence section is based on food-borne, either pathogen or resistance determinant, links that we would better serve the interests of both parties.

With that, I would conclude my comments and be open for questions or comments from the committee.

DR. LEGGETT: Are there any immediate comments?

Just in terms of examples, when I read the guidance document, I thought those were just examples, not that they were supposed to be set in stone. So I may have misunderstood. It seems you also interpreted those as set in stone, but I read them as examples.

I certainly personally agree that rankings need to be justified scientifically and in a transparent fashion.

You mentioned penicillin and neurosyphilis. It doesn't take me long to go from penicillin in animal feed

in the United States to potential emergence of resistance. That doesn't seem to be too many links apart. Can you explain, first of all, how penicillin is used currently? Is it therapeutically used in animals or also as growth promoters? And how that wouldn't have an impact on human illness.

DR. APLEY: I'm aware of one growth promotion claim for penicillin G, could not speak to the extent of use of that. Therapeutically it's very important to us for treatment of diseases. It's got a label for respiratory disease. The problem with the label of procaine penicillin G is that the labeled dose is ineffective, so we then go within the constraints of the Animal Medicinal Drug Use Clarification Act and use it in extra-label fashion. And we get withdrawal information from Food Animal Residue Avoidance Data Bank for that use.

It's used in cattle for indications such as infectious pododermatitis, or foot rot, therapy of some types of pneumonia. It's important in swine for some respiratory --

DR. LEGGETT: Right. What I'm saying is, penicillin is mostly used therapeutically. I don't think the committee -- at least my interpretation of the way things are going -- that's not where the concern is. The concern is the huge numbers. The way that we think of

emergence of resistance is, for instance, in an intensive care unit where you've got the sickest patients, just like the sickest animals, and you put them all together and then they have a very high pressure to develop resistance. The other way you do it is you give a little bit to a sea of people, so the population part of it brings up your resistance.

I think that my concern in trying to come up with these rankings that we're going to try this afternoon to sort of get our fingers around, is how do you attack the problem as we know it in terms of the processes of the emergence of resistance. So I think everybody's goal is to come up with something that everybody can understand.

Dr. Rupp.

DR. RUPP: I guess I would just again point out this is a very dynamic process, and it's extremely difficult to predict the potential significance of an agent sometimes now based upon what's going to happen. I guess the best example of that would be the situation currently with virginiamycin. Ten years ago nobody cared that virginiamycin could have been used in animal use or animal feeds. Now we have a huge degree of cross-resistance of enterococci with a therapeutic agent, Synercid, that was not developed and there was no need for it at that time. That's clearly use of antibiotics in animals that is now

influencing human disease. Nobody would have been able to know about this a few years back.

DR. APLEY: I recognize and respect your concern about that. I think the other side of that, in my view, is where we draw the line in pursuing those concerns. I messed around with applications one day, and if you start thinking if you can name one organism that perhaps has a cassette carrying four different ones, or if you think about potential class cross-resistance, or you think about potential uses, you could come up with reasonable possible problems with almost any compound. The question is how far you go in requiring some level of evidence to establish that that's a likelihood.

And again, we're not saying let's just go on with no consideration for human health. What we're saying is we need to go back and forth on the criteria that are being used, so we can strike a ground where we retain the ability to address therapeutic concerns in our patients and you do also.

DR. LEGGETT: Dr. Brown?

DR. BROWN: I think some of us in human health feel like we're in a quagmire of ignorance because we don't know the relative importance of the use of these antibiotics in feed lots versus the amount of drug which is used in therapy, versus the amount of drug which is used

for human use. Could somebody give us that perspective in some order of magnitude?

DR. APLEY: I can speak to the feed lot aspect. Are you talking about drugs that would be labeled for therapeutic or growth promotion purposes?

DR. BROWN: I don't think we have a good feel for either volume or which drugs are used largely in feed lots. So I think we're sort of ignorant right now.

DR. APLEY: The volume comes to be quite a contentious issue. I believe -- Dr. Tollefson, I'll put you on the spot -- that there are regulatory processes, or in development, to address reporting to that?

DR. TOLLEFSON: Amount used is a problem. Essentially we don't know. But let me answer the question in a different way.

Many of the drugs are approved for subtherapeutic or growth promotion use as well as therapeutic. So the example of penicillin, we have a number of approvals for growth promotion use of penicillin. Many of these are also in combination with other growth promoters.

It very much varies by species also. Feed lot cattle are not going to be seeing a lot of growth promoters. There are non-antimicrobial drugs like hormones and so on that can be used.

The issue of amount. There are more of the penicillin, tetracyclines, virginiamycin type of drugs, growth promoters, used for growth promotion simply because of the number of animals and the length of time that they are administered. So the therapeutic use is going to be naturally much smaller.

There have been some estimates. One group of estimates is something done by the Animal Health Institute, where they surveyed their members and were given rough estimates anyway. I don't know if Rich could speak to that.

But I don't think the amounts are going to mean anything to you other than the fact that it's a big number. There are a lot of animals. We slaughter, what, some 9 billion chickens a year. They live 42 days. So they're all getting fed growth promoters, virginiamycin primarily in that case.

DR. LEGGETT: Basically what we're trying to say is that for us to have the maximum valid input this afternoon in discussion, it would help us a lot to put this in context, if not at this meeting, certainly before the next meeting. We have to come up, I think, as I stated earlier, with a more mathematically tenable and testable hypothesis or way of getting about this model.

DR. TOLLEFSON: One thing that I elected not to

show in my presentation is Table 4 in the guidance document, which addresses use, limitations on use, and how we came about assigning risk categories to that issue.

DR. LEGGETT: Page 25.

DR. TOLLEFSON: Page 25, Table 4. When we speak to the extreme right column, flocks or herd of animals, this is where all the animals in any kind of a confinement facility are getting treated with that drug. So it would be all chickens in a house. Not all chickens in a flock. They're divided up into houses, but it could be 30,000 birds, up to about 100,000, I think. It would also be maybe all swine within one building.

See, part of the problem is it varies very much by the kind of production unit it is. It could be 500, it could be 1,000, it could be any number I think.

Then we had the duration of use in combination with that, to get at the question of what are the animals seeing, selected for pressure.

DR. LEGGETT: As an example or follow-up, can you tell us what of these antibacterial food additives that Dr. Carnevale talked to us about would be typically used in chickens and would be typically used in swine?

DR. TOLLEFSON: The antimicrobials that Dr. Carnevale talked about?

DR. LEGGETT: On page 13, he talked about the

antibacterial food additives. Then you talked about table 4, and you had this category of high where flocks or herds or animals were used. And I just want you to fill out the example for us.

DR. TOLLEFSON: Got you, okay. For example, carbadox is -- I wouldn't consider that. Erythromycin is the first one. Avoparcin is not approved. The erythromycin is the first one. That's almost exclusively used in swine as Tylosin as a growth promoter. Yes, feed lots to a certain extent.

DR. LEGGETT: How about lincomycin?

DR. TOLLEFSON: Lincomycin is a swine drug. And poultry too?

DR. LEGGETT: As growth promoters? No?

DR. CARNEVALE: No, mostly therapeutic.

DR. TOLLEFSON: Yes. That's mostly therapeutic.

Penicillin is approved in all classes of animals for all uses -- growth promotion, prophylactic, therapy. In general, the old drugs, penicillin, tetracyclines, sulfa drugs are approved for everything.

DR. APLEY: Yes. I think just in cattle there wouldn't be a growth promotion penicillin.

DR. TOLLEFSON: No. That's an injectable.

DR. APLEY: Poultry and swine.

DR. TOLLEFSON: Right.

DR. WALD: Which one of those is a sulfa drug?

DR. TOLLEFSON: Oh, I'm sorry. Sulfa drugs are used in combination in growth promotion. Sulfa methazine -- anybody from 157 here? Sulfa methiazole.

DR. WALD: So it's not on this list?

DR. TOLLEFSON: No, you're right, it's not. There is no single sulfa drug used as a growth promotion. Correct? I don't think so. So they use it in two- and three-way combinations.

I think the point is that the way we tried to address the issue was through table 4, and then if you look at the risk management table, that's strictly limited to category 3. Growth promotion uses would only be available on category 3, the least category of concern.

DR. LEGGETT: Dr. Wald.

DR. WALD: Yes, I think it's easy for us to agree that healthy animals are the basis for a healthy food supply, and to be sympathetic about the use of antimicrobials for either treatment or even prophylaxis when there is illness in some of the animals in a herd.

I guess for me the big question would be as growth promotion, and I'm sure that this is a controversial issue. But there must be areas in the world where these things are not added to the food that animals eat. And I

wonder what are the data that they are essential for growth promotion, and could we hear some discussion of that.

DR. LEGGETT: Do you want to try in 30 seconds or less?

(Laughter.)

DR. APLEY: That's one that I'm surely not the resident expert on. There may be some others later who would be willing to comment. A lot of that goes around the Danish experience or what's gone on in that area of the world with withdrawal of these. The key thing that rests in my mind is the total amount has gone down due to removal of those products. We've seen therapeutic use go up.

Let's say that is a two-hour deal. It would be something that if this committee would be interested in, there would be the availability of having someone come and present on that because, as usual, there's data that can be interpreted in several ways.

DR. TOLLEFSON: Yes. We have a fair amount of data on that. What tended to happen -- and I've got to say from a personal point of view I thought the way the European Union handled the issue was a little draconian, in that they just removed them. So they did find animal health problems in the use of therapeutic antimicrobials rose.

When all the dust settled over a period of

time, the Danes and the Swedes are getting along pretty well. They have some problems with predictable areas, like weanling pigs. When the baby pig is removed from the sow and put into the first growth phase, that's still an issue. They do have disease rates that they need to treat with therapeutic drugs, and for a relatively short period of time. But they do need to use antimicrobials. I think the experience has shown that you can't raise animals without antimicrobials. In general you can't.

DR. LEGGETT: Dr. Poretz.

DR. PORETZ: Although we occasionally see advertisements for hormone-free and antibiotic-free animals in the food stores, what percentage of chickens and what percentages of cattle, swine that are sold commercially are given antimicrobials of any type?

DR. TOLLEFSON: Most of them. Antibiotic-free animals are antibiotic-free. The companies raise the animals, and if they need antimicrobial treatment for health reasons, they'll divert them to regular commercial channels. Hormones are only given to cattle, pretty much in this country. Poultry don't have hormones at all, but they do have growth promoters. So pretty much all animals see antimicrobials -- that's true -- at some point in their life.

DR. LEGGETT: Dr. Maxwell.

DR. MAXWELL: I don't see it on the list, but I just wondered, are any quinolones used for growth promotion?

DR. LEGGETT: Absolutely not. It's approved. There are very limited approvals. There are approvals in poultry. All are therapeutic and under veterinary prescription. The poultry one is highlighted because the FDA has decided to go through the process of removing that approval. Yes, we are in the middle of the process of doing that, and it's long and involved.

There are also therapeutic fluoroquinolones for use in cattle and in swine, and those are both injectable.

DR. APLEY: No, there's not one for swine. A fluoroquinolone isn't.

DR. TOLLEFSON: Just approved.

DR. APLEY: Oh, okay. I didn't read that one. The two for cattle are respiratory disease only.

DR. TOLLEFSON: Oh, the other one's a Bayer product and another one for cattle. I'm sorry. Yes, that's right.

DR. APLEY: Yes, okay. That was a new one to me. There's danofloxacin and enrofloxacin. They're approved only for use in bovine respiratory disease and any extra-label use is prohibited.

DR. MAXWELL: I just had an additional

question. I don't know anything about it, but I know that I have heard that some people access animal drugs for human consumption. Do you have any comment on that?

DR. APLEY: The one that made the news recently was individuals going into pet stores and acquiring them through that. If that does occur in the veterinary chain, it would surely not be intentional. They're controlled and dispensed for animal use. But that was going in and buying aquarium caplets and using them as an example.

We had the question about how are drugs used in the production setting. I could give you a two- or three-minute rundown of exactly how you'd see it in a feed lot, how they're used, if that would interest you.

DR. LEGGETT: Yes, I think so.

DR. APLEY: What we do is on arrival the animals are processed, put into pens. There are compounds that may be used in the feed. One of the ionophores is very typically used in cattle, and that would include Monensin and Lasalocid. They're used as a coccidiostat and used as a performance enhancer, altering rumen flora. Tylosin may be used as a liver abscess preventive.

There was an article in the New York Times about the --

DR. BELL: That's a macrolide.

DR. APLEY: That's a macrolide, a macrolide not

used in human medicine, but it is a macrolide.

DR. BELL: In case everybody didn't necessarily know that Tylosin was a macrolide, I just wanted to mention that.

DR. APLEY: There was a New York Times article about the vats of hormones that were put in the feed. We don't put any hormones in the feed. If they are given a growth promoting hormone, it's an in-ear implant.

For animals that display signs of respiratory disease, we have labeled products that include the two fluoroquinolones discussed. We have a macrolide in erythromycin, Tylosin. Tilmicosin is a macrolide labeled for respiratory disease. We have a third generation cephalosporin, Ceftiafur, which is labeled for the use in respiratory disease and in foot rot, infectious pododermatitis. We also have a thiamphenocol derivative, florfenicol, which is approved for that.

Of those drugs, we have two of them that are also labeled for -- we use the term "metaphylaxis" -- high-risk animals on arrival that are considered to be in the early stages of respiratory disease, and that is the case in feed lots, where we may apply a drug in an injectable format to the entire group of cattle, a pen of cattle coming in, or a load.

Then we also have other drugs approved for

respiratory disease. We have some sulfa dimethoxine, sulfa methazine. We have oxytetracycline.

In the feed we have oxytetracycline and chlortetracycline as individual agents, and then we have a combination tetracycline-sulfa agent that can be used in the feed for therapeutic prevention of respiratory disease. They have defined periods. I think they're all less than 14 days or so.

When animals are detected in the pen as having respiratory disease, which is about 70 percent of our morbidity and about 50 percent of our mortality, we usually -- respiratory disease case fatality rates will run 5 to 10 percent in highly stressed cattle down to 1 percent in cattle that are not. When they are identified, they are typically brought to a central treatment facility where they are treated. Some hospitals keep them there, some take them back.

I work with feed lots up to a 100,000-head capacity. That translates to about 21 miles of feed bunk in that facility. We had each animal individually identified with a tag, and they were entered into a treatment computer, and as a consultant I'd start my day there every day, when we came there twice a month, analyzing treatment response. We would perform necropsies on all the animals so we could go back and see what exactly

was happening.

So with the larger units and the progression of the industry, we're actually progressing towards tighter and tighter veterinary control of the therapeutic agents than we've ever had before. In this case we've got 100,000 head of cattle in a two-square mile area that each have their own individual identification number, and if they're treated, their response is tracked on computer.

DR. LEGGETT: A question. They're still in the herd when they're being treated? They're not sort of ostracized or isolated?

