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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR VETERINARY MEDICINE

VETERINARY MEDICINE ADVISORY COMMITTEE

Tuesday, January 26, 1999

8:30 a.m.

Holiday Inn Gaithersburg
Ballroom

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Abigail Salyers, Ph.D.
Lyle Vogel, D.V.M., M.P.H.

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P R O C E E D I N G S

DR. STERNER: Good morning. I will now convene the second day of the VMAC Committee dealing with issues of antimicrobial approvals and antimicrobial resistance.

We are in the final portion of our public comment phase. We have two speakers scheduled this morning.

Representing the American Association of Bovine Practitioners is Dr. Jim Jarrett, and he will be giving his view on the questions from the Bovine Practitioners perspective.

Dr. Jarrett.

Public Speakers

Dr. Jim Jarrett

DR. JARRETT: Thank you, Mr. Chairman.

I appreciate the opportunity to speak, particularly at this time. My personal thanks to you for allowing it.

DR. STERNER: Jim, I need to interrupt just one moment, and give your disclaimer.

DR. JARRETT: Right now. Next sentence.

I have no financial interest in this matter. My expenses to this meeting were paid by the members of the American Association of Bovine Practitioners.

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I am a veterinarian. I am a former dairy owner, part owner of a 1,000-cow dairy. I practiced for some 30 years in a dairy practice and still do some practice. In fact, we will be on the farm one day later this week trying to explain the proceedings of yesterday and today to a dairy client.

Currently, my day job is the executive vice president of the American Association of Bovine Practitioners, and, Mr. Chairman, I have an idea that I will more than likely give back some time that has been allotted to you and continue with the trend set yesterday with the early speakers that kept everyone on schedule.

The American Association of Bovine Practitioners is an organization of veterinarians with over 5,800 members, mostly in the United States. We feel that the health of every bovine in the United States is impacted either directly or indirectly by one or more of our members.

We are proud to be a part of an agricultural industry that provides food for this nation that is the safest, most wholesome, least expensive ever known in the history of mankind.

We know that in the United States, food from animals is purchased by the consumer on a voluntary basis.

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To think that any producer would do anything to discourage or endanger that voluntary purchase is to abandon all sense of reality.

We agree that there could be a problem associated with the use of antimicrobials in animals, but to use the vernacular of the day, is it a high crime and misdemeanor? We don't know for sure.

At the same time, we would note the many disagreements among the extremely well-qualified presenters of papers from this desk yesterday as to the cause and solution of this problem.

You have heard many fine presentations made by highly qualified individuals regarding the document under consideration. In order to save time and reduce the redundancy of some of these presentations, I would just say that I agree in principle with the remarks made by Drs. Burkgren, Apley, Cullor, and Vogel, and the positions of our sister organizations, the American Veterinary Medical Association, the American Association of Swine Practitioners, and the Academy of Veterinary Consultants. So, my comments will be a little more global.

As an organization and as individual members, we have a great concern over this issue. This certainly

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includes the concern for the health of the human consumers of the products produced by our clients. We are dedicated to the maximum safety of these products through the health and well-being of the animals we treat.

To reach that goal, we from time to time need tools such as antimicrobials to treat, control, and prevent disease. As an organization, we reached early on a consensus and an understanding that this matter can have a great impact on the way we practice and the service we render.

So, we quickly embarked on several efforts to inform and educate our members and others as to its importance, such as including sessions at our annual conference and other meetings regarding antimicrobial resistance, including items in our monthly newsletter on this issue.

We had a committee appointed very early on to formulate a set of prudent use or judicious use guidelines, and actually this committee was appointed and began work even before the AVMA Committee was appointed.

We are a part of the financing of the database project that Dr. Apley mentioned. We are a part of the AVMA Committee on its judicious use principles, and other

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activities which I will discuss later.

We applaud the Center for Veterinary Medicine in its efforts to reach its stated goals of protecting human health, and heartily agree with the motives, while disagreeing with some of the methods.

We fear that the adoption of this proposed framework document as it is written would further restrict the availability of products needed by the cattle veterinarians to reduce and control pain and suffering in the animals we treat.

More importantly, we feel this action could lead to increased animal disease, which could create an even greater risk -- and you notice I have not yet used the words "risk assessment" -- that could create an even greater risk to the safety of the human food supplied rather than reducing than risk.

Particularly, we fear that this would increase the cost of moving the frontier of knowledge in the area of new technology needed to continue to reduce pain and suffering in animals.

I feel this issue to a great extent may be based on what may have happened in the past, and not the way antimicrobials are currently used on farms today. The

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practice has changed, and as a dairy practitioner I can attest to that. We do not use antimicrobials in the ways on farms that we did 10 or 20 years ago.

In the dairy industry, as an example, the advent of residue tracking. In the dairy industry, as an example, the advent of residue tracking has forced us into using less antimicrobials, and it has been a good thing, because we have seen increased management and improved management to take the place of these activities.

As to specific comments regarding the document, and specifically the five questions that were posed earlier, first, do the concepts of the document provide a sound scientific basis for achieving the goals of the CVM. The answer, of course, is yes, but at what cost in increased animal suffering and human risk?