DR. APLEY: Yes. The problem is when you isolate them in what we call our hospital facility, then you mix cattle from different groups. That happens somewhat. Some facilities have gone so far as to treat them and quickly return them to the home pen so that they're not exposed to whatever others might have. This is a case where one of our biggest management procedures is preventing viral effects, bovine viral diarrhea, IVR, which is a herpes virus. And it's just like in human medicine. It hides out and comes back under stress. We try to address those in a lot of our successful programs. By addressing those viral etiologies, we drastically decrease their need for antimicrobials.

That in a nutshell is how we use it.

DR. LEGGETT: Could either Richard or you give us an example of, for instance, you say 50 percent of the mortality in cattle would be respiratory, so we could sort of think of those antibiotics that you're using there. What are the illnesses for which swine are most often treated therapeutically? What antibiotics would most likely be used, do you know?

DR. CARNEVALE: I'd prefer to turn to some folks in the audience who are swine specialists to answer that question. Paul?

DR. LEGGETT: Please identify yourself.

DR. SUNDBERG: I'll ask you to restate the question too.

I'm Dr. Paul Sundberg. I'm with the National Pork Board and I'm asked to be part of the open comments this afternoon as well, so maybe we can address some of those then. But again, specifically your question?

DR. LEGGETT: Trying to get a handle on what would be typical antibiotics used therapeutically for the major causes of mortality. Dr. Apley just said it's mostly respiratory, for which there would be fluoroquinolones and the sulfa things. What would be the correlate in swine?

DR. SUNDBERG: In pork production, there are really two times of primary risk for disease. One is as a neonate and a young animal. That's diarrhetic diseases.

Those are diarrheas. So you use those antimicrobials that would be effective on diarrhetic disease. It happens in the feed lot too, if I understand correctly.

As the animal gets older, then that risk from diarrhea transfers over to a risk of respiratory disease. So you see little diarrheas during the older stages of the animal's life and more of the respiratory disease and the antimicrobials that would be used for that.

For example, Tylosin, penicillin, tilmicosin. Those could be used for respiratory diseases in pigs. Chlortetracycline. The tetracyclines are used commonly, both for prevention and for treatment.

DR. LEGGETT: And in the diarrhea?

DR. SUNDBERG: For the diarrhea, it's Tylosin again. Some of the Gentacin, for example, is labeled for diarrhea in neonatal pigs.

DR. LEGGETT: Any cephalosporins?

DR. SUNDBERG: Not for diarrhea.

DR. LEGGETT: Thank you.

Dr. Maxwell.

DR. MAXWELL: Just a general question. What percentage of respiratory illness is of viral etiology?

DR. APLEY: This is an excellent question that we continue to ask for the final question -- actually in the bovine respiratory disease we call it the complex. We

think that viruses are a big part of setting it up. We treat animals with elevated temperatures, displaying signs of depression and appearing to be suffering or in danger of not making it if not treated. For those animals, when we do deep nasal swabs, et cetera, there are varying percentages who are able to recover something. I couldn't give you a good percent of how many are involved. There's a possibility that in a lot of the cases it was laying somewhere in there as one of the instigators, although there's a bacterial cause now.

And along that line, which I think the question is probably leading to, are there any ways of trying to avoid putting antimicrobials in animals that are just viral. One of the things we do is in the yards I've worked with is we institute what we call a non-eater treatment, and in that treatment the animal is identified in the pen as displaying signs of respiratory disease, being depressed, off feed, nasal-ocular discharge, et cetera. If, when they get to our hospital facility, we find that their temperature is not elevated to a sufficient amount and they've stopped displaying the signs of lethargy, et cetera, some places may revaccinate, some may give them some oral vitamins, some hydration but don't put an antimicrobial in. It's been very successful. We've found in those programs that our case fatality in the ones that

are just treated as an observe or a non-eater is actually less than the ones treated for true respiratory disease.

And that's one of the reasons we watch our case fatality so closely. If we get a case fatality of almost 0 percent, that tells us there are a lot of animals being treated that don't need to be, and we go back and change our treatment criteria.

DR. LEGGETT: Would you estimate that the number, the percentage of veterinarians who give antibiotics for viral illness is as high as it is among doctors who give antibiotics for viral illness?

(Laughter.)

DR. APLEY: I don't know how to answer that and win.

(Laughter.)

DR. APLEY: I will tell you that veterinarians are extremely concerned about this. I do a lot of continuing education, and one of the reasons is because I talk on antimicrobial resistance, prudent antimicrobial use, case definitions, and applying those in production settings. Veterinarians are very interested in that and there are two reasons. One is there's an obligation to animal and public health. The second is the profit margins for our clients are really narrow.

For example, on our feeder cattle, to use some

of those antimicrobials I talked about could take $15 to $20 per animal. Over the long haul, people would hope to make $15 or $20 per animal, over the long haul feeding those animals.

That's another reason is economically this -- in the New England Journal of Medicine, that editorial about we'd rather just lace them with antibiotics instead of applying management -- that's so wrong. That is so unbelievably wrong, not just because of our ethics and our obligations but because we can't afford to do that. The food animal sites, the food animal segments within the industry that think they can rely on antimicrobials to cover up management practices are not going to stay in business. We don't want to do it and we can't afford to do it.

DR. LEGGETT: Dr. Goldberger.

DR. GOLDBERGER: Could you talk a little bit about the current threat areas in terms of not having available or adequate therapy, the things that are driving the need for new antimicrobials in animals?

DR. APLEY: I think we're finding some of the same areas, and that there are some Gram-positives giving us some fights. We see some streps that are tough to deal with with the drugs we have available. We see enteric disease similar to you. Some of the enteric diseases that

are moving around in some of the neonates are very tough to treat and we've always focused on prevention and it brings a newer emphasis to it.

Some of the Gram-negatives, the enterobacteriaceae can give us a really big challenge. There are some Actinobacillus that are starting to show up with some resistance. A lot of the enteric disease, the same as in human medicine, gives us a real fit.

DR. GOLDBERGER: Are most of the examples you're using, individual or small numbers of animals treated, or are some of these situations where you might end up having to treat large numbers of animals for some of those infections?

DR. APLEY: For some enteric outbreaks, there would be the need to address a pen or a room or a group of animals. On the cattle side, our enteric disease is almost all individual animal, and our enteric disease usually takes place out on the pasture. Then as Dr. Sundberg stated, in swine it would be earlier on.

Most of our enteric disease occurs the furthest away from going to the slaughter facility as possible. It occurs early on in the animal's life, so there's quite a little time between there and harvesting the animal.

The respiratory cases, depending on the species, in the same way. They may require addressing the

whole group, or they may require individual animals.

One thing we've found is that if we delay in some of these cases and wait for individual animal therapy -- for example, in what we call the high-risk cattle -- that we end up having to use a lot more antimicrobials on the one we treat later.

DR. LEGGETT: Could you clarify? By threat areas, do you mean bacteria that are resistant to current antibiotics, just so we're all clear on that?

DR. APLEY: Yes. We're finding some that we have some resistance issues with.

DR. LEGGETT: Like do you have Klebsiella, Citrobacters, Enterobacters that are resistant or these other things?

DR. APLEY: We've got some salmonellas that are very resistant, and I've seen a couple of streps lately that are resistant.

It's interesting in the small animal section of the veterinary hospitals we're seeing MRSA's. I saw a report on a dog the other day that had a very scary enterococci. It wasn't a VRE. When you go over on the companion side, it's very much the same issue.

DR. LEGGETT: Dr. Rupp.

DR. RUPP: Just kind of a hypothetical question. In your opinion what percentage of therapeutic

antibiotic use in animals is related to the current sort of industrial approach to raising animals? We know in human medicine that you take a group of people and you crowd them into a military barracks, they get a bunch of Group A strep and a bunch of meningitis. My guess is if you take thousands of swine or thousands of cattle, crowd them into a feed lot or into a swine confinement building, you get a lot of disease. If we didn't raise animals in that way, how much antibiotics would be used?

DR. APLEY: First of all, I'd hate to conjecture a percent. I just don't know.

One of the popular things about that -- and I'll use swine production as an example -- is that you put them all together and it's disease city. But when you go through those facilities -- and David had the opportunity to tour one -- you shower in and you shower out, and the dirty side is the outside. The dirty side isn't the inside. You shower in, you shower out. You switch clothes. They very carefully control air flow, they very carefully control room temperature. They hang thermometers at different heights. Some of them data log the temperatures.

What these facilities have provided is, true, a more condensed livestock population, but the other thing they have provided is a way to avoid disease exposure, all-

in, all-out, complete cleaning and sanitation between groups of animals.

And then we find in so many of these species that climate is a big, big part of disease, with the stress of adverse climate conditions. What they're able to do in these facilities with, again, air flow, fresh air exchange, temperature control -- I just talked to a veterinarian who manages a large sow unit and they have had a significant impact on some diseases in the nursery by going to some zone temperature control.

Agreed, when you put animals together there is potential for increased transfer, but it's given us the opportunity to do some other things that we wouldn't running loose in the field.

DR. LEGGETT: Dr. Bell.

DR. BELL: I just wanted to follow up on that. It's actually fascinating how societies raise food to feed themselves, and it's very complicated. It's too bad. I kind of suggested we maybe didn't have a 15-minute kind of primer on how this is done and how the drugs are used.

But I've actually had the pleasure of being heavily involved in this area for several years now and have had the opportunity to visit several -- well, some of the major cattle, beef, dairy, swine, dairy, poultry. There are similarities and differences.

The hygiene in the facility -- I was very pleasantly surprised on a swine farm when I went out to one of the larger ones in Iowa. You know, it's like you said, you had to shower in, shower out. They made me take off everything, including my underwear and my glasses, and to get out I had to do this again. They said, oh, by the way, leave the towel on the dirty side, and the dirty side was the people side. I mean, they try. There are precautions to prevent rodents and birds from getting in. So even though there are 1,400 animals in fairly close confinement, my impression was that everything inside was very clean and they went to great lengths on this swine farm.

Now, that is quite different in a poultry operation, where I also visited some of them. There's just a big house and there are tens of thousands of chickens in there and you can hardly even see with the dust and the feathers. Partly for that reason, to medicate these animals they have to add the antibiotic to the water because you can't just find one and inject it like you can in a swine or a feed lot.

The feed lot was kind of in between. I mean, they're segregated in small groups, but there was kind of a level of feces on the ground there that periodically got, I guess, shoveled off.

So it's different, and there are small and

large operations. The trend of course is to be larger

But there are other aspects of production that influence antibiotic use and there are people here more expert than me. But I'll give you just one example, like how soon animals are weaned. I mean, breast milk has protective substances in it, and if they wean too early -- let's just say the earlier they're weaned, the more the young animals are at risk for various bacterial diarrheas because they're given artificial feed. So the way the producers try and deal with this is to give them prophylactically antibiotics in the feed. This would be on a swine farm, for example.

But it's partly a business decision how early they're weaned because they want the sows to get pregnant again and produce more pigs. Now if they're weaned too late --

DR. LEGGETT: Business is a little bit far afield from where we want to go in this meeting.

DR. BELL: Yes, okay. There was a lot here.

DR. LEGGETT: I think we're going to cut off the questions now.

The only thing I might charge to the American Veterinary Medical Association in terms of coming up with the better product that we are in charge of coming up with in human importance, the same applies to Dr. Carnevale's

group, and what I would ask your group to do is to provide us with more specific information about which antibiotics, what resistant bacteria, that sort of thing, so that then we can make the best informed approach to work on the parameters and to optimize that last portion, which is what I think you both care about, but we need your help in our doing the best job on our end.

DR. APLEY: We'd be glad to work with you.

DR. LEGGETT: Thank you.

The next speaker is John Powers, who will talk to us about the process of ranking of drugs by importance in human medicine.

DR. POWERS: Thanks, Dr. Leggett.

This is really what we wanted the committee to address today, is Appendix A that's in the guidance document, and how it relates to the ranking of antimicrobial drugs according to importance in human medicine.

What I'd like to do today is try to define the problem of antimicrobial use in animals, and talk a little bit about its relationship to antimicrobial resistance in human pathogens, and then give just a little of the background on the ranking process as it relates to the ranking of the drugs according to human importance, which is what our colleagues at the Center for Veterinary

Medicine asked us to do as part of formulating this guidance, and then go through the factors that we used in ranking the drugs for human use according to their importance, and divide them up looking at the factors based on drug efficacy, factors based on drug resistance, and factors that led us to conclude that some drugs were of low importance.

The issue of antimicrobial drug use in food-producing animals is actually an old one and was first addressed back in 1969 in the Swann Report that was issued in the United Kingdom and the debate has continued since that time. So what we're talking about, this relationship, has been something that has been debated for quite a while. The idea is that the use of antibiotics in food-producing animals may result in bacteria in animals that are then resistant to the drugs used to treat human illness, and that those resistant bacteria in food-producing animals may be transmitted to humans.

Above and beyond that, resistance determinants from bacteria in food-producing animals may be transmitted to humans as well.

And also there's the concern that non-pathogenic bacteria originating in food-producing animals may transmit resistance traits to human pathogenic bacteria, and as was pointed out this morning, sometimes a

non-pathogenic bacteria in an animal is a pathogenic bacteria for a human being.

All these three bullet points are actually highly debated.

The problem is that antimicrobial use in humans contributes to most resistance in man. There is no doubt that antimicrobial usage in human beings is the major driver of resistance.

The question that comes up, though, is does antibiotic use in animals also contribute to this, and if so, how do we measure it? Several authors debate how large a problem this actually is, and there is a great discussion of this in a forum that's in the Lancet Infectious Disease that came out last week that has six different authors presenting various sides of this issue. It's very instructive to read that as well. You can see sort of both sides of the issue there.

But the question for us that we can ask is, how large does the problem have to be before it poses a significant risk to human health? So the issue also comes to be, do we want to do something about it before it becomes a significant problem?

Also, because it is very difficult to measure. As Dr. Carnevale pointed out this morning, some of these studies are very difficult to design, if not impossible, to

look at the actual linkage between animal and human usage. Therefore, because these are difficult to do, does it mean that this relationship does not exist and that we shouldn't do anything about it?

I give you an example here of debate which is the avoparcin story. Avoparcin was a glycopeptide antibiotic that was used in animals formerly in the European Union but never in the United States. Avoparcin resistance also results in cross-resistance to vancomycin. It was shown that avoparcin usage in animals resulted in vancomycin resistance in the enterococci that animals carry.

The next question that comes up, though, is, does that avoparcin resistance in animals result in vancomycin-resistant infections in humans? As you can imagine, that's a very difficult question to answer.

The folks who have posed that it is not an issue say, well, the majority of vancomycin-resistant enterococcal infections occur in the United States, not in Europe, where in the U.S. avoparcin has never been used. But does this really address the question or does it just point out the global nature of infections in man, animals, and in the food supply as well?

I just sort of harken back to an outbreak of cyclospora that occurred a couple of years ago, that when

the outbreak was traced back, it came from raspberries in Mexico, and yet the people got sick in Wisconsin, which points out the global nature of the food supply as well.