Question No. 2 has to do with the categorization of drugs. This categorization seems to be rather complicated and cumbersome, and particularly concerning the Category I compounds, and could easily be exclusionary in the availability of compounds for us to use to relieve pain and suffering in animals.

Monitoring, the third question. Certainly some monitoring could be helpful in determining any changes in

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the susceptibility of microbes to antimicrobial compounds. There is an old practice axiom that I use constantly that says, "If you can't measure it, you can't manage it."

We would note again, however, we have concern about the methods, not the motives, for this one question. Resistance threshold. We have concern regarding the definitions of what is resistance and what is a shift in susceptibility, and who and how breakpoints will be established, and what actions may be taken once these thresholds are established.

The fifth question relates to on-farm testing and monitoring. This sounds good, however, when and where and how will these samples be taken? What will be the impact of management on individual farms as relates to the outcome of the testing on these samples, and the concern regarding the fact that these samples will be taken a long way from the consumer, and could they just as well be or include samples closer to the consumer.

In addition, we would have concerns over another layer of regulations laid upon the industry especially in light of the difficulty of the agency to enforce those already on the books.

I would point out some of the areas of extra-label

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drug use as an example of some of these concerns.

Many areas of the document are not clear. The continued use of words like could, might, maybe, if, and the description of one speaker, murky area, and it would make me wonder if this is an indication of some of the controversy over the basis for this document.

I agree with Dr. Bell regarding the lack of understanding between human medicine and veterinary medicine. We in the veterinary profession, we in animal agriculture, we know that the problem is all in the human field, and the human profession know that the problem is all in the veterinary field, when, in actuality, the reality is somewhere in between.

This lack of understanding has led to a polarization of two groups that should have the same goals on this issue.

I think we can agree, all of us in this room can agree on a few things as a starting point. No one in this room would knowingly do anything to endanger the safety of the food supply in this country. In the case of food from animals, any negative effect we realize could have a direct effect on the sale of these products.

I think we can agree on the fact that the exposure

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of microbes to antimicrobials can, not always does, can lead to some reduced susceptibility in the area of treatment. I think we can agree on the ways and the fact that the ways we have used antimicrobials in agriculture does need some changes to minimize the development of antimicrobial resistance.

We are already in the process of doing that. I would sympathize with the committee in having to interpret very complex information and make recommendations to the CVM, however, I feel every confidence that you are capable of doing this, and I would urge the CVM to seriously consider any recommendations that you might make.

I would urge that you deliberate your recommendations regarding this document, that it continues to allow the involvement of the professional practicing veterinarian in this effort. Please try not to restrict the tools of modern technology needed to relieve animal suffering and assure the wholesomeness and safety of the products of American agriculture.

AABP stands ready to execute and help in any way the furthering of these goals.

I mentioned earlier that I would discuss one additional area of AABP activity in this area. In an effort

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to improve the understanding on both sides, in the past year we have arranged some visits to livestock operations by CDC personnel.

One such visit was to a family operated 350-cow dairy farm, literally managed and run by a family, a man and his wife and four sons. One of the questions that came up during that visit -- and I will close with this illustration -- was, "Do you think you need new products to use to treat your animals?" The answer was, "yes."

The next question was, "Why?" The answer was, "I don't like it when my cows die."

Thank you.

DR. STERNER: Thank you, Dr. Jarrett.

You have some time remaining. Are there questions at this time from panel members? Yes, Abigail.

DR. SALYERS: This is a comment on a number of talks in the same general direction. It is something that I am a little confused about. I have heard a lot of comments of concern about suffering of animals and treating animals, and it seems to me that the reason that confuses me is it seems to me that one of the things that this guideline would do is to help to reserve some compounds for later treatment.

No one seems to be concerned about the fact that

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the first victims of agriculturally causes antibiotic resistance are likely to be the farmers or rather the farm animals themselves.

I heard of at least one case of a calf farm in this case, that had gone out of business because they had something, Salmonella typhimurium strain get loose that was untreatable. Are you concerned about that? I mean aside from human medicine, that possibly the agricultural use of antibiotics would create a situation on these large, highly centralized farms with crowded animal populations, that you would have organisms like the shrimp farmers have over in Southeast Asia, have basically run out of antibiotics to use to treat their animals.

Now, most people here are not going to shed a tear over the death of a shrimp, but -- maybe some of the seafood fans here would -- but what do you think about that? Are you concerned about the possibility of strains that are so resistant, of animal pathogens that are so resistant that you might have problems treating them?

DR. JARRETT: As I understand the question, are we in veterinary medicine, food, animal veterinary medicine, particularly concerned on-farm as it applies to out activity about the development of antimicrobial resistance, and the

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answer is certainly yes, and in that regard we feel it is the activities we are taking so far, as an example, in AABP and in AVMA, coming up with guidelines, recommended procedures for use of these compounds to help reduce that capability.

We are also concerned that if further restriction is added to the development or, as I mentioned, moving the frontier of knowledge in this area, that it could impact the availability of products in the future, as well.

DR. SALYERS: It just seems to me that this framework document, properly developed, could actually have more benefit for the farmer than for human medicine, if anything. I mean by reserving, by restricting use at the present time and thus reserving, as we are trying to do in human medicine, the front line compounds for later on when we need them.

DR. JARRETT: I think your comment, "properly developed," I could certainly agree with.

DR. STERNER: Further questions for Dr. Jarrett?

[No response.]

DR. STERNER: Thank you, Jim.

Our final public speaker of the morning represents the National Cattlemen's Beef Association, Ran Smith.

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Dr. Ran Smith

DR. SMITH: Good morning. My name is Dr. Ran Smith. I am a Doctor of Veterinary Medicine, feed lot operator, chairman of the National Cattlemen's Association's Beef Quality Assurance Advisory Board and Beef Quality Assurance Subcommittee.

It is my pleasure to be here today and to offer some brief comments to the Veterinary Medicine Advisory Committee on behalf of the National Cattlemen's Beef Association.

The NCBA was established in 1898 and serves as a trade association for America's one million cattlemen with offices in Denver, Chicago, and Washington, D.C. NCBA is a consumer-focused, producer-directed organization representing the largest segment of the nation's food and fiber industry.

Since its establishment, NCBA has provided leadership on the national scene to ensure the consuming public of a plentiful supply of safe, wholesome, and affordable beef.

For example, in the area of food safety, in 1985, the National Academy of Science recommended the U.S. meat inspection system move to a hazard analysis and critical

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control point approach to inspection.

NCBA worked hard for over 10 years to put this new science-based system into place. HACCP is now employed in the nation's largest packing plants with implementation in medium-sized plants to begin this month.

In addition, consumer education initiatives, such as the Fight Back program, continues to increase food safety. These initiatives have resulted in reduction of disease caused by major zoonotic pathogens of concern, namely, Salmonella and Campylobacter, to levels below the Year 2000 target established by the Department of Health and Human Services.

We are confident that these initiatives the NCBA supports to improve food safety are paying off and reducing the need to take other action at this time.

In addition, in 1987, we initiated an aggressive, industrywide beef quality assurance producer education program. These efforts have resulted in beef and beef products which are virtually residue free.

These policy decisions, educational programs, and food safety research initiatives are driven from NCBA's annual investment of over $5 million, coupled with millions of dollars of other public and private sector investments.

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In order for drugs to retain their power over pathogens, they must be used in a responsible manner in human, plant, and animal treatment. NCBA recognizes that the use of feed additives and drugs and antimicrobial aerosols are a necessary tool in efficient production of livestock.

We encourage FDA to evaluate new products using clear, logical, science-based systems for approval. Drugs and feed additives should be evaluated individually using scientific risk assessments to determine their likely effect on public health.

These assessments should be based for establishing safe, realistic residue tolerance levels. The increased ability to detect residue in smaller and smaller levels should not automatically result in decreased tolerance levels or removal of drugs and additives from the market without sufficient scientific proof to establish reasonable public health risk.

NCBA believes that animal drugs and additives can be used by the beef industry to produce safe, wholesome meat products for the consuming public.

We encourage livestock producers to use animal drugs and additives in conformity with dosage directions,

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requirements, and withdraw periods. Through the efforts of the industry's beef quality assurance education initiative, producers commit to using sound animal husbandry and preventative practices to limit the need of antimicrobials.

NCBA recommends and participates in long-term producer and veterinary education on the prudent use of antimicrobials in food animals. The beef quality assurance program is being expanded currently to include greater emphasis on proper drug use beyond the current focus of residue prevention.

This effort is being conducted in concert with the American Veterinary Medical Association, the American Association of Bovine Practitioners, and the Academy of Veterinary Consultants.

We are extensively involved in the scientific discussions regarding potential for the use of antimicrobials to generate resistance. NCBA has policy which supports our commitment to proper use of antimicrobials and residue prevention.

Let me emphasize when there has been scientific basis to support action on behalf of the beef industry, NCBA has always taken aggressive action. We are very concerned that no such scientific basis exists to support the proposed

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framework.

We believe additional research needs to be initiated to determine the proper course of action. NCBA supports post-approval monitoring systems to evaluate the potential impact of new animal drugs.

We believe such data and other research will over time assist the production sector in making accurate scientific-based decisions.

The National Research Council in July of 1998 report the use of drugs in food animals, benefits and risks, states, "Information gaps hinder the decisionmaking and policy process for regulatory approval of antibiotics used in food animals. A data-driven scientific consensus on the human health risk posed by antibiotic use in food animals is lacking."

NCBA encourages FDA to conduct a comprehensive scientific risk assessment that takes into considerations antimicrobial use in all sectors of society. Completion of such a risk assessment will enable officials to monitor the level of antimicrobial resistant pathogens in the environment in a more efficient scientific manner.

Perhaps an alternative to the action listed in the proposal would be to work to establish a strong system of

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national monitoring for trends in antimicrobial resistance. If trends indicate the number of resistant bacteria are increasing, APHIS and ARES could work together to perform epidemiological studies of these bacteria in order to pinpoint the cause of such changes.

As a result of this research, a task force consisting of industry, veterinarians, public health officials, and government should work together to establish practical, meaningful solutions.

Products in question should be reviewed by the task force and appropriate changes in labeling or distribution should be made.