So the next question comes up, are there examples of resistant bacteria transmission from animals to humans? As Dr. Patterson pointed out this morning, there are some examples of outbreaks that have occurred in the past. This doesn't address how commonly these occur or how big a problem it is, just the fact that these things do occur. For instance, in a recent New England Journal of Medicine paper, Molbak and colleagues pointed out an outbreak of Salmonella that was traced back to pigs. This is an example of enteric bacteria in animals causing food-borne disease in man, which is our most direct linkage of transmission of resistance from animal to human.

However, there are also examples of non-enteric bacteria to animals to non-enteric bacteria in man as well. For instance, back in 1986 there was a report of the ROB-1 beta-lactamase and Actinobacillus pleuropneumoniae, which is a respiratory pathogen in pigs, which transferred its plasmid to Hemophilus influenzae in man. Again, not saying that this happens every day or that this is common, just that this points out the possibility that this could occur.

Also there's the possibility for gene transfer from enteric bacteria in animals to non-enteric bacteria in

man. Dr. Bell pointed out this morning the concern that the vanA gene in enterococci may actually manage to make its way into methicillin-resistant Staph. aureus in man, given the fact that in places like decubitus ulcers that most Staph. aureus and enterococci may be present in conjunction.

But has this ever really happened in animals? There actually is an example of this, which unfortunately I did not put up on this slide. Back in the 1980s there was an aminoglycoside antibiotic called apromycin, which was used, again, in Europe, in France. When this was approved in the 1980s, by 1984 E. coli resistant to apromycin, which also generates cross-resistance with gentamicin, were found in calves with diarrhea. This resistance was mediated by a plasmid called AAC3IV.

By 1985 to 1988, strains of E. coli, Salmonella typhamuria, and Klebsiella pneumoniae, which also obviously causes a respiratory disease in human beings, namely hospital-acquired pneumonia, were also found in human beings in France as well. It was found that these had the AAC3IV plasmid.

Now, one could also make the argument that perhaps it was gentamicin usage in humans which resulted in the human resistance pattern. However, the interesting thing was that when these organisms were genotyped that

these organisms also had resistance to a drug called hygromycin B, which is only used in animals and has never been used in people, showing that that transmission could have come from human beings. And again, I want to emphasize that I'm not saying that these are very common occurrences, just the fact that these are examples of things that have happened.

So again, that's actually an example of transmission of a resistance gene that started out in an E. coli but ended up in a Klebsiella as well. So there is this potential that this may expand beyond just food-borne disease and into other diseases as well.

Also, since that was information from the 1980s, let me quote a more recent example. Again, I don't have a reference for this one because it was presented at a symposium at ICAC so it's only in abstract form. But a group from France showed that E. coli isolates from urinary tract infections there had identical features to E. coli in food animals as well. Again, organisms like E. coli can be enteric pathogens in human beings but can also cause urinary tract infections, and again they can cause respiratory disease like hospital-acquired pneumonia.

Showing that these organisms have similar features to those in animals, again, doesn't make that direct, absolute link, but it certainly raises the

possibility as well.

Some authors argue that this is also a cycle of transmission, and this is very clearly elucidated in that Lancet ID paper that talks about this, and that man may actually transmit resistance pathogens to animals via sewage. For instance, when there is flooding of fields that the animals may then be exposed to human sewage. This resistance can then get amplified in animals, as was pointed out several times this morning, that the animals come more closely in contact with feces, and certain animals like chickens are actually coprophagic so they even eat their own feces and circulate the organisms back into their own gut. Then it's possible that these are transmitted back to man.

Again, this is primarily theoretical. Has this ever been demonstrated conclusively? The answer right now would be no.

So in any case, our desire is to preserve the usefulness of antimicrobials that are of greatest importance in the treatment of human disease. This guidance actually includes the categorization of drugs based on their relative importance in human medicine.

This guidance gets very confusing. Even though I work on it, there are a number of highs, mediums and lows included all over this guidance which make it sometimes

very difficult. So what we're talking about here is we ranked the drugs in Appendix A by high, medium or low based on their importance in human medicine.

Now, that ranking of human drugs actually is used in both the hazard identification and the consequence assessments as a part of this guidance.

There are a couple of things to keep in mind here, though, and that is, that the ranking of the human drugs is not the only or the overall driver of the final risk estimation for the drug use in animals. So even though, as presented in the example that Mary Bartholomew showed this morning, a drug may be considered of high importance in human medicine. It may end up as medium importance in the overall risk estimation.

The other thing I think that needs to be emphasized is making a drug of medium importance in the overall risk estimation does not necessarily mean it will not be approved and will not be available for animal usage. All it really talks about is the risk strategy used to manage that drug when it's used in animals. It doesn't mean it won't be available for the treatment of animals.

A joint CVM-CDER team developed guidelines for the categorization of the drugs by coming up with these factors which I'm going to show you shortly. We were asked by our colleagues at the Center for Veterinary Medicine to

rank all drugs, not just those used in the treatment of food-borne pathogens. As I've tried to show you, the drugs used in human medicine for food-borne illness are also sometimes used to treat other non-food-borne diseases.

You've heard this morning the example of Tylosin, which is a macrolide antibiotic. As we discussed at length yesterday, macrolides are often used to treat respiratory tract infections in humans, but the IDSA guidelines for the treatment of diarrheal illness also recommend erythromycin as one of the potential therapies in the treatment of Campylobacter disease in human beings.

Also drugs used to treat non-enteric disease can affect enteric bacteria, so when one ingests an antibiotic for respiratory illness, it may affect the enteric flora as well.

Also as we said, transmission of resistant elements can occur from enteric bacteria and other pathogens which do not encode for enteric disease. For instance, the recent two cases of vancomycin-resistant Staph. aureus infection appear to have acquired their vanA gene from vancomycin-resistant enterococci.

I think Dr. Apley was right. Climate does affect illness because every January I get sick. I'm losing my voice.

What we did was the ranking of drugs is not a

regular part of the CDER review process, as Dr. Goldberger talked about this morning, and it is not necessary for an antibiotic to be approved in humans to show that it has some importance. It just has to be safe and effective. The approval process entails showing that the drug doesn't have to show a specific level of importance in human medicine.

However, regulatory initiatives do recognize that some products may be of greater importance in human medicine. For instance, Subpart E and Subpart H regulations take into account whether the treatment is used for serious and life-threatening illnesses.

This is a qualitative rather than a quantitative system, and we realize that multiple factors may apply to some drugs, and I'll show you those factors in a minute.

There is a degree of subjectivity in these determinations, and it's interesting to me that when we look at comments from the docket, that some of the criticisms of this were that this process of ranking drugs is subjective. Unfortunately, there is no science in ranking drugs according to its importance. There is no body of medical literature implying that one drug is more important than another, and also it was very interesting to note that Dr. Carnevale's presentation showed a lot of

subjective data from people as to what the importance might be of drugs for their use in animals or the ranking of animals according to their importance in human medicine.

Again, that's not to say that that's not valid, but that's the state of where we are right now given our lack of information. Again, ranking importance, there are whole books on what importance actually means.

Also, it does not necessarily include all antimicrobial drugs and classes that have not yet been approved. So there are things in the pipeline that are not on this classification listing.

Again, for that reason we would need to review this ranking over time, not only because new drug classes may be approved, but also new diseases may emerge, there may be changes in prescribing patterns. So we expect to have to review this ranking process every few years or so.

These are the 10 factors that we came up with to try to rank drugs according to their importance for human medicine.

The first is, is the drug a sole therapy, or are there limited available therapies to treat the disease for which that drug is commonly used?

The second is, although there may be other therapies available, is it the therapy of choice for that particular disease?

The third is, does the drug have a spectrum of activity of particular importance in human medicine?

The fourth is the importance for oral therapy.

The fifth is the importance of treating food-borne infections, which are the most direct link with animals.

The sixth is, does the drug have a unique mechanism of antimicrobial action?

The last four factors are related to development of antimicrobial resistance. Namely, is there cross-resistance within the drug class for that particular class of drugs? Is there cross-resistance across other drug classes, similar to what we talked about yesterday with penicillin resistance predicting macrolide resistance as well?

The ninth thing is the ease of transmissibility of those resistance determinants across various species or within species.

And then finally, cross-resistance between animal and human drugs.

Actually that list is what we're going to ask you to comment on a little bit later, so let's run through those 10 factors just so I can explain them in a little more detail.

The first is, is it the sole or limited

available therapy? This is pretty self-explanatory. A drug would be considered of high importance until widespread resistance to humans precludes use or other therapies are available. For instance, vancomycin or linezolid for methicillin-resistant Staph. aureus infections be considered of high importance.

The second, is it a therapy of choice? So, for instance, we can use a number of drugs for pre-operative prophylaxis. However, cefazolin is very commonly used for this indication.

Or is it important when treating diseases of high morbidity or mortality, such as third generation cephalosporins in the treatment of acute bacterial meningitis?

Next is, does the spectrum of activity of the drug have particular importance? For instance, dalfopristin/quinupristin is used primarily for the treatment of vancomycin-resistant enterococcal infections, although it does carry some other indications as well.

Fourth, is the drug of importance in oral therapy, so if a patient is in the hospital and then can be transitioned over to oral therapy and leave the hospital sooner, that drug may be important. So fluoroquinolones or trimethoprim-sulfa are examples of this where patients can be transitioned from IV to oral therapy for Gram-negative

infections.

Next is the importance in treating food-borne infections. Again, this is the most direct link between infection or colonization in animals and infections in humans, but again, not the only one. The potential for transmission of resistance elements also exists from animals to humans, as we've already discussed. So this includes drugs used for the treatment of disease, which may be severe or resistant to other therapies, such as fluoroquinolones for the treatment of multi-drug resistant salmonella infections.

The next is, does the drug have a unique mechanism of action? And this is especially valuable to human medicine if there is no widespread resistance to the drug already existing in the environment. For instance, linezolid for Gram-positive infections. So limitation of the use of the drug beyond treatment in human disease in these particular drugs may limit the emergence of resistance.

But what we consider a unique mechanism of action may change over time as more drugs get marketed within a class. For instance, when norfloxacin was released, it was the first fluoroquinolone to come on the market. Now that we have several other quinolones on the market, one might not consider that the DNA gyrase

inhibiting ability of fluoroquinolones as novel at this point. And the other question is the emergence of resistance to members of a given class may no longer make this of importance.

Next is cross-resistance within the drug class, so the importance of drugs within the same class which have activity against organisms resistant to older members of the class. For instance, organisms resistant to cefazolin may still be susceptible to ceftriaxone or cefotaxime, even though both of those kinds of drugs are cephalosporins.

And this may vary within the organism or drug class. For instance, aminoglycoside resistance comes in several flavors. Gram-negative organisms resistant to gentamicin still may be susceptible to amikacin; however, organisms like enterococci which are resistant to gentamicin are almost always resistant to amikacin.

The next is cross-resistance across drug classes. Plasmid-mediated resistance may transmit multiple resistance genes at once. For instance, plasmids in Gram-negatives carrying resistance genes for beta-lactamases may also carry genes for resistance to sulfa drugs and chloramphenicol.

If this cross-resistance is linked, the drugs would be ranked according to the class considered of highest importance. So, for instance, if we know that

beta-lactams are important and it's on a Gram-negative, even though we might not consider chloramphenicol as really important, if we consider chloramphenicol resistance as a marker, that might be something that would be considered important.

Drugs which do not have linked resistance to other antimicrobials are considered of particular importance. For instance, drugs which do not have plasmid-mediated resistance but in whom the resistance is most likely chromosomally mediated, like fluoroquinolones, it's harder to transmit that to another organism. That would be considered important to reserve that drug for human usage.

That actually gets to the next point of ease of transmissability of resistance. Low ease of transmissibility would mean actually it's hard to transmit that resistance from one organism to another, such as chromosomal mutations and resistance in fluoroquinolones.

On the other hand, a drug which is considered high as far as transmissibility of resistance means that single or multiple drug resistance is easily transmissible via plasmids or transposons, such as occurs with plasmid-mediated beta-lactamases.

Then finally there's cross-resistance between drugs used in animals and drugs used in humans. The actual drug proposed for us in animals is often different from the

way the drug is used in humans. However, resistance in the animal drug may result in resistance to human drug. Again, I use the avoparcin example that I quoted earlier. Therefore, the animal drug would be a sign of importance according to the human drug.

How do we then define drugs that are of lesser importance? This is actually drugs which have little or no use in human medicine. They're neither the first choice nor an important alternative for human infections, such as the ionophores, and we included polymyxins on this list. However, we received a comment to the docket from the Infectious Disease Society of America, commenting that they thought that polymyxins should be ranked higher because of its increasing use in resistant Pseudomonas infections.

One of the issues that probably is important to talk about today, though, is even though we've shown some examples of drug resistance that can be transmitted to other forms of bacteria in human beings, are there some places where this just doesn't occur or is unlikely to occur? For instance, polymyxin B for Pseudomonas. Is that really an issue in that Pseudomonas is not a pathogen which we have any experience with of being transmitted from animals to human beings? One could also put something like Mycobacterium tuberculosis, which appears to be a sole human pathogen, on that list as well.

So, in summary, the ranking of drugs according to importance is only one part of the overall framework document and guidance, but it's the part that we'd like you to comment on today. Again, I'd reiterate that this is actually a guidance, meaning that it is not an absolute regulation that industry has to follow. It's just our best opinion of what they should do.

We have opened the docket for comments about the ranking process and we received some of that, and we consider this the next step by bringing this before the committee to hear your comments on this ranking process.

I'll stop there.

DR. LEGGETT: Thank you, Dr. Powers.

Are there any questions?

(No response.)

DR. LEGGETT: You did a great job, then, obviously.

DR. POWERS: Everybody wants to eat lunch.

DR. LEGGETT: Yes. It's a little earlier today than yesterday, thank goodness. So why don't we break for lunch and come back. Stroll in and be in your chairs hopefully by 1:30 so we can begin the open public hearing. Thank you very much.

(Whereupon, at 12:23 p.m., the committee was recessed, to reconvene at 1:30 p.m., this same day.)

AFTERNOON SESSION

(1:34 p.m.)

DR. LEGGETT: Good afternoon. This next portion of the meeting is devoted to an open public hearing, after which we will have committee discussion. Several things I'd like to point out. I have a watch, and the open discussion for each person is 10 minutes -- not 11, not 12 -- 10. So whatever you can get through, that's what you've got.

Following that, we have been asked to talk about the ranking in that Appendix A. I would like us not to spend a lot of time deciding whether streptomycin is high, medium, or low. I want to spend time on do we weight one factor 3 times and another factor .5 in terms of coming up with high, medium, and low. Do we get rid of some of these things? Do we make it smaller, etc.? So I want to try to structure the discussion about points in general, but I'd like us not to meander since about half of the committee is leaving in a single taxi at 4:00 o'clock.

With that, I think we can get started. I do not have the list of who is speaking and what order they're speaking. I'll let you guys decide.

Are you Dr. Sundberg?

DR. SUNDBERG: Yes. Good afternoon. I'm Paul Sundberg. I'm a veterinarian with the National Pork Board.