In the document, a proposed framework for evaluating and assuring the human safety of microbial effects and antimicrobials, new animal drugs intended for the use of food producing animals, NCBA is concerned that FDA has created a risk assessment tool without first establishing the risk.

NCBA cannot support the current framework document and encourages FDA and CVM to continue this dialogue, as well as engage in additional research before taking action in this regard.

Thank you, Dr. Smith.

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Are there questions from the panel members for Dr. Smith?

[No response.]

DR. STERNER: Seeing none, Richard, you have the floor to make comments on two written submittals.

MR. GEYER: Did you have a question?

DR. ANGULO: I believe the last speaker didn't present his support nor his travel expenses.

DR. STERNER: Thank you, Dr. Angulo.

Ran, that is a detail I overlooked. It's my fault. I had intended to ask you your affiliation and your support.

DR. SMITH: I am sorry, Mr. Chairman, I should have mentioned that. I am representing the National Cattlemen's Beef Association, and my expenses were paid by the National Cattlemen's Beef Association.

DR. STERNER: Do you have any financial interests?

DR. SMITH: I do not.

MR. GEYER: Advisory committee procedure requires that at the close of the public comment period, we summarize briefly any written comments that were submitted by those who did not make public oral presentations, and I will do that now.

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We received two written comments. Copies of those comments have been made available to everyone, and I will present a brief summary of them.

The first was submitted by Pharmacia and Upjohn, or I will refer to them as P and U, provided comments on the framework proposal in general and on a number of specific issues.

P and U supports the CVM initiative to develop an appropriate risk-based framework to address the human health impacts of antimicrobials used in food animals, however, P and U contends that there is no evidence for an imminent hazard from the use of antimicrobials in food animals that would demand immediate changes in the pre-approval process for new animal drugs.

They would prefer to have a complete risk analysis performed before implementing any changes in regulatory policy affecting animal drugs. P and U commended CVM for putting forward concepts of risk characterization and exposure assessment, but believes that the resulting nine categories, such as 1H1M, and so forth, overly simplifies the process.

P and U recognizes the need for an expanded surveillance system to gather more data. P and U supports

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systematic monitoring of drug susceptibility patterns and zoonotic pathogens from animals at the time of slaughter, but emphasizes that such data is insufficient to set monitoring and resistance thresholds.

The company states that on-farm monitoring of zoonotic organisms is not needed at this time as a post-marketing tool to assure human food safety.

A second comment came from Dr. Kelly Lechtenberg, a veterinary consultant, Midwest Feed Lot Services.

Dr. Lechtenberg shares concerns over the continuing emergence of antimicrobial resistance. Dr. Lechtenberg believes that the cost-to-benefit ratio of on-farm testing will be much higher than collecting the data at slaughtering plants.

Dr. Lechtenberg recommends focusing resources on four things: first, continuing the process of risk assessment; second, educating consumers and meat industry workers and veterinarians; third, increase support for the national antimicrobial resistance monitoring system; and, fourth, development and implementation of judicious use guidelines for veterinarians.

That concludes the summary of the written comments, and while I am on my feet, let me introduce a

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couple of people who are at the front table in the first row here who did not speak yesterday, and they are available today as resource people to us for the benefit of the committee and consultants.

To the far left is Joy Dawson, who is from FDA's Office of Chief Counsel. At the table on the right, to the left is Al Sheldon from the Center for Drug Evaluation and Research; and then to the left of Dr. Goldberger is Dr. Kaye Wachsmuth from the USDA.

We have had two others who were here yesterday, and hopefully will be here later on today, Eric Flamm and Jesse Goodman, both from the Commissioner's Office.

Just one more thing if I might, Keith, I would like to recommend everyone today, when you speak, if your name hasn't been mentioned as you start to speak, please say your name for the benefit of our reporter.

Thank you.

DR. STERNER: Now that we have the audience assembled and things quiet, I need to introduce a member of the Veterinary Medicine Advisory Committee who was not here yesterday, Dr. George Cooper. Dr. Cooper, would you background the rest of VMAC and the audience a bit about yourself?

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DR. COOPER: Good morning. I am deputy administrator for the Partnerships Unit in the Cooperative, State, Research, Education, and Extension Service of the U.S. Department of Agriculture. This is my last official meeting, I think, with VMAC. I am pleased to be here, regrettable and sorry that I could not be here yesterday, but I had an offer related to my job that I could not refuse on yesterday. I was in Dallas/Fort Worth. I got in last night about 11 o'clock.

Based on what I heard about the meeting, I probably could have come by at that time and participated in some of the discussions, but I am glad to be here today.

DR. STERNER: Thank you, Dr. Cooper.

Questions from the Committee and from the Floor

We are now at a point where it is the opportunity for the Veterinary Medicine Advisory Committee to ask questions of invited speakers and public speakers. Those public speakers who remain, please make yourselves available to come to a microphone.

I would like to open the questioning, exercising again the prerogative of the Chair, the questioning to Joy Dawson, having to do with some comments that Dr. Vogel made

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in the AVMA presentation yesterday regarding the authority for regulation of microbial contaminants as a food additive, and could you give CVM's position on that. Thank you.

MS. DAWSON: If I understand the question correctly, it is whether the agency has the option of regulating the resistance issues under the food additive provisions of the statute versus the animal drug provisions of the statute.

Unfortunately or fortunately, the statute does not provide flexibility in this area. If the substance results from the use of a drug in the animal, it must be considered under Section 512, which is the new animal drug provisions. The only way to get it under Section 409, which is the food additive provisions, we would have to establish or it would have to be established that the resistance was not a result of the use of the drug for treatment, that it was separate and apart from that.

DR. STERNER: And a second question. Does CVM make a risk-benefit calculation when addressing an approval in NADA?

MS. DAWSON: When you say risk-benefit, do you mean the risk to humans versus the benefit to humans or to animals?

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DR. STERNER: Yes, that is correct, humans and animals.

MS. DAWSON: No. In the context of a determination for approval of a new animal drug, the statute requires the agency to make two determinations. One is as to the effectiveness of the drug, and the second is to the safety of the drug, and looking at the safety of the drug, we are looking merely at the risk of the use of the drug, not any benefits to either humans or animals from the use of that drug.

So CVM and then the new animal drug context does not do a risk-benefit determination as may be done in the context of a human drug.

DR. STERNER: Dr. Barker.

DR. BARKER: Whoever wants to take this question, feel free. I think it would be beneficial to the committee to understand something about the evolution of the framework document, who contributed to it, who are the primary authors in bringing this document forward to us.

DR. STERNER: I think the department director or Linda, one of the two of you

DR. SUNDLOF: Let me just go back and talk a little bit about what prompted us to engage in this activity

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of developing a framework document.

We were faced with a very sticky legal dilemma in that there was significant concern that the use of antimicrobials in animals causing resistance was at the level where the agency needed to look at the food safety aspects of that in making a determination of whether the drug was safe.

It was at the request of the animal drug industry that the agency take immediate steps to develop a policy, a regulatory framework for reviewing these products because without that kind of consistency and specific guidance, they found it very difficult to get their drugs through the approval process because the issues seemed to keep changing.

So, as a result of that, we made it the top priority of CVM to devise what we thought was the best regulatory framework we could to address the specific issue of antimicrobial resistance in animals, and how to regulate that without disrupting the process by which we review animal drugs and move them through to approval.

We recognized very early on that this was not just a CVM issue, that this issue had broader ramifications, and so it was important that we involve people outside of CVM, but within the FDA, and those included individuals from the

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Center for Drug Evaluation and Research, and Mark Goldberger was the primary contact person from CDER. Al Sheldon also participated.

They were part of the team that wrote the document. In addition, we had individuals from our Office of Policy, Dr. Eric Flamm, was looking at the broad policy issues and making sure that any policies that were laid down in this document were consistent with other agency policies.

Dr. Jesse Goodman participated in that from the Office of the Commissioner, and Dr. Goodman has a lot of experience in the area of antimicrobial resistance from the standpoint of managing the teaching hospital at the University of Minnesota, where he was responsible for managing how pharmaceuticals were used in an attempt to minimize resistance within the hospital situation.

From CVM, I participated in the writing of this. Peggy Miller participated, Linda Tollefson was a participant. Sharon Thompson participated in it. We had additional help from Marissa Miller and Kathy Hollinger, and I am sure I have left out some people, but that large team of people was responsible for authoring the document as you see it.

If I can just go on a little bit further because

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it is apparent that our intentions in writing this are maybe not well understood. The intention was to develop a document by which we felt we could make a determination prior to approval that there would be reasonable certainty of no harm, which is the only legal basis that we have for making the determination of approval.

We recognized that we were dealing in an area in which the science was not very clear, in which there were a lot of data gaps as was indicated in the recent NRC report, and where there is insufficient data, it is difficult to make the determination of reasonable certainty of no harm.

Now, let me, if I may, just read you what the statute says. This is from the Code of Federal Regulations, Title 21, 570.6. It says that before we can approve a drug -- and this is a food additive standard, so this does not apply to human drugs, it does not apply to companion animal drugs, it applies to the food safety determination -- and then it says, "Safe or safety means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use."

How you make a determination of reasonable certainty of no harm when there appears to be a great deal

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of scientific uncertainty surrounding this issue*. We have heard the concerns of many that we haven't done an adequate risk assessment and that an adequate risk assessment is necessary, I can tell you that we have attempted to develop a risk assessment. We are still doing that. We have under contract one of the world's authorities in risk assessment who is assisting us with the issues, but in the end, we don't believe that the data exists out there to be able to determine the specific impact of resistance on public health, and we don't want to get to the point where we have data that will allow us to make that decision. Once we have gone there, once we have hard data that shows that antibiotic resistance as a result of animal drug use has caused harm to people, then, we have gone beyond the reasonable certainty of no harm standard, we have surpassed that.

So, we have to rely on surrogate endpoints in order to make the assessment of reasonable certainty of no harm. In this document, the surrogate endpoints that we were considering were surrogate endpoints regarding resistance thresholds. Recognizing that those are going to be difficult to establish, but we felt that it would be possible to get scientists together who could address the

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issue and make a determination of what they thought was the best available knowledge was a level of resistance below which there is reasonable certain of no harm.