I was in practice in Nebraska for nine years. I went back to Iowa State and got a Ph.D. in veterinary microbiology with a specialty in preventive medicine.

I'm part of a contingent here today to speak with you about what was referred to this morning by the producer and veterinarian groups and giving you some background about what happens on the farm and with the animals. I deal with animal health issues and welfare issues on behalf of the pork producers.

I think it's important for me to start out by saying that on behalf of the pork producers and the farmers, we pay attention to our animals. That's our business. If we didn't have animals, we wouldn't make a living. We pay attention to the production of food. That's our business. If we don't pay attention to the production of food and a safe product, we also don't have a living. But we're also part of the community, and the health of farmers, the health of ourselves, the health of our families, and health of our community is important to us. We're consumers as well as everybody else.

Pork producers recognize their responsibilities. First of all, we recognize our responsibilities in providing food and a safe product to the consumer. In doing that, we have to form our policies and our recommendations to our peers, based on information

and based on data that we can gather.

To gather that information the pork producers have a professional staff -- I'm part of that -- that is charged with gathering data, with reading the science, with interpreting it, with putting it into perspective for the producers so they can make the decisions about their use policies and about the direction they want their industry to go.

As part of that we participated in the WHO meetings in Germany and Switzerland, in Denmark. We participate in national and international meetings, and we met with the CDC, went down to the CDC, took pork producers and their representatives down there.

We also fund research into basic mechanisms, we fund research into, for example, the prevalence and the characteristics of integrons in Salmonella that's isolated from pigs. We fund applied research, and the applied research, for example, the effects of our uses on the farm, the way that we use antibiotics on the farm, the way that that affects resistance. And we also fund research into learning about the experience of others, and under that I think this morning there was a question about hearing something about the consequences of antibiotic use patterns, of antibiotic use policies.

We've gone over to Sweden and we've gone over

to Denmark. We went over there with a group of producers as well as with some scientists, and we asked them specific questions. We wanted to understand what their policies were, how that affected the pork production, how that affected their production on the farm and what the producers did, and also how it affected public health in those countries.

I can tell you from the Danish experience, on that Danish side there's a little bit of difference in philosophy. They have approached the issue of antimicrobial resistance as banning or affecting different uses of antimicrobials. The guidance document approaches antimicrobial resistance not in affecting uses but using that use as a factor in looking at the clearance of antimicrobials.

Therefore, if you try to meld those two together -- and we heard comments this morning about growth promotion uses and other uses, if you try to mix those together, what very well could happen at the end of Guidance 152 is that we will have even higher restrictions, even more restrictions on the U.S. producer than are on the Danish and the EU producers now.

Going on with that, as far as the industry goes and pork producers, we take that information and then we develop educational programs and get that information out

to the producer.

You heard this morning that AHI said your advice is critical as it will affect veterinary medicine, and AVMA said Guidance 152 is biased toward the concept that there are no potential adverse effects from unnecessary restriction. I want to make a few comments about that.

Unnecessary restriction or your advice that could lead to unnecessary restriction could very well affect our animals and the way we do business and the way that we provide food. It will affect the welfare and the health of our animals. We deal in population medicine a lot. That's what we do. We pay attention to the individual, but many times our individuals are the herd, and we have to pay attention to the population medicine of the herd, the epidemiology, the way bacteria move and are transmitted around, including the diagnostics and prevention.

I think we talked a little bit this morning about some of the mechanisms of preventing disease. Extremely important for our pork producers and for farmers. There was one comment about weaning, early weaning of pigs, for example. We use that early weaning with pigs as a tool to help prevent disease. What we've done is we found out that if you wean at certain ages, you can preclude the

transmission of bacteria from the sow, from the mother, to the pigs. Therefore, weaning at different ages can affect the bacterial exposure and the potential for disease later on in the pigs. So that's just one example of some of the preventive things that we have to do.

It's not at all different, a lot different than the analogy of day care or of putting populations of kids into schools or into colleges. We have that issue where deal with a population and how things are transmitted among and between our individuals and our populations.

Your advice is going to have an effect on food safety. The pork producer is the first link. The food animal producer is the first link in a long chain of events that have to happen to get food from the farm to the table. Our primary interest is providing a healthy, robust animal to that market because if we can't do that, then the rest of the chain is also going to be affected. We are responsible for that. We take our responsibility very seriously in providing that product.

There was a question this morning about validating the model for exposure and the factors that go into a validation of a model. I just want to quickly read part of our comments on Guidance 152.

For example, it is a difficult situation to address because it is multi-factorial. Campylobacter

jejuni causes over 90 percent of the human cases of campylobacteriosis, but C. jejuni is rarely found in pigs in the United States. It's not as simple as just saying Campylobacter and Salmonella. There's a speciation that is very important in how it affects the different species and looking at exposure.

Campylobacter coli is a prominent serotype found in pigs, and yet it is isolated only in 3 to 4 percent of human cases of campylobacteriosis.

Assigning an exposure assessment based only on the prevalence of Campylobacter genus unfairly penalizes the availability of antimicrobials to pork producers. That would include as well other comments including that further processing will help to decrease the exposure. For example, the data that FDA says they're going to use for the exposure assessment is based on the FSIS data that is taken from carcasses in the plant. Further processing in the products is going to help decrease that exposure, so we think that just as a comment overall on the guidance, one of the things that needs to be addressed is the issue of over-estimation of risk.

So with that said, I want to get back to the issue, though, of ranking and the issue of importance to human medicine because that is where I hope that you focus this afternoon.

I feel it's important to take into account the statements earlier today about the conservative philosophy of the different sections of the guidance document. The guidance document defaults to conservatism, which is fine. I'm not arguing that point, but the fact is that it does. Therefore, the fact also is that if you advise CVM to rank all of the antimicrobials as of high importance, that will have an effect on the availability of antimicrobials to producers and to veterinarians both.

One of the examples is the availability of antimicrobials to be able to treat our individual, which is our herd. If the antimicrobial in the guidance document ends up in that medium category, it will affect -- and that medium category is going to be affected by your advice on importance. The medium category will affect the availability because it does put at risk the availability of an antimicrobial -- I'm looking at table 4 and 5 -- to be able to treat a herd or a group of animals. We can't go through and inject 1,000 pigs with individual injections for five days. It can't happen. We have to use antimicrobials in the feed, in the water, in other ways besides individual injections in order to treat those populations. It will affect the availability.

There was another question that I just have to clarify. There was a question about the percentage of pigs

that get antimicrobials. The NAHMS, the National Animal Health Monitoring System, which is a survey done by USDA, will tell you that the vast majority of pigs have exposure to antimicrobials at some point in their life. That doesn't mean that they have antimicrobial exposure from the time they're born to the time they go to market. It's really not all that different from the exposure of antimicrobials in children at some point in their life. Pigs do get antimicrobials at some point in their life, but we are working so they do not get constant exposure and it's an important distinction between yes, they get antimicrobials -- all pigs get antimicrobials, but that doesn't mean they have them all the time, so there isn't always that constant exposure.

Your advice to the FDA could affect animal producers, food supply, animal welfare, by holding the animal producer, the farmer, responsible for resistance in tuberculosis, in Legionella, in Neisseria, in Pseudomonas, those type of things. I'm going to have a really tough time going back to the pork producers and telling them -- and being credible about it -- that their use of antimicrobials on the farm causes multi-resistant tuberculosis in people.

DR. LEGGETT: I'm going to have to have you sum up here now, please.

DR. SUNDBERG: I'm going to sum up right now.

Your advice will have effects, however, on animal welfare, on food safety, on animal health, and on veterinary medicine. While it's debated that it may have an effect on the resistance that will cause an effect on public health, it will, in fact, have an effect on the way we do business and the availability of antimicrobials. So please focus on that and keep in mind the farmer, the producer, the animal, and the veterinarian.

DR. LEGGETT: Thank you very much.

The next speaker will be Dr. Burkgren, of the American Association of Swine Veterinarians.

DR. BURKGREN: Thank you for the opportunity to comment this afternoon. The association I work for is a nonprofit association. We're based in Iowa, in central Iowa. We have approximately 1,000 members inside the United States that are tasked with maintaining the health of the swine herds in the United States. About 100 million pigs a year is what we harvest.

We certainly do have some concerns or I wouldn't be here. From the time I stepped outside of my house yesterday to the time I stepped inside this hotel was seven-and-a-half hours. We traveled by car, plane, train, and taxi, so it's kind of like being trapped in a John Candy movie.

Certainly your discussions decisions, I assure you, are going to have an effect on the farm. This is not an academic exercise. My members have that responsibility of treating on the farm, but you have responsibility that you're going to affect what they do on a daily basis in their practices.

I just want to give you a quick glimpse of the swine industry and how we practice veterinary medicine. Veterinarians do not take lightly the use of antimicrobials. We don't do it in a cavalier manner for several reasons.

First of all, medically it doesn't make sense. On the farms we've been dealing with resistance for just as many years as the human doctors have. We do antibiograms, we monitor that, we keep track of records on the farm. So we know the pattern and we know the antimicrobials we can use and the ones we can't use and the routes of administration.

Again, economically, veterinary products are a line item. On every budget that I've looked at in the past 15 years, it is a line item. If that line item goes over, depending on the unit, but if it goes over 50 cents per pig, it's too high. Some accountant somewhere is going to say, that's too high. You need to decrease your use of products or your services. So economically it does not

make sense.

We do practice population medicine, as Dr. Sundberg said. We often treat large groups of pigs, but we also treat individuals. But if you can imagine a pasture or a barn with 1,000 pigs weighing 80 pounds, and you're tasked with treating that pig individually twice a day for three days, I can assure you there's not one person in this room that would last to catch every one of those pigs and treat them individually.

Water and feed delivery is important for our production, not just for growth promotion but for therapy. We consider therapy to include both treatment, prevention, and then also control. A lot of times it makes more sense for us if we're treating in a barn -- for instance, Actinobacillus pleuropneumoniae. We go in one morning and we treat -- in one pen we have one or two pigs sick. The next morning all of a sudden we're treating 3 to 5 percent of that barn. We know it's going to make more sense to go in and treat that entire barn. We'll use less antimicrobials in the long run by treating the entire barn rather than treating individuals for the next four weeks as they show up sick. Mortality will sometimes approach 25 percent unless you get in and treat aggressively.

I'm reminded just recently in my kids' school we had an outbreak of whooping cough, and that whooping

cough outbreak was one case. And they treated, I think at last count, about 30 percent of the kids in that high school. So there is preventive use in human medicine. Now the difference was about half of those kids were in the bathroom most of the time because of the adverse effects. And I thank Dr. Bell for some advice with my own kids in not treating them with erythromycin. So we do use mass medication.

Also, we don't have a very large or very modern armamentarium of products to use in swine medicine. I think fluoroquinolones were approved for use in humans in the mid-80s. At the same time you were celebrating approval of fluoroquinolones in humans, we were celebrating the new formulation of tetracycline for injection in pigs. And today we still do not have an approval for fluoroquinolones in pigs. I just want to clarify that. We do not today have approval for fluoroquinolones, nor have we ever had approval for fluoroquinolones in pigs.

Our members are concerned at the degree of subjectivity throughout the document. I know you're tasked with just the ranking part, but there's a lot of subjectivity built in, and depending how it's applied, it could end up being the application of the precautionary principle as we've seen in other countries. By our estimation, there are two products that are in the low

category that we use on a fairly routine basis in swine medicine.

We've made previous comments at another public meeting where we requested more transparency to the ranking process. While we certainly enjoy the example that was given this morning, the Miracin example, we thought that maybe today we would actually see that example extended down in how do they go through the ranking process, rather than just having one line on the slide. So we were disappointed in that. We'd still like more transparency, taking the example of Miracin, to go through those 10 factors and look at the weighting and how they arrived at the high level of importance.

So as we look at the factors, I think we'd recommend that there be ranking, there be prioritization of those factors.

The first one would be the treatment of food-borne illnesses. It makes common sense. If an antibiotic is important for treatment of food-borne illnesses, yes, that's an important factor.

And second would be the transmissibility of the resistance determinants. Again, if there is evidence, scientific, defensible evidence, that this occurs, then yes, that should be a consideration in the ranking. But if you have a no answer to both of those questions, it seems

to us anyway that the disconnect is complete. Why consider the other eight factors when those are noes? So we would recommend prioritization in the ranking of those.

Last comment I would make would be, in a conversation with who I consider to be a very reliable source last night, he indicated that there is some concern on the PhRMA side and human side that some companies are going to abandon R&D for antimicrobials because of the fear of cost with no approvals. I think that we pick up the same rumors. We pick up the same rumblings except to a greater degree on the animal health side. Companies are looking at the process, saying is this really worth it.

I think if you look at the size of our markets from a financial standpoint for these companies -- and I could be wrong, but I doubt if there are very many markets for food animal antimicrobials that are over $100 million a year, whereas in PhRMA I understand it's $2.2 billion. So if you guys have companies on the human side saying no to future development of antimicrobials, just consider what our future is on the animal side.

I thank you very much.

DR. LEGGETT: Thank you very much. The next speaker will be Dr. Tony Cox.

DR. COX: Thank you for the opportunity to comment. I'll keep this to 10 minutes.

I wanted to talk on the theme of what is it we're trying to do and then comment on whether the proposed ranking criteria help us to do that.

And I don't know what is meant by importance in the contexts that are being used today. Before lunch we heard that there are whole books on the subject. I'd be interested in a definition of what is meant by importance.

But I think that what we should be talking about is how to make better decisions, and we should be ranking not drugs and not problems, but potential solutions to problems. We should be ranking the ones that are most beneficial high and others low. So I'm going to use that as the framework for my comments.

Suppose that this ranking process is intended to serve the needs of rational decision making, so it's a server for which decision making is the client. Well, what does rational decision making require?

First, it requires identifying risk management alternatives. For example, to continue to use a drug, to ban the drug, to restrict it and so forth. I note that banning a drug is not the same thing as continuing to use it. Assessing the importance in one context doesn't tell you necessarily anything about the desirability of the other. I think with affection of my favorite example of fluoroquinolones where there's been a risk assessment that

looks at what are the risks of continuing to use fluoroquinolones and never look at the question of what are the risks of banning fluoroquinolones, which I estimate to be about two orders of magnitude larger than the risks of continuing to use. So risk management alternatives, let's identify them and rank them.

Secondly, rational decision making requires assessing the probable human health consequences of each decision option and, of course, picking one that has most desirable distribution, probability distribution of consequences. So let's see how well this ranking approach can help with these tasks.

My conviction that I want to share with you is that crucial quantitative information needed for rational decision making is omitted from this process and from the ranking process. I guess the bad news is that risk is quantitative and these factors are qualitative. They could apply equally well whether one person in a million years is affected or a million people in one year is affected. But that basic numerical information I think should make a huge difference in what is considered important and how important it's considered.

I've said over and over, and I'm hoping to talk CVM into paying attention, that the quantitative extent of exposure is essential information. You can't ignore it.