Making that decision prior to the approval, so that we could stay within our statutory framework, so that we can establish what consider a priori before the approval to be the reasonable certainty of no harm standard, and we had a basis for regulating to that standard, and the basis would be using our monitoring programs both in animals and humans to look at the development of resistance and use our reasonable certainty of no harm standard as the trigger point for taking additional regulatory actions.

Once you cross that line, it would be clear that the standard for reasonable certainty of no harm has been surpassed.

Without that, being able to establish what a reasonable certainty of no harm is, I don't see how we can continue to approve drugs based on the assumption that there is more information coming, that there is an additional risk assessment that is going to give us additional information under which we can establish reasonable certainty of no harm.

Reasonable certainty of no harm has to be

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established prior to the approval. It can't be established sometime out there in the future past the approval. So, if it was the wishes of this committee and the animal drug industry and the animal agriculture sector that we should wait with any kind of regulatory framework until such time as there is an adequate risk assessment, until such time as, for instance, a blue ribbon panel met and gave us guidance, we could do that, but in the interim we would not be able to make that determination of reasonable certainty of no harm because we are still awaiting information.

The only other way around that I see from a legal standpoint is that we make the determination that there is no risk, that the agency makes the determination that there is no risk as a result of antimicrobial resistance development as the result of antimicrobial use in food animals, and we have gone on the record -- and that is Policy Guidance Document 78 -- that announces that the FDA now believes it is necessary to evaluate the human health impact of microbial effects associated with all uses and classes of antimicrobial drugs.

That, the agency has already determined. We have determined that there is a need for assessment, that there is a need to comply with the standard of reasonable

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certainty of no harm when making an approval decision.

Now, I think some of the ideas that we have heard about risk assessment and science-based decisions, I think were enlightening. I would just say that if you look at the way we regulate residues, for instance, from the toxicologic basis, those are using surrogates, too. They are not using the impact of those residues on public health. You cannot go through the literature, you cannot go through epidemiologic records and find where the residues in food with the exception of a handful of cases have resulted in adverse public health impact.

We use laboratory animals as a surrogate model for humans, and we apply exaggerated uncertainty factors which we call safety factors in determining what an acceptable daily intake is, and we don't look at that in the light of how many people are adversely affected.

If we were doing that, then, obviously, we would have again crossed the boundary, the standard of reasonable certainty of no harm.

When we do risk assessments, and there are cases where we do use a quantitative risk assessment in the evaluation of animal drugs, and those would be in the case of carcinogens, and in those cases we use a model, a risk

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assessment model, which is based on giving rats and mice generally the maximally tolerated dose of the product which is suspected to be a carcinogen over the lifetime of the animals, and the top dose is the maximally tolerated dose, and there are some other doses in between, and then extrapolating well, well below the data to determine the risk of a one in a million chance, an increased risk of one in a million that an individual may develop cancer.

One of the speakers yesterday talked about having validated models. Well, that model has never been validated, that model can't be validated, but they are models which are used. They are used for the purposes of setting standards, of having consistency in the regulatory process.

In terms of setting resistance thresholds, that is another area where it is going to be very difficult to determine the absolute cutoff point at which resistance becomes an intolerable threat to public health, but I can tell you that there are a number of policies which are not exclusively based on science because the science is not clear.

So, where there is scientific uncertainty, then, we have to interject policy decisions, and this framework

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document once again was an attempt to establish through both science and policy a regulatory structure that would allow certainty, stability within CVM in the regulation of these drugs.

It is complicated. There is a lot of stuff in here. It is intimidating, it is complex, the issues are also complex, and so I think, you know, maybe that might help the committee. Sorry for taking so long.

DR. STERNER: Thank you, Dr. Sundlof.

Dr. Holland, I saw your hand next.

DR. HOLLAND: Dr. Goldberger, should the framework document be accepted and implemented, and microbial resistance problems in humans continue, what is next?

DR. GOLDBERGER: Well, I think that several speakers asked yesterday, I think both some of the prepared presentations and some of the speakers during the open public hearing about the issue of what is happening on the human side as opposed to this initiative on the animal side.

As you can imagine, this concern about the development of antimicrobial resistance and its implications for the treatment of infections in human beings has produced concern more widely within the FDA than simply within the Center for Veterinary Medicine, and we within the Center for

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Drug Evaluation and Research are obviously quite concerned about it.

We are also involved in some initiatives that have not yet gotten the same degree perhaps of attention as this meeting although they have been discussed or at least discussed in a preliminary way at a couple of more open meetings.

I think things that we are particularly interested in doing are thinking about how we can provide information in product labeling that at least will give practitioners and perhaps patients information and advice about issues related to antimicrobial use and the development of resistance.

We think that that is obviously an important component. Some things as simple as just reminding people that antimicrobials are not very useful for viral infections, that antimicrobials ought to be used in situations where the organism is believed to be susceptible, for instance, to that given antimicrobial.

So, that's an initiative that we are currently working on. Another initiative that we have been working on -- and, in fact, this was part of a large public advisory committee meeting that we had in this past October -- is

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how, for instance, we might facilitate the development of products that are referred to as narrow spectrum products, that is, new antimicrobials which are more likely to be active against some of the resistant organisms that we are concerned about, but otherwise don't have the same broad spectrum that drugs, for instance, like the fluoroquinolones have that might encourage these products ultimately to be used in more selective circumstances.