It's bad for your soul. It leads to poor risk assessments. So in this ranking process somewhere the extent of exposure must be considered or we have no basis for talking about importance

Also, as the previous speakers mentioned, I think that the current proposed system requires those who would use it to come up with subjective probabilities for events that are not well defined. So I look at the probability of resistant bacteria being present in animals. I first flinch because "present" is a dichotomous concept, and I am convinced that you have to say, well, how much is present? Not just, is there any present.

But stalwartly persevering and getting past that, I then come to the phrase, "as a result of the drug use." What does that mean? In general you don't find resistant bacteria as the result of drug use. You find that they are selected by drugs. They are not created by drugs.

That fine point aside, if you have a person who gets sick because they have a sufficient microbial load to cause illness, and if one of those bugs is resistant, and let's say 999 are not, do you consider that illness was a result of the resistant bug due to drug use? Who knows? I don't know. The guidance doesn't tell me.

Under the consequence dimension, the words

"result in," when does exposure result in adverse consequences, I think are similarly ambiguous and need to be pinned down.

Reading through the rest of this, "hazard" refers to illness caused by a specific resistant bacteria attributable to a specified animal-derived food commodity. The word "attributable to" is left undefined. The definition of risk is probability of human illness caused by a specific resistant bacteria and attributable a specified commodity. So that puts both of these ambiguous phrases together.

Again, I think a great deal about fluoroquinolones these days, and in the fluoroquinolone context what "attributed to" actually turned out to mean is, CVM didn't attribute it to anything else. Therefore, by default it was attributed to chicken. That's explicit finally in their comments, but the thing is there's a list of at least a dozen other sources for fluoroquinolone resistance to which no risk was attributed.

So my point here is that attribution of risk is not only left undefined but its operational definition, the way it's actually then implemented, is contrary to common sense and tends to exaggerate risk and could give very strange risk rankings.

Now I want to talk about performance, or the

expected performance of the proposed qualitative risk assessment and ranking scheme. Again, what we should be trying to do is to recommend actions based on the probability distribution of their net benefits, but I don't see the information in any of these criteria that address net benefits. For example, do you cause more problems by increasing the number of drug-susceptible bacteria than you prevent by decreasing the number of drug-resistant bacteria? A crucial question, not addressed.

In the case of fluoroquinolones, I estimate that the effect of the susceptibles outweighs the effect of the resistance by more than a factor of 100 to 1, so it would have been good to have included that somewhere in the ranking process.

Others have spoken about disconnects. I think the most important disconnects are that -- for the ranking purpose -- the potential of human health consequences to exposure cannot be estimated from the human medical importance of a drug, whatever that means. The importance of a drug doesn't tell you what will be the consequences of a ban or some other action. The typical example is one in which a drug is very important, whatever that means, by the criteria proposed today or others, and yet the actions that are being contemplated don't change the efficiency of the drug or its use or anything else. It's not the importance

of the drug that matters. It's the importance of how the drug's usefulness will change that's important. So it's change that we should be ranking, not importance.

The three factors of release, exposure, and consequence can't in principle be used to estimate or rank human health risks because they ignore the two key questions of how much harm does exposure cause, and how would this change if a ban were implemented? But I think that many of the ideas in the ranking methodology are good ideas. They are ideas that should be preserved and applied. What they should be applied to, however, is changes that are likely to follow if certain actions or decisions are taken.

Right now I believe it's the case that there is zero correlation between the qualitative risk ranking of drugs and the quantitative ranking of actions such as which drugs to ban or to refuse to ban. Since no simulation has been done, I can't prove that but I'll bet that it's true.

Now, I want to take a particular example, virginiamycin, with Synercid being a human drug, and look at the factors that were discussed this morning. Those that I've put in bold here, the sole therapy, the spectrum of activity and so forth, at least at the time that Synercid was the only available treatment, might I think easily have put Synercid in the category of being an

important drug, one that we should worry about and ranking high in the qualitative ranking. And yet, a quantitative risk assessment shows that a reasonable upper bound on the number of statistical mortalities prevented by banning virginiamycin so that Synercid would be safe for mankind, might be about one-sixth of one statistical life over the next five years.

Now, of course, if I quote numbers, I expect you to challenge me. Where did this come from? And, of course, also I don't have time to go through with this paper, which will be coming out --

DR. LEGGETT: In fact, that's why I'd like you to sum up here. If you can, please sum up. I've let you go over a minute.

DR. COX: I'm sorry. I showed another 40 seconds remaining.

What I'd like to call attention to is what kinds of risk factors go into a quantitative risk assessment and perhaps not into a qualitative one, and those include where did the resistance come from, they include genetic information. They include the percent of resistance and how it changes over time.

In conclusion, I believe rough-bounding quantitative estimates to be quicker, easier, and less costly than the qualitative type. You end up talking about

things that matter, the factors that really drive risk, instead of imponderables like high, medium, and low.

I'll conclude there, and thank you.

DR. LEGGETT: Thank you very much.

We have a fourth speaker, Steve Projan.

DR. PROJAN: Thank you, Dr. Leggett, and good afternoon. I'm from Wyeth Research. I'm the Director of Antibacterial Research, but I'm speaking for myself, not Wyeth and not Ft. Dodge, which is a wholly owned subsidiary of Wyeth.

My background is that I have a degree in nutrition and food science from M.I.T. and a Ph.D. in molecular genetics from Columbia. I'm on four editorial boards, including the Journal of Bacteriology, Infection and Immunity, Antimicrobial Agents in Chemotherapy, and Microbial Drug Resistance. I was informed yesterday I'm the chair-elect for Division A of ASM. That's Antimicrobial Agents in Chemotherapy.

First of all, I think we should realize that PhRMA, the Animal Health Institute, and the veterinarians and farmers do not constitute an axis of evil antimicrobial use. I think that as the swine producers pointed out, they're human beings too and they're affected by the use of the agents that we're talking about, both professionally and as individuals. And I think that more good will is

what's needed in investigating these problems and less animosity.

That being pointed out, I'd also like to suggest that this advisory committee, in doing this rank prioritization, together with the FDA, seek additional guidance from medicinal chemistry experts who understand the structures of the compounds we're talking about and their mechanisms of action, scientists such as those in the ASM who are experts in gene transfer, which is very important to the questions we're investigating, as well as mechanisms of action and resistance.

One comment that I should make, after listening to Dr. Carnevale's talk is that -- and I think generally sensed by the committee -- is that arguments on transmissibility of resistance determinants are really quite silly. There are multiple examples of identical resistance determinants in resistant strains of animal and human origin. And if you have identical resistance determinants, these determinants had to get from one strain to another by some mechanism: horizontal, vertical, upside down, right-side up. Frankly, not having a smoking gun or direct in vivo evidence is akin to the arguments of the creationists that because there are gaps in the fossil record, human beings did not evolve from other animals.

So unless we take the creationist's view in

antimicrobial resistance, I think that it's foolish to even argue the subject, that we know transfer takes place. It almost undoubtedly takes place in both directions, from animal to human and vice versa, and also from the environment. That should be taken as a given, in my opinion, in this committee's considerations.

In addition, one thing that has been missing from these considerations, and I think could be useful, is if the American Veterinary Medical Association and their producer colleagues formulated their list of what their high priority antimicrobials were. I think that could be very useful in judging the relative utility and the importance of these agents in animal health and in protecting the food supply and providing high quality products to the consumers in this country. I think that could have been done, but I think there was more concern about being shut down for antimicrobial use in the animal health community.

I would also suggest that the committee consider in their evaluations from your own clinical use of antimicrobials what you would consider as the best in class in given categories of antimicrobials. I personally would not like to see any use of carbapenems in animal health. I think we would want to limit as much exposure as possible to these high-end beta-lactam agents. We know that there

are resistance determinants already out there, the metallo-beta-lactamases, for example.

Any suggestion that increased use of antimicrobials does not result in increased resistance I think again is disingenuous. We saw an excellent example yesterday just comparing the MIC levels of Ketek looking at erythromycin-resistant versus erythromycin-susceptible strains in an analysis the FDA presented.

As we use agents in a given class such as the macrolides, we select for increased levels of resistance and we get what's been referred to as MIC creep, and this is a bad thing.

So again, to sum up in less than 10 minutes, I think there should be more good will on all sides. I think we need more input from the veterinarian groups, the producers as to what is necessary and useful, and what the unmet medical needs are in animal health, at the same time we're considering what the important medical needs are for human health. I think that can help balance the risk-benefits approach that we heard Dr. Cox refer to.

However, I think it's very important that this group do assign relative values for antimicrobial agents because frankly the CVM, the FDA, the producers, the farmers, and the American public can understand what are the important agents, what do we have to reserve for human

use.

I can say a lot more, obviously. Like many on this panel, I love to listen to myself talk, but I'll stop now, and thank you very much for your attention.

(Laughter.)

DR. LEGGETT: Thank you.

Dr. Goldberger, could you please assign us our task?

DR. GOLDBERGER: We have really one big, broad question with a few elements in it. Basically what we'd like you to do, and again, although we want you to focus on the factors used to rank drugs according to their importance in human medicine, we still felt at this meeting it was very valuable for you to be given some broader background, as well as to hear the concerns of some of the other important stakeholders. I do want to say that we do want you to focus on the drugs according to their importance in human medicine.

There is an expectation that there may need to be further discussion of how this is factored into the overall plan, but we would like to think that at least this element everyone would be reasonably comfortable with, and then we can deal with some of the controversies that you have heard a fair amount about in the course of the presentations.

Basically our questions here are pretty simple. Are the factors used to determine the importance of drugs adequate? That is, are they clear enough? Are there factors that should be added, factors that should be subtracted?

Now, you notice we basically had broken things down to factors related to drug efficacy, factors related to the development of antimicrobial resistance. We, for instance, did not include, when we had done this, a specific section on factors related to drug safety, although I think one could argue that number 2 under efficacy, therapy of choice, actually takes into account safety issues as well. But if you feel, for instance, that's an issue that requires more attention, then that's something that would require some degree of modification.

Then the question of weighting. Are some factors more important than others, should they be weighted according to importance, and then ultimately, of course, the key question if you're going to do that, which are most important and how should they be weighted?

So that we don't appear to be totally without a clue, I will point out that we've been working on this intermittently for a few years. I actually presented at a CVM advisory committee, I think in January of 1999, some of the things you've seen here. So we've been working on it

for a while. We revisited it a year, year-and-a-half ago. We actually in many versions did have weights. I did not bring them with me, and I think that even given that I don't think I'd show them because we want to hear an unbiased assessment.

But we certainly recognize the possibility that weighting could be useful, although one could argue that also brings in it another level of subjectivity, some of which is almost invariable in this process. When you start talking about therapy of choice, and then you link that to the way physicians actually practice, that inevitably brings in a certain amount of subjectivity because often that varies from physician to physician which particular therapy is the therapy of choice.

I agree with some of the other comments, that the third element is certainly worth some additional discussion. You actually heard that touched upon by some of the speakers in the open public hearing, some of the areas that they thought should be accentuated.

But these are basically the issues we would like to touch upon so that we can see whether or not we need to do minor revisions, major revisions, whether the approach we've taken seems fundamentally sound or seems significantly flawed, so this can serve as a basis for some of the further work that undoubtedly is going to need to be

done.

Thank you.

DR. LEGGETT: With that, I'll open it up for anybody who wants to dive in first. Go ahead, David.

DR. BELL: First, I want to pay the highest tribute to the FDA for struggling for some years now with this new issue. They're the only agency in the world that I know that is really trying to struggle with this and develop this kind of an algorithm, science-based, risk-based approach, and it's difficult and they deserve a lot of credit.

I also want to pay tribute to the American Veterinary Medical Association for its efforts to address the problem of drug resistance on the farm through developing various principles to guide the therapeutic use and various educational programs that Dr. Apley has been involved in.

I think whatever the FDA comes out with, at the end of the day it has to work. It has to get the farmers the drugs they need and it has to protect the public health. Whatever comes out, if it turns out that some set of criteria are devised that result that farmers don't get any new drugs, that's not realistic. On the other hand, if it's too loose, then that's not helpful either.

Before I get to my specific suggestions, I want

to -- because we're properly focusing on just the single component of this complicated document and we've got to remember that. And I am struggling to focus on just that single component, but there are two other aspects that I'm trying not to focus on, but I want to mention them to you because I'm struggling in my efforts not to focus on them.

One is that whatever is the end ranking in terms of category that the FDA assigns to a drug, whether it's category 1, 2 or 3, once this is assigned it is almost impossible to change. Absent some determination by, I guess, the Secretary that there's an urgent threat to public health or something like that, it's almost impossible to change. The companies would be entitled to due process, which frequently involves fighting it tooth and nail and it just takes a long time.

That's a heavy burden here because, as we discussed yesterday, drug resistance is something that develops later. So the FDA is in a position of having to assign something here that's almost impossible to change, but in fact the problem is going to develop later. As we discussed yesterday, by the time you prove the extent of the problem and define it with all the resources that takes, resistance rates could be rising and you've lost the drug. That's a big problem here and that's one of the reasons that, unfortunately, you have to try to be somewhat

conservative.

The other issue I just want to mention is that these categories 1, 2, and 3, it doesn't strike me as all that conservative, some of what these restrictions end up being. Most everything turns into medium, at least under the current, I think. What does medium mean? Medium means it's prescription only. Well, big deal. Restricted in some cases in terms of extra-label use. In other words, sometimes they can use it off-label, sometimes not, as opposed to always or only.

Extent of use: low, medium. Well, you get back here to low or medium. Select groups of pens or animals. They don't say exactly how many animals would be given this at once, but the swine farm I was in, there were 1,400 animals I think in a barn so this would be some subset of them. Chickens, there are 30,000.

So, anyway, I appreciate the concerns of the industry.

Having said that, and trying to forget that and concentrate only on the importance for human medicine, I actually think that this list is a little too strict. I think that some factors are more important than others, and that if we classify a drug as very precious or high, whatever it is, because we need it to treat tuberculosis, that's just not realistic. We don't get drug-resistant

tuberculosis from drug use on a farm.

And I think there should be some weighting. I'm just going to skip right to bullet 3 here. Some factors are more important than others. Food-borne infections and, I guess I would say, enteric flora, whether or not they're food-borne, but infections caused by enteric flora which would predictably be in contact with either bacteria or genetic determinants ingested in food, that's where we should really be focusing.

Then to some extent -- I'm not sure exactly how to phrase this -- but flora that might be in contact with enteric flora -- stronger than "might be" -- I mean, are predictably in contact with enteric flora, and there's some reason to believe that resistance determinants could be transferred. I mentioned Staph. aureus this morning. The issue of respiratory flora I'm not totally sure what to do with because particularly in hospitalized, debilitated patients we find Gram-negative flora in their respiratory tract.

But I guess just to close here, I think that what's more important is enteric flora. Antibiotics used to treat infections with enteric flora, and then to a lesser extent, infections caused by bacteria to which enteric flora might quite predictably transfer resistance determinants. That's my thought.

DR. LEGGETT: Dr. Patterson.

DR. PATTERSON: I would like to say, being from Texas and having a family heritage of farmers from the panhandle, I do have an appreciation for the industry and I was glad to hear that most of the speakers from industry today were appreciative of the issue from the human side as well.

With regard to the questions, number 1A, I would say the factors that are listed are adequate.

For B I would say, could somebody add it or subtract it. I think that they probably could. And I think I would probably, in terms of those factors -- and I don't know if you want to put those back up there, those numbered factors -- I could in my mind combine factors 1 and 3. That is, the sole therapy, limited available therapies, and spectrum of activity of particular importance, because to me a spectrum of activity of particular importance would be one where it is the sole therapy or limited available therapy. Examples of that we've talked about for Gram-positives vancomycin, linezolid, quinupristin, dalfopristin, and then for multi-drug resistant Acinetobacter and Pseudomonas polymyxin, and also somewhat the fluoroquinolones and the carbapenems, as have also been mentioned. I would see that one as the most important factor.

Then as the second most important factor, the importance in treating food-borne infections.

The third most important factor, which is now number 9, ease of transmissibility of resistance determinants.

Then as number 4, I think you could combine numbers 7, 8, and 10, the cross-resistance issue, if there is cross-resistance within a drug class or across drug classes in a drug or drug classes that are used in both animals and humans. I think that concept could be combined.

To me the issue of therapy of choice is a little less important because, as Dr. Goldberger pointed out, that can sometimes be interpreted different ways. So I see that as a less important issue, as well as importance for oral therapy and unique mechanism of antimicrobial action because, again, I think that enters into the limited available therapy issue.

Then just as a comment, we talked a lot about risk yesterday actually, but I think risk cannot be totally quantitative and actually we have to use some qualitative principles and common sense in approaching some of these issues like we do in human drug approvals. On the other hand, I think it would be very useful for more data to be generated by those with interest in human and animal

microbiology to get more quantitative data regarding specific organisms and antibiotics in this issue.

One other comment, there was a concern about the release assessment to address the issue of giving high ranking to a parameter where data was not provided. My suggestion would be that those parameters did not seem overly cumbersome, and to go ahead and provide the data so that it could be more accurately ranked.

DR. LEGGETT: Could you clarify that last point?

DR. PATTERSON: Well, it's on page 3 of Dr. Bartholomew's presentation, the release assessment of Miracin. There are some relevant parameters listed there. I believe Dr. Apley in his presentation expressed concern that if one of these parameters was not provided, it would be given a high ranking. Is that correct? So my suggestion would be to provide the data. This is the data we typically see in human drug approvals and they don't seem overly cumbersome.

DR. LEGGETT: You're saying that drugs for animal use should have those as part of the new drug proposal?

DR. PATTERSON: Right, and that to me would be the solution of giving it a high ranking if the data wasn't provided.

DR. LEGGETT: And what to do about drugs already on the market in those same circumstances, since the future is to then go back and look at existing drugs?

DR. PATTERSON: Well, again I don't think that would be overly cumbersome. As far as I'm aware, I think most of the drugs that are on the market, these things are already available so it would just be a matter of compiling it.

DR. LEGGETT: Go ahead, John.

DR. BRADLEY: Can I make a comment without voting yet?

DR. LEGGETT: We're not voting today.

DR. BRADLEY: Oh, good, good.

DR. LEGGETT: We're being like the rest of the American public.

DR. BRADLEY: Being a practicing pediatrician and reviewing the FDA briefing document before coming, this is a very well thought out, comprehensive assessment and clearly maximally protects human populations, including children, from antibiotic resistance that may be of animal origin, and I want to acknowledge the amount of work that must have gone into this.

During the discussions this morning, however, the other side of the story became very clear with respect to how important antibiotics are in animal and flock use

and how critical they are to maintaining these healthy animals. What's really clear is that there's a lack of data for us on which to judge and make an opinion valid. The clear fact that anytime you use an antibiotic you develop resistance, we know this from the human experience. It's got to be true with the animal experience, as was brought up earlier. And that we've got the expertise to be able to study this is also very clear.

So I'd suggest that the FDA develop a standard format for evaluating the impact of new animal antibiotics with respect to development of resistance within herds and flocks and evaluate the extent of colonization of resistant organisms of both farm workers and consumers. In working with the American Society for Microbiology, the veterinary societies, the IDSA, I'm sure there is a way -- it will be rough at first -- but a way to evaluate the impact of antibiotics on development of resistance and assess the risk of that resistance for humans. Until we have a way to measure it, everything is qualitative, and I can understand the concerns for industry on fears of resistance tending to steer the boat in a direction of being more conservative than we actually need to. But until we have data, some of these concerns are very real.

Also, if we make more restrictions on the use of antibiotics, then an alternative to antibiotic therapy

in prevent of disease in animals, particularly in cows and pigs with respect to vaccines, which of course are used extensively in kids, may be able to decrease the number of antibiotics used. If there are vaccines that are used for viral disease in animal populations, then the illnesses that may be treated as bacterial infections, or as one speaker pointed out, the viruses set them up for bacterial infections -- if we restrict antibiotics in animal populations, then the impetus to investigate vaccines to prevent viral infections will be increased, which would be a good thing overall because it will increase the health of the herds as well.

DR. LEGGETT: Barth, are you ready?

DR. RELLER: Several comments. As I listen to the discussions, and having read the background materials, I think that we want to avoid -- there's the possibility and this tone came out -- of polar positions on this issue.

This is a huge, pervasive, longstanding, growing, and global problem, and clearly use of antimicrobials in animals is not responsible for it all, by any means. On the other hand, there are probably quite substantial data that a part of the problem is related to animal use. It's getting that balance that is the crucial way to be successful on this because it will be a long and arduous effort.

I listened carefully to the concerns voiced by persons being responsible for animal health and ultimately our own health through responsible use in veterinary practice. Those concerns seem to me to come repeatedly back to worries about undue limitation of critically useful agents. I think there are some ways around that, and there are some subsets to that.

For example, concern that if there's no evidence that the default position would be a high. Well, maybe one way around that is if there's no evidence to make the best judgment and then do a categorization on the basis of the evidence for that judgment, like is done in guidelines, so that if this is a big issue and the data are substantial, you say so. If you think it may be a big issue but there are no data, you say so. And rather than default to high, this is the best as we see, but we are honest that there are no data to support this. So it would give more maneuverability. So those points for which there is little or no evidence, one would have much more flexibility of not being locked into a categorization or a ranking.

There has been some hint that this may be too soft, too qualitative. I think the arduous attempts on the part of the FDA and others coming up with this system is an attempt to be more systematic about it, to avoid the

pitfalls of just an opinion about it. So the way that I think might be helpful to go about this is I think rating the relative importance for human use systematic assessment, as has been outlined, is important.

But I think equally important is the counterpart on the veterinary side so that if where we come out in the categories from a human perspective are at odds with where you would come out for the veterinary, it's sort of like the Senate and the House, and then you have a conference committee that resolves those differences, so that one could look at it from the different perspectives and then in the implementation come about with the resolution.

An example of this is Dr. Brown's forwarding information from the IDSA. As a fellow for more than two decades, I think the sense of that statement is supportive of what the FDA has done. But then when one goes through the fine print, there's this preservation, for example -- I'm giving a specific example of polymyxin that would get a much higher ranking. Well, if polymyxin came to this committee based on the data for safety and efficacy for the things preserved, I have serious questions whether it would make it. So it's just an example of where, rather than everything being critically ranked high, there needs to be some balance.

I mean, I agree completely on the relative importance of polymyxin versus fluoroquinolones and carbapenems. I mean, we're on different planets. I think there are ways to seriously meet the problem, but to take into balance what could be an adversarial and get it back into a collegial approach without which we are never going to get the kind of cooperation that would be necessary to keep us together over the long haul that will be required to do something about antimicrobial resistance as a growing problem for both humans and for animals.

That's all. Thank you.

DR. LEGGETT: Dr. Rupp.

DR. RUPP: Just a few comments. Initially I'd say I agree with many of the comments my colleagues have already made and I'll try not to reiterate those.

First of all, I think that the FDA has made a nice effort in taking something that's obviously inherently qualitative and somewhat subjective in trying to apply some quantitative measures to it. I think that from a global standpoint of looking at this whole problem, we really are hamstrung with regard to a lack of data. Studies haven't been done to some degree. Clearly in our discussions this morning we don't have a good grasp on the use of antibiotics in agricultural practice, how much are used, how they're used, how much as growth promoters, with

amounts and types of agents. I think that's one thing that we clearly need to know more about.

I think that I would agree very strongly with the statement that we need to cross-reference this list of antibiotics that we're putting together for human use, and cross-reference that with the list that our veterinarian colleagues draw up of what antibiotics are important in their practice, and concentrate clearly on the drugs that we think are both important. If there's a drug on our list that is of high importance and it doesn't make the list in veterinarian practice, well, that's easy. You don't have to worry about that too much and vice versa.

I think that perhaps this can be done in stages. I think we all agree that the main risk is involved with food-borne pathogens and enteric organisms and perhaps that's where we can initially concentrate and then, from there, perhaps extrapolate.

Then lastly, I would agree with the suggestion that Dr. Projan made that the FDA consult with additional experts in medicinal chemistry and people who really know about antibiotic resistance determinants and how they're cross-reactive and how they are transmitted and work on this list a little better.

DR. LEGGETT: Dr. Maxwell.

DR. MAXWELL: I just wanted to echo the

sentiments of Dr. Rupp and Dr. Reller.

I do believe that the effort that the agency has made is actually very good, but I believe that there can be unintended consequences for anything that is done, and part of the unintended consequence might be hurtful to the industry that we need to help.

On the other hand, I also believe, like the last speaker said, there should be some items that the industry recognizes that should never have a use in animal medicine and that both the industry and the agency should get together and decide what's most important for each of them. That way I think there would be a better ability to accumulate some knowledge that we don't currently have now, and yet get the data that we need to make some of the decisions that we need to go forward.

I really feel that there should be nothing that's made in stone, and guidelines are a good way to go. However, guidelines need to have some enforcement mechanism to them or else they cease to be helpful as far as the agency is concerned.

DR. LEGGETT: Dave.

DR. BELL: We need to help the FDA here, and in doing so, if we do this right, we will help the agricultural community and also the human medicine, public health community.

Here's the situation as I see it. There have been calls for additional data, and we definitely need additional data. On the other hand, there is a fair amount of data already. I'd even say a lot of data already from surveillance and epidemiologic studies and so on.

My experience in the five years that I've dealt with this, and also even previously, is that the studies tend to be interpreted differently by different groups of people. It's not random. I mean, the people who are specialists in human medicine and public health tend to, from their experience at the bedside wrestling with the dilemmas of how to treat a patient with a drug-resistant infection, have a certain training and perspective as to how they look at data. Then there's another community whose whole background is spent wrestling with the problems of raising healthy animals, and they have another perspective on how they look at data.

So although we certainly need more data, I think we're all just fooling ourselves if we say, oh, well, if we just did some more studies then suddenly the light would shine through, we'd all have consensus, and we'd all sit here and just kind of agree.

The position that the FDA is placed in -- and I'm taking the liberty of speaking for them -- please correct me -- they are a regulatory agency and a company

wants to introduce a drug for approval in agriculture, and they have to make a decision. And they're stuck. Just like we often have to make decisions based on an evolving evidence base or incomplete data, well, they're in this position all the time. So what are they supposed to do? Hold up the drug forever until more data come? License it, and then, when more data come, have to move heaven and earth to try to get it back, like they're doing now with fluoroquinolones in poultry?

Other countries, like the European Union, have just made decisions based on -- but they just ban things. This is at least a transparent process to come up with, okay, in the face of inadequate data but public health problems and needs for drugs, what are we going to do. So to say things like, well, we should rank evidence in this guideline -- I mean, they have to have a mechanism to move forward. The thing that concerns me the most is once they come up with something, it's very difficult to change it, but that's not my problem.

But I think what we need to do is help them here with one component of this algorithm. I assure you that the other two components to the algorithm that are not up for discussion today are under vigorous dispute in the Center for Veterinary Medicine public hearings and advisory committee hearings. I think that there isn't the expertise

around the table to get into those other segments and talk about larger issues.

What the FDA is asking us to do today is look at the human drug list and what do we think about that list, and the factors that are used to come up with it. I think if we stray from that, we're just not going to end up being very helpful.

DR. LEGGETT: Dr. O'Fallon.

DR. O'FALLON: Since I'm not a medical doctor, I felt that I didn't have a whole lot to say about a lot of the issues here.

Sitting here just listening to it as evidence, I was struck by what appeared to me to be a very rational suggestion that in addition to what are already being considered, all these things do seem to me to be reasonable to be considering. The suggestion that was made by Tony Cox that they also look at what the outcomes of the different decisions, what would happen if various decisions were made, I think that seemed like a very reasonable component as well.

I have no idea what it means. I can see the dismay on certain faces. But as an idea, as a concept, it struck me as a reasonable thing, that we also have to be concerned with what are going to be the likely outcomes of decisions that are made.

DR. LEGGETT: Dr. Ebert.

DR. EBERT: Again, hopefully not to reiterate a lot of what has already been said, but I think as Dr. Bell mentioned, I think we're somewhat at a loss here because of a lack of knowledge, primarily in the whole area of the therapeutics of these drugs in the veterinary setting. Obviously, the literature that we're aware of is replete with treatment guidelines in humans regarding when to initiate antibiotic therapy, as well as what choices of antibiotic therapy should be used in select circumstances, and when a new drug is approved we can place that antibiotic into that setting or that framework.

It's difficult I think for us to know how that would happen from a veterinary standpoint, and obviously I'm not aware of the veterinary literature. Perhaps there are treatment guidelines as far as the treatment of many of these animal-associated infections as well. But without knowing that, it becomes very difficult to really assess how we're going to use those agents and what their relative importance is from the veterinary side as opposed to from the human side.

Having said that, I don't want to spend a lot more time on that because I think the issues that Dr. Bell mentioned as far as we need to focus specifically on the areas regarding human infections. I had some similar

comments to those of Dr. Patterson concerning some of these various criteria, and I think some of them can be lumped together, as she mentioned. I have maybe a slightly different grouping of those than she did.

But I do believe that agents related to the single therapy or the therapy of choice are important with regards to criteria in human infections.

I do think that the importance of treating food-borne infections is also important, but I think that that could probably be incorporated into either the spectrum of activities so that if the spectrum of activity included gastrointestinal pathogens, that somehow those could be incorporated, or it could be rolled into therapy of choice, meaning that one of the therapies of choice that is important is the treatment of food-borne infections.

I think that the unique mechanism of antimicrobial action is a somewhat vague concept because it doesn't really allow us to differentiate within drugs, for example, within the beta-lactam class. They have unique mechanisms of action; yet, some of them I think are more important than others.

I do think that cross-resistance within a drug class is an important issue. If you have drug resistance to one agent and it confers class resistance, obviously that's a very important concern.