One of the issues is how to encourage development of such products and also how to do basically clinical trials of such products since often they need to be combined with a second drug. So, that is something that we are working on, as well.

I think that what other initiatives might be necessary will depend in part on the success of these initial ones, but I think that it is important to make clear that although at the moment obviously this particular initiative with the Center for Veterinary Medicine is getting the most attention. This is a problem that we recognize more broadly across the FDA.

The other thing, just as an aside to mention, is there is also an interest in seeing what we can do to help facilitate the development of newer diagnostic tests that

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might make it easier to identify and organism earlier in the course of an infection, and therefore, tailor antimicrobial therapy more specifically to that organism.

One of the issues that frequently comes up in the management of complex infections in people is that you are uncertain what the infecting organism is when the person comes in who may be quite ill, and individuals end up getting put on multiple antimicrobials, sometimes a clear-cut cause of the infection is not identified, and people remain on several drugs for an extended period of time.

One of the goals is if we could identify such infections earlier, we might be able to tailor antimicrobial therapy more specifically to that infection. So, there are some things that we are doing. I suspect that after these initial initiatives we will have to look and see how useful they have been and then decide on what other things might need to be done, as well.

DR. HOLLAND: The nature of this meeting has focused on food-borne. I am surprised that no one talked about pocket pets as being a major contributing source of Salmonella to young children. That is just a surprise to me here.

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What about consideration for such creatures as pets and pocket pets in the future, as well?

DR. ANGULO: We do recognize companion animals as a source of Salmonella and as Campylobacter. Our current estimate are probably that about 3 percent of all Salmonella in the United States is attributed to owning pet reptiles and another smaller proportion of Salmonella cases are attributed to owning other companion animals, particularly companion animals that have diarrhea.

Campylobacter, we are in the midst of a national case control study, the first national case control study of Campylobacter, and we will evaluate more fully the role of companion animals with transmission of Campylobacter. It is probably on the same order of magnitude in terms of companion animals being the source of Campylobacter infection for people.

We do recognize a small risk, but again the predominant source of Salmonella and Campylobacter in the United States is eating contaminated foods, most of which are foods of food animal origin.

DR. STERNER: Dr. Tollefson.

DR. TOLLEFSON: I would like to add to that, that the FDA feels also that when you are treating a companion

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animal with an antimicrobial, there is an education element which is very easy to transmit from the veterinarian to the person, to the owner of the pet, recognizing that there is a risk from the disease in the animal.

Say, for example, that a pet is given fluoroquinolones. The veterinarian could advise the owner that pet animals do carry Salmonella, it may become resistant due to the use of this antimicrobial that is being used to treat the pet, and therefore, that humans can take additional precautionary measures. That is not the case when we are dealing with the resistant pathogens arriving on food, you know, where there is a large disconnections.

DR. STERNER: Dr. Holland, would you care to share with VMAC the results of some of your own culture work, please?

DR. HOLLAND: Well, we have been to different area zoos, farms, and cultured animals for Salmonella, and we can find Salmonella in pets, of course, in the house, in the carpet, in the basement, in the back porch, you know, all over, so pets are a major source.

My concern is once again although food animals are a major contributing factor to the food-borne problems, they are not the only problem, and I think we need to also bring

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up -- if you are going to make a broad statement, then, we need to look at all factors, and not just one factor perhaps.

DR. ANGULO: We recognize fully that Salmonella can be present in the environment and feces that are shed by animals that are colonized with Salmonella. We know you can find it very easily wherever you culture feces. We can provide the data, if you would like, but it is the collective wisdom and experience from the food-borne and diarrheal branch at CDC that the majority of human Salmonella infections are largely derived from contaminated food, and although you can find Salmonella in feces of dogs and cats and other animals, those feces of those animals just don't get into our food supply very frequently.

The way most Salmonella gets into our food supply is through foods of animal origin.

DR. STERNER: In the interests of getting as many questions answered as possible, I hope that our committee members keep their comments as brief as possible.

Dr. Hock.

DR. HASCHEK-HOCK: I would like to ask Dr. Tollefson a question regarding the pre-approval process.

Could you just briefly summarize the current

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regulations in force for determination of pathogen load and resistance and what the proposal is for this framework, how to alter that?

DR. TOLLEFSON: Sure, I would be glad to, but Peggy would rather do this.

DR. MILLER: Yes, I am really the pre-approval person. Currently, the microbiological safety studies that I discussed yesterday, which are the Salmonella shedding study and the coliform study, which have both a component of resistance and patient load, are required for all antimicrobials administered in the feed for more than 14 days.

DR. HASCHEK-HOCK: It was difficult to determine what the proposed changes were from document.

DR. MILLER: Okay. In the framework document, we would change that from a broad-based exposure only scenario to incorporating a public health component, so that if an antimicrobial has no utility in human medicine, they would only have to look at the pathogen load component, not the resistant component.

DR. HASCHEK-HOCK: So, you are actually decreasing the requirement, is that correct?