I do think that, again, potentially the other variables such as cross-resistance across drug classes and transmissibility, again there are a lot of similarities there for primarily dealing with plasmid-mediated resistance and multiple drug resistance, that there may be a way to combine those particular measures as well.

DR. ELASHOFF: It seems to me that although, from the point of view of action, one needs to think about where you're classifying things, and to end up having a classification for each thing as high, medium, low, or whatever you decide, that in the long run part of the importance of it all is that in the process of doing the ranking, one produces a document which discusses in detail what is known about the various factors so that you have something that you could show for what's been done, and when new knowledge comes, a place to update that and part of the process of perhaps reclassifying things as you go on. So we shouldn't be concentrating on, okay, now we've got it high, now we're done, but in documenting and in maintaining the documentation of the thoughts that went in to thinking about each of the factors that go into the categorization.

DR. WALD: I do agree with a lot of what has been said. I think the one thing that we can do, to not fail the FDA, is I think we could, in fact, rank-order

these things. I think we've all agreed that some are more important than others and that maybe that's something we could do right now. We could actually create a different phrase for the ones that we think could go together.

DR. LEGGETT: Right. That's how I wanted to end up. I wanted everybody to talk first, so we all know where we're coming from because a lot of these things are coming together. For instance, what Dr. Elashoff just said was what Dr. Reller said, but she said it in a different way. She wants an ongoing document. He wants A, B, C; 1, 2, 3. It's the same thing.

It's time for me to bore you.

My first question, is there a harmonization process underway for this, and if not, should there be? The point was made that the infections are worldwide. The statement was made that the Europeans are too draconian, perhaps, and the need for input from all players. Whether we call harmonization or whatever we call it, I think that we should try to work towards making things the same, or as much the same in Europe, in Japan, the United States, wherever, so that the pharmaceutical companies working to bring an antibiotic on board don't have to do 15 things in 15 different countries.

I don't know if there is any sort of outcomes data along with this. It would be nice, in terms of things

that are being proposed, that we could look back upon it, not only in terms of just pure data but also in terms of how this ranking thing works.

I have one question about what I counted in my looking at this, the tenth sort of parameter which is "serious infection." I didn't quite know what that meant. I don't know if that means deadly in 12 hours, or 100 percent prevalent in the community. I didn't find it on the list of the other 10 things. So I don't know how to bring that in.

I think that the Gram-positives versus Gram-negatives on these different line categories is not really what we're after. What we're really after is broad spectrum versus limited spectrum. So I think that we can rethink how we're doing it.

I think generally there are too many parameters. There are lumpers and splitters, and I think it's going to be much more flexible for the document to lump and then use different categories as subtexts. I think the best way to go forward is to make it flexible and that can be easily manipulated so that people have an idea of what you're talking about, but each new drug is a specific new drug that comes forward. The way things are done for human drug things, we don't have 15 zillion things. It's either safe and it's efficacious.

Then under that, from a long history drug companies sort of know what they have to do and they're in contact with the FDA going through that whole process. So I think it's better to be more flexible perhaps and staying qualitative than trying to be quantitative in that sense.

I like the idea of the enterics better than the food-borne, but I do think that whether it's enterics or food-borne, that's sort of got to be the focus of whether it's the first thing we work on, or whether it's the most important part of those parameters for human illness, it makes the most sense because it's linked the most, as everybody knows.

In a subcategory of that, I would think that we could in those sort of things -- if, for instance, Campylobacter is more prevalent than Shigella and Campylobacter has developed new resistance, that that sort of has a higher priority in terms of things going on than the Shigella. The way things were sort of qualitatively, arbitrarily distributed as low, medium, high, if it's less than 5 percent, 5 to 15, whatever it is, over a range of prevalences where some things are 90 percent prevalent and the other things go from 1 to 5, it can't be fixed in that. It should be fixed overall so that if something is 90 percent prevalent, it's not just high because it's greater than 25 percent. It has to be over the whole thing. So

something that is 25 percent prevalent, even if that particular bug is only 25 percent prevalent, that's still less than 90 percent of another bug that could be a pathogen. It's going to be difficult. I understand.

I also agree about the statements about transmissibility being a given, and I also like the idea of certain things are definitely off the table in terms of carbapenem use in animals. We'll just have to get around to that certain point.

Having grown up on a farm myself, we still killed the pigs and the beef cattle in the fall. We didn't kill each other. Well, the Hatfields and the McCoys did, but other than that.

With that, unless there are some other sort of general statements, why don't we try to go around as a group and follow Dr. Wald's suggestion and see among us what are the important things and how could we in a utopian world come up with a great list.

DR. WALD: Why can't you sort of say sole therapy as an item? I don't know if you want to get a show of hands or have someone try to consolidate it with another category. It might be a more efficient way.

DR. LEGGETT: So, Jan, your position was sole therapy/therapy of choice as sort of one thing?

DR. PATTERSON: Well, I think that was Dr.

Ebert's suggestion. I could go along with that, but I saw 1 and 3 sort of being the same thing. Sole therapy, limited available therapy, spectrum of activity of particular importance. I guess you could even put maybe 1, 2 and 3 as a consideration. What I said before was you could combine 1 and 3, and I think Steve said you could combine 1 and 2.

DR. LEGGETT: Comments?

DR. BELL: Maybe I don't understand the process that's been proposed.

DR. LEGGETT: I think they would like us to comment on the actual parameters there and what we would like to do. I think we need to give them at least some sort of concrete first approach at this.

DR. BELL: I seriously question whether sole therapy matters at all if we're talking about the treatment of tuberculosis. I want to start with enteric infections.

DR. LEGGETT: Yes, enteric infections. I think we could call it enteric infections. So, instead of Gram-positive, Gram-negative, you would just sort of say enteric infections, yes or no?

DR. WALD: Right. And there was a lot of consensus about that. I think everybody agreed is food-borne is something we know a lot about.

DR. BELL: Not just food-borne.

DR. WALD: And related Gram-negative.

DR. LEGGETT: I think when we were talking about the transmission already occurs, I still think the idea of the transmissibility, low or high, is worth keeping. Any comment? Feedback? John.

DR. BRADLEY: I agree. 1, 3, and 9 were at the top of my list, so the 1 and 3 I am in agreement that they are very important and could be lumped together. Although there can be lots of mechanisms for development of resistance and cross-resistance, if it's not transmissible, then it may not be a public health problem. It seems as though there are a lot of antibiotics that have been used out there and relatively few events which have been picked up and reported on. I think transmissibility is very important because if it's low transmissibility, then it shouldn't be a high problem.

DR. LEGGETT: I would sort of think we could also use this -- the way I saw sole therapy fit right in with unique mechanism because to me a unique mechanism is not going to be unique forever. The sole therapy is often the sole therapy because of the unique mechanism. So to me that sort of goes together nicely as a parameter. What we're going to call it I don't know. Uniquely sole or something.

Go ahead, John. What we're trying to do is

just get a rough thing of --

DR. POWERS: No, I think this is very helpful. One of the questions I wanted to try to clarify was the idea of ease of transmissibility, and the idea of suppose a Gram-negative in an animal has a resistance element on a transposon. We know that that may be capable of being transmitted to another pathogen. How much evidence would you consider before one checks off that box? One of the things I heard was this idea several times around the table of more data. Would one consider an in vitro experiment showing that that can occur as adequate evidence? Or what kind of information on ease of transmissibility would one want? Or is the very fact that the resistance element exists on a transmittable element good enough?

DR. LEGGETT: To me the fact that it happened once is enough to pull the trigger.

DR. POWERS: In vitro? In vivo?

DR. LEGGETT: No. In vivo. The United States story here this past fall was enough for me.

DR. RUPP: But in general anything you can do in the test tube happens in nature.

DR. LEGGETT: Yes, but it took a long time for us to get VRSA, and we'd been doing it in the test tube for decades.

John.

DR. BRADLEY: My concept was, as an antibiotic is introduced into a herd, to take a test herd. Once you check for colonization in the animal herd to look at development of resistance in a previously unexposed herd, you will get data on how quickly resistance gets transmitted between cows, between buildings. If you also do colonization studies on the workers in those barns, you'll get some information on how easily those organisms with their resistance determinants may be transmitted to humans.

So I'm not necessarily looking for disease, but transmission of organisms that have those transposons in them. There is beautiful molecular techniques that can track specific resistance elements as they move between people, or animals and people.

DR. LEGGETT: The other thing, to me looking at the list, splitting cross-resistance within and between classes, as new drugs or old drugs that we revisit come through for animal use, it's going to be a drug-by-drug situation. So you're going to know whether there exist cross-resistances within that class or between classes, so all you're really interested in is the cross-resistance. Then you can assign a value of low, medium, or high based on whether you know it's widespread and it's cross-resistant. It wouldn't seem to help me, trying to find out

whether a drug comes on the market, to know those particular things because they're all incorporated into, is there cross-resistance.

Sorry. Barth.

DR. RELLER: I like to think in groupings rather than splitting it out. I think the factors related to development of antimicrobial resistance are basically two. That is, what resistance means within and across classes, and it also relates to -- and even these agents -- if it's a different compound that's used in veterinary medicine but it's a similar class. I have no illusion that a fluoroquinolone used -- even though it's not prescribed in humans, if we've got resistance in animals and humans, it's going to go. So basically it's cross-resistance and ease of transmissibility. There are two concepts, so you've got them down to two there.

Up in the beginning, I agree completely that the unique mechanism is linked in with sole and principal. I mean, those three elements are pretty much one. Is this the best drug available? And if it's the best drug available for staphylococci, whether it's a unique mechanism or whether it's the only drug or whatever, that's one that we can't mess with because the pathogen is important and it's far and away the best agent.

DR. LEGGETT: Yes, the example with carbapenem.

DR. RELLER: Exactly.

So I think actually lumping some would make the decisions easier. We discussed getting at it from multiple approaches that the carbapenems and the fluoroquinolones, not that they're the only ones, are ones that should be able to get the job done in animal health without using those categories of compounds.

DR. LEGGETT: Celia.

DR. MAXWELL: I just wanted to add one thing to what Barth said. In addition to cross-resistance and ease of transmissibility, shouldn't it also be virulence? The virulence of the bug? Isn't that what really we're concerned about?

DR. RELLER: I think that virulence is important. To me the way you get at the virulence is up in the sole, only, unique mechanism, preferred drug, and I think that some targets of antimicrobial therapy are more important than others. I'm not saying that it's more related to the issues we discussed with veterinary medicine, but to me Staph. aureus is a more important agent intrinsically than Campylobacter jejuni is in the overall spectrum. Not that Campylobacter jejuni isn't important, and clearly the implications for how drugs are used in veterinary medicine are far more important for Campylobacter jejuni. But for humans, Staph. aureus is a

much more important global organism.

Now, the importance of making those relative distinctions I think is it gets us out of some difficulties because what may be crucially important -- Mycobacterium tuberculosis, Staph. aureus -- means that the implications on the veterinary side may be relatively small. So I think that actually making these distinctions gives us ways to have collegial resolution of issues as opposed to the opposite.

DR. LEGGETT: So could we consider this just importance of the pathogen in terms of a parameter, and then under that parameter we would then weigh whether this new drug was going to have a big impact on Salmonella or a big impact on Staph. aureus or something? So really it's not whether it's enteric or not or food-borne or not. That's subsumed under the fact of how important is that pathogen and how connected is it to food animal-human connections.

By the puzzled looks, I didn't make myself clear, especially to David.

DR. BELL: Well, I wasn't sure what the last phrase meant. The way the challenge to the human drug is presented is we're saying it's acquired, that the bug is acquired through the food-borne route, that either it causes resistant infection itself or has a resistance

determinant that can be transferred to other bacteria with which it will predictably come in contact in humans.

I actually like the point that some of these bacteria are more worrisome than others if such resistance might develop. But I still think we need to exclude the tuberculosis and the congenital syphilis and stuff like that as a parameter in its own right before we go into the rest of it.

DR. LEGGETT: I'll go back to what I said earlier. When I read this, I thought those things were examples of things that could potentially be considered under that. I did not think they were actually stamped in stone, this is what we're going to consider. I may have been mistaken.

DR. TOLLEFSON: No. The categorization would be lifted, the ranking would be lifted straight from the document.

DR. LEGGETT: Then I totally agree. TB and neurosyphilis and all that stuff goes. That's not the way you try to make the decision.

DR. TOLLEFSON: Okay, it goes as a reason. Remember, we still have to look at each drug class. So the way we got to the TB and the neurosyphilis is through the factors. So what you're doing will take care of that once we rank them, in terms of importance to the issue, as it

relates to animal drug use. I think.

DR. LEGGETT: Help us out, Mark.

DR. GOLDBERGER: I hopefully would just really be playing devil's advocate. But just to follow up on the TB, again, you know, we did not take into account at all how likely veterinary use was to influence, you know, for instance, changes in the resistance patterns of tuberculosis. We simply used tuberculosis as an important infection and therefore that had to be taken into account with certain classes of drugs. So, I don't disagree at all with this discussion.

But to flip it around, assuming that safety issues and residues were not a concern, what we might, for instance, be saying is, if we're not concerned about tuberculosis, then we would have no objection, for instance, to rifamycins being developed for substantial animal use if in fact that turned out that they might be useful for some of the veterinary infections we're talking about.

DR. LEGGETT: The way I thought about it, and when we were talking -- what Barth was saying -- the rifamycin question gets kicked out because of the cross-resistance. So, in other words, when you look at rifamycin and you know that it's really important and that emergence or resistance is very easy if you use the drug alone, then

that drug doesn't get used. I'm talking about rifampin.

DR. GOLDBERGER: Okay, yes. In other words, we're saying that resistance does develop quickly, but the infection that's really important for the rifamycins is tuberculosis. I mean, we'd be arguing there would be no linkage based upon what people have been saying, so why would we be worrying about that? That's what I'm trying to understand. It seems a little bit in conflict with some of the other comments and I want to make sure I understand this.

DR. RELLER: Dr. Goldberger, the way I would look at this is if we say there's a ranking of the organisms, having to do with virulence and potential for human disease, the big intrinsic pathogens, I mean, the Staph. aureus, Mycobacterium tuberculosis, that as an agency that anything that might mitigate the effectiveness owing to cross-resistance, how it would be used, of an agent that is essential for the treatment of tuberculosis, that that would be a very high barrier. I mean, there would have to be some super-compelling reason to ever consider it in animal use.

DR. LEGGETT: And it wouldn't only come under that cross-resistance. It would come under the sole, unique, principal therapy.

DR. GOLDBERGER: And that's fine, but then

we're saying that even though the connection between what goes on in animal therapy and resistance in tuberculosis may be tenuous, the need for a drug like rifamycin is so great that that would overshadow it, which is the way the document is written now, but, yet, I thought I heard committee members thinking that the tuberculosis issue as an example was not important.

DR. LEGGETT: If you're using only tuberculosis, I think we're going to miss the point, because now we've got DMAC, you know, and rifamycins are important for DMAC, so it's not only TB. So, then you've already dug yourself in a hole by just saying TB.

DR. GOLDBERGER: But just to follow up on that, they're in fact not that important for disseminated MAC. The real example, when we wrote this, was tuberculosis. And I understand the arguments that have been made, that what's the link, it's so tenuous. Yet, in fact, the need for the rifamycins is so great in that infection, it would seem to me that would overcome it. But, I'm not clear in which direction people on the committee are going. I just want to make sure we understand this clearly.

DR. LEGGETT: The way I've tried approaching this, trying to horde people together is that we want a document that you can use when a sponsor is in front of you. So it has to start from the drug. And so we've got

to go through the drugs rather than going through human diseases. The human diseases get brought into it by all the people that are sitting around the table and it starts from the drug.

Steve, and then you, Mark.

DR. EBERT: Well, just some thoughts from what Dr. Reller said, and I think this might be part of the issue, is that as you look at examples of problems, first of all, I would think the most important would be if you have a commensal in an animal that develops antibiotic resistance and that organism can directly cause infection in humans. That would be first.

Second, though, would be where you have resistance that develops in a commensal and that resistance is able to be transmitted to a pathogen in humans. So to use your example of Staph. aureus, let's say VRE, where that would be a secondary but certainly equally important issue.

And then, as you get into some of these other issues, if it's a spontaneous, but yet not transmissible resistance that may be of importance, but I would probably put that third on the priority list.

DR. RUPP: I guess I would go to your example of the rifamycins. You don't exclude it or discourage it from use in animals because you're worried about

multiresistant tuberculosis evolving in animals. You're worried about it because it's used for adjunctive therapy in staphylococcal disease and orthopedic implants and things like that.

DR. PATTERSON: Well, I agree that the sole therapy issue kind of takes care of the TB thing and the Staph. aureus thing, because we don't see much, although we have had some bovine TB in Texas lately, and I think some companion animals can transmit Staph. aureus to humans, but not in the industry setting. So I don't think those are big issues, but the sole therapy issue takes care of those, for things like MRSA, linezolid, and so forth.

But I think maybe the factor that we're missing and kind of maybe what we're getting around in some of this discussion is that one of the factors should be whether there is evidence of transmission from animals to humans of a particular organism that that drug would affect. An example of that would be Salmonella and fluoroquinolones, for instance. So while some of these considerations are theoretical, we know that there are some instances of transmission of some of these food-borne things definitely from animals to humans, and that evidence should probably be a pretty important factor in all this.

DR. LEGGETT: I think that's what Barth and I and others had stated, that under the transmissibility and

what kind of evidence is enough, one episode. And so transmissibility/transmission to me is sort of the same thing.

DR. RUPP: I guess I would just emphasize again either the organism or the resistance determinant.

DR. LEGGETT: Right.

DR. POWERS: I want to get back around to that, though. And that is the idea when you talk about things like vancomycin-resistant Staph. aureus, as Dr. Bell pointed out, that in vitro phenomenon was pointed out years ahead of when we actually saw it in vivo, which one would estimate that might be a predictor.

The other thing that Dave said was, we keep coming around to, well, studies that show. Those studies will most likely be interpreted completely differently depending upon who reads them.

So, what I'm trying to get some clarity from the committee about is, what level of evidence would be enough? Suppose somebody mixes MTB and a Gram-negative in a test tube and shows that this resistance determinant gets transmitted. Somebody could read that and say, oh, that's never going to happen in vivo, ever. So, what level of evidence are we talking about here?

DR. PATTERSON: Well, in my mind, you know the VRE example, to me, would fit under ease of

transmissibility as a factor. Whereas the salmonella and fluoroquinolones is a stronger factor in that there's evidence that that's actually happened. So, to me, I can kind of fit the other potential thing, the VRSA from VRE as an ease of transmissibility factor.

DR. LEGGETT: I wouldn't think it's a yes or no. I would think it's graded, so that if you have in vitro you'd take that into account, but if you've already shown that in vivo, that's more of a red flag.

DR. POWERS: So that gets back to what Dr. Reller was saying about sort of grading the strength of the evidence. So you could say, ease of transmissibility, but this one we know happens. This one, well, theoretically it could happen in the test tube.

DR. LEGGETT: Right.

Steve.

DR. EBERT: Along with that grading part, it's not just one criteria that's going to make or break this issue. You may have transmissibility, but it may be transmissibility of resistance to a drug where that's the only drug that you're using. For example, vancomycin, last resort type of an agent. That might be different from transmissibility of a beta-lactamase where you have a lot of different alternatives. That might not be graded in the same way. Even though there is transmissibility, you still

have a lot of other therapeutic options available. So, I don't think we should take each one of these criteria as if one of them is true, it's all true.

DR. LEGGETT: Right.

The way I envisage this is you guys helping the sponsor along the way to developing a drug and by locking them into low, medium, or high as things move along, sort of tell them, well, we think it's going to be a low priority, but things might come up during that drug development and you say, whoa, hold on a second, have you guys thought about. It should be something that allows them some guidance along the line, not just one hoop to jump through one time.

Dr. Brown, could we get your input as having worked in industry in the past?

DR. BROWN: I've been thinking more of the old saying that says it's better to remain silent and thought a fool than to open one's mouth and demonstrate it.

(Laughter.)

DR. LEGGETT: But, more in the sense of the difficulty in the "jumping through the hoops" that the agency comes through, as we envisage it, is this an unworkable situation or do you have a sort of gestalt that industry could live with it?

DR. BROWN: I'm not sure who I should speak

for, but I think in comparison to the problem of finding new agents, that problem dwarfs this issue. I can tell you that 20 years ago one of the major companies was screening 30,000 new soil samples a month and not coming up with anything new. Then, if we look at the number of new classes of agents, which have been discovered since 1965, we can count them on one hand. So, that problem, I think, overwhelms this one.

DR. LEGGETT: Go ahead, Mark.

DR. GOLDBERGER: Let me make sure that I understand. For instance, vancomycin is essential for life-threatening Gram-positive infections. Linezolid is also essential. Rifampin is essential for tuberculosis. The carbapenems we use, as an example, are believed to be essential across a broad range of serious Gram-negative infections. And the fluoroquinolones, in fact, are really essential for certain life-threatening Salmonella infections. We could argue, I suppose, about that, but in fact there are very few options.

But what we're saying is in any case -- and we can could argue about the fluoroquinolones or not -- if you make that type of statement, that's basically all you need with regard to the importance of those therapies. If we truly believe that they are essential in those settings, that's what everybody is comfortable with. I mean, you can

argue about what's really essential or not, and that's fair, but if there's a consensus that they are essential -- and certainly the first four I gave, I think there is consensus -- that's all we need to say, that these are going to be considered very important in human medicine.

DR. LEGGETT: Yes, but remember, we've been thinking about this all the last 90 seconds, not the last 4 years. So, I'm sure there are big holes in our thinking.

DR. GOLDBERGER: I will say that in some respects, when we thought about an actual weighting system, I can tell you that the idea that something would be essential for a serious or a really life-threatening infection carried enormous weight in the process without regard to how veterinary use might relate. And that I think represents, from a human practitioner, the level of risk we would be willing to accept that any veterinary use would result in a diminution in effectiveness in the treatment of humans. So that's sort of one of the basic things that our weighting system took into account. That was our thinking over the last several years. I will say that now that we've had a chance to talk about this in more detail.

DR. TOLLEFSON: If I may make one comment, we understand that way of thinking, but when we go to put the ranking list into use, it doesn't give us a tool to take

the direct link, the link that we know exists, with enteric pathogens, picking up resistant bacteria that are commensal in the animals and pathogens in the humans. That comes out the same. In other words, there's no differentiation of high. So we have more evidence for one subset of that high, much more evidence that it really occurs and really does have a human health impact, public health impact, than we have -- I guess the essential therapy is more of a future issue, a potential, more a potential issue.

DR. LEGGETT: To me there is ranking in that the link with Salmonella and fluoroquinolones is A-1 evidence. Some of the other things that are brought up is B-2, C-3. So that in the ranking, the A1 that you already know and you already know is a problem, Campylobacter, Salmonella, Shigella, E. coli, whatever, those are all A-1.

DR. TOLLEFSON: Okay, fine, so if we can get there that would be helpful.

DR. LEGGETT: Do you want to add to that, Barth?

DR. RELLER: Well, related thereto, the way I would envision this might work is that we have these essential agents. Let's say one of those agents came up on the veterinary medicine as being essential, just conceptually, that if we don't have fluoroquinolones, the production of pork in this country is going to be

decimated. There will be no pork industry. Then you weigh the importance of those two things, and if in that situation there was clear evidence, as there is with Campylobacter and the fluoroquinolones, for example, then that would be easy. It would be devastating if it were to happen, but the weight of the evidence is that it hasn't happened yet, it's never been demonstrated in vitro. Then you may say, well, for right now we're going to have some use with some constraints in animal care.

DR. LEGGETT: Go ahead, David.

DR. BELL: Maybe somebody from the FDA wants to address this, but my understanding of the legal basis for FDA regulation of drugs in animals is that drug use in animals must pose no risk of harm to human health. No. A reasonable certainty of no harm to human health. That is the law under which FDA approves use in animals. The FDA does not consider the economic effects on the pork industry. It is reasonable certainty of no harm to human health.

Let me just make one other comment. Although we sit around the table and say, oh, well, when cases of transmission from animals to humans are known or shown or proven, I just have seen enough cases now where evidence that we might accept is actually vigorously disputed by some folks in the agricultural sector. So I think we need

to be wary of hinging this on "evidence," "studies," "transmission." I mean, unless there's some clear-cut guideline that everybody agrees on.

You'd be surprised at how many people dispute that the major cause of drug-resistant Salmonella infections in humans is drug use on the farm. When I say people, I mean in various kinds of agricultural groups. I get all kinds of stuff about drug use in hospitals and human sewage that pollutes the farm. So stuff that we kind of believe based on epidemiologic and laboratory data, there are folks out there that dispute it.

That's where I'm kind of saying, well, drugs that are used to treat infections with enteric bacteria, or bacteria that would predictably receive transmissible elements from enteric bacteria, those are the drugs where we should start, and we shouldn't necessarily get into what's the evidence for transmission from animals.

DR. LEGGETT: In that case we'd never use erythromycin. We'd never use lincomycin because of MLS. We'd never use penicillin. We'd never use tetracycline. They would not be used in animals if that law is the way you're saying it.

DR. BELL: No, I mean we start there.

DR. LEGGETT: You said the FDA already has that. That's the only criteria they have. And then I

would say, well, then why do we have all these drugs here?

DR. TOLLEFSON: Because when those drugs were approved, we didn't have this issue or we weren't evaluating the safety of those drugs based on this issue.

DR. LEGGETT: Maybe we'll have to change the law.

DR. BRADLEY: It seems as though the debate centers around whether drugs will be available or not, and I think to pull it back into the original discussion, if it's high, the drugs are available. It's just that they're controlled, high or medium. So it's not like we're preventing important drugs for the pork industry from being available. It's that they will be under the use of a veterinarian.

DR. LEGGETT: Yes, recognizing the fact that the use of a veterinarian might raise animal production costs so high that people will get out of the business.

DR. BELL: Yes, I don't hesitate to advocate my personal view that antibiotics are drugs, and when they're used in animals, it should only be under the supervision of a veterinarian. I don't think we have to be embarrassed about any such requirement. I don't think it's a particularly burdensome requirement.

DR. LEGGETT: We could spout on and spin circles forever, Mark.

So basically the way I understand it, we have sort of thought about twisting and turning these things and changing these parameters into sort of maybe five, one being what is the organism that could be affected by this class of drug, whether we call it enteric, Staph. aureus, whatever, sort of like name this organism, is it important or not.

The next one would be that 1 and 3 combined, which we would call sort of spectrum broad versus limited, with limited being good and broad being less good except that you'd have to also take that into account for the kinds of infections that are going to need to be treated in animals. Oftentimes it's going to be more empiric. I would imagine that they don't get cultures as often as we do.

The third factor would be this sole use, unique mechanism, principal drug, in other words, best drug availability as a factor of the more the drug for humans seems in that category, the more restricted it has to be in animal use, so that it goes toward the high, or category 3, is it?

DR. TOLLEFSON: 1.

DR. LEGGETT: 1.

Then with the fourth one being cross-resistance among drug classes and between people and animals.

The final one being the transmissibility/transmission issue, whether it's the organism, the determinant.

And then in all these things I guess you could use the classification that we sort of do for the human guidelines. So I guess you could work on an A-1, B-2, C-3 type thing for the enterics for the spectrum. Do we know that something has happened with broad spectrum antibiotic use in the past, or is this sort of theoretical?

The sole, unique, principal, I guess we could go with A-1. If we know that the drug is the same that's already in humans, that sort of is a no-no. That would be sort of towards the A-1 category.

Does anybody want to define or sharpen or add or subtract to that?

DR. MAXWELL: Which factor, which number would include virulence? Because I think ease of transmissibility doesn't necessarily speak to virulence.

DR. LEGGETT: Barth, do you want to speak out loud?

DR. RELLER: I think that the virulence is an important part of what the ranking of the organism is. So that was a major factor in organisms that are more important than other organisms. It has to do with their intrinsic virulence.

DR. LEGGETT: My voice has given out. Time for concluding comments if you're going to make any.

DR. GOLDBERGER: I think this was very helpful. I think we could probably go around a little more about this, but the truth is it's probably time from our perspective to take back all the suggestions that you've made to see how this can be modified. I think you've given enough specifics that we have a pretty good idea about it, and then to see what the next steps might be. We have to do this obviously very much in concert with the folks in CVM to see whether some of the other scientific questions that have been touched upon here, in terms of links between humans and animals, need themselves to be at some point revisited in a similar setting to this, perhaps a joint meeting with the folks from the CVM advisory committee and other relevant experts because I think that ultimately we will have to come back to that point about links between animals and human and what that does in the overall process, even if it's not specifically in the ranking in human medicine. So I think that that's something that may be for the future.

But I think that this has been extremely helpful to get this discussion, and particularly the ideas about consolidation because I think that we agree that if we can simplify this, that alone simply begins to increase

clarity for people. Some of these things truthfully, even I was very much involve, frankly, in writing all these things, now since I haven't looked at it in a few years, when I try to think exactly what we meant, unless I go back and look at all my notes, I'm not sure that I fully remember all the distinctions. So simplifying it I think would be very good for everybody.

I was asked to remind everyone that we have re-opened the docket so that we can receive additional comments with regards to discussions at this meeting. The docket number I've been given is 98D-1146. I think that we would certainly welcome additional comments. I would like to encourage the folks from the veterinary community and producer community not only to provide additional comments, but to encourage those folks who may not have been able to attend this meeting to look at the transcripts, et cetera, and see what comments that they would like to make. I think that would be extremely important getting the best possible picture.

I'd like to thank everybody for sticking it out here until the end. Even though we are finishing a little early, it is frankly nothing short of remarkable to see that the entire committee is still here without having to lock the doors or anything. I want to certainly commend all of you.

DR. LEGGETT: Great. Thank you very much.

(Whereupon, at 3:38 p.m., the committee was adjourned.)