DR. MILLER: In some cases, that would be the

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case, yes. So, for an ionophore, for example, now they would have to do the whole 558.15 studies, whereas, under the framework document, they would only have to look at the pathogen load component of those studies.

DR. HASCHEK-HOCK: Thank you.

DR. STERNER: Dr. Lein.

DR. LEIN: Steve, in a way, the last antibiotic for a food animal being Batril for beef cattle has started into this process, and we are looking at again a post-approval monitoring program.

How is that going? Are we learning something from that? That is one of my questions. The second question is we do have a very complex framework here, we all know there is a lot of things that have to be answered in there.

To do this, obviously, we see that there has to be research that goes forward. What are your plans for solving these framework problems, is there going to be money available for at least private government ARS's, other research groups, universities, to solve some of these problems to go forward? Thank you.

DR. TOLLEFSON: To discuss the first question, the Batril 100 approval last August of feed lot cattle does have a voluntary post-approval monitoring program associated with

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it. We have not yet received any results on that. We can't discuss that in a public forum anyway. Those data are all owned by the sponsor.

The second question on the research issue, we actually have received approximately a million dollars that we have put out in extramural contracts for 1998, and we anticipate doing the same for '99 and 2000, and all of those involved research on various aspects of antibiotic resistance.

We can get you more information about that. Actually, the awarded programs are on our home page. We try to support as much as we can on the research end, but are very limited by resources.

Many times if we do put as much money as possible into the research area or the post-approval monitoring area, you need to be aware that these funds, assuming we have them, are often at the expense of other programs within the Center which can include the pre-approval area.

DR. STERNER: Richard Wood.

MR. WOOD: This is also for you, Dr. Tollefson. I believe yesterday in your presentation, you talked about the on-farm monitoring program. In some of the presentations, concern was raised about the nature of that aspect of this

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framework document.

How do you envision the data being collected? What kind of verification might there be from the standpoint of the FDA of that data? What kind of authority exists to go on farm? Would on-farm management strategies also be looked at in terms of strategies that might reduce the pathogen load or the risks of antibiotic resistance occurring?

If that is not enough -- I would support this on-farm step, but I want to make sure that we agree. Basically, what is your rationale for including an on-farm strategy as a part of the framework document?

DR. TOLLEFSON: Our plans are not well formulated at all, like many portions of the framework document, a great deal of additional work needs to be done to implement any piece of it, and that includes a lot of public input.

But what we were thinking about on the on-farm studies, FDA was not going to do these at all. That would be left up by the sponsors. Now, what we envisioned was that it would not need to be done on a drug-specific basis, that seems wasteful to us, that probably on a species-specific basis.

You could monitor for many drugs. You could

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monitor for many pathogens. It is due to the expense, and we don't want to appear to underestimate that expense, it would probably be most beneficial to have those done in a cooperative agreement type with drug sponsors of the Animal Health Institute, and a government agency, but not FDA, possibly APHIS, maybe other parts of USDA, such as ARS.

FDA does actually have the authority to go on farm, but we are not even thinking about that. We don't have that kind of expertise or resources to do it. The reason for those on-farm studies is really to provide more information about the actual resistance as it emerges.

The national program is a good start, but it is chronically underfunded. We cannot expand it to the level that we feel would make it robust enough to be able to detect a problem should it exist, let alone -- I know a lot of concern is expressed about identifying little pockets of resistance and going out and doing some kind of regulatory action based on that, but in reality, that is not the problem with the system.

The system is limited by the amount of information we can collect on each of the species, the number of pathogens we can collect, the number of antimicrobials we can screen for, and it is really a matter of not having a

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lot of confidence in the data, that if a problem is out there, we are able to detect it, and that has to do with the representativeness of the sample, as well as the number of samples being taken.

So, the on-farm studies then would provide more information about why that resistance is occurring, and it is not only due to drug use, we know that. It could be a number of things, and it would allow the sponsors, animal producer groups, veterinary practitioners to go in early and take mitigation steps, some kind of intervention steps to try to control it. That was our thinking.

Does that answer your question? Okay.

DR. STERNER: Dr. Lein.

DR. LEIN: Following up on that, this sounds a little different than what was presented or what I anticipated, because it seemed like it was drug related to the drug that was going to be brought up for at least approval for licensing.

Now, I would buy more what you are talking about from the standpoint of a constant monitoring program, to increase that monitoring, and we have all looked at, at least the national program. I think almost every one in here is excited about that, would support that.

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I, coming from a diagnostic lab background, say that we are missing a lot of information in those laboratories, and today, the laboratories are under accreditation. They are following the standards that are set up through NCCLS, at least a good share of them.

I think that material is valuable and it does give you a wide view of what is happening in several species. Not only that, but we tend to run at least human antimicrobials also in those, because we are fearful from what you have indicated that we do get resistance coming back to these animal industries, not through drug use, but from contamination, and some of this from human waste or human use or pet use or other use.

This brings up the idea that we need to look at this as a society. I think the last NCBA statement here about societal needs to look at this become very important. I think when we first started to talk about antimicrobial resistance and monitoring, which goes back some years now, I know I sat in that room and I was excited from the standpoint that we had human medicine, veterinary medicine, and at least universities, government, others sitting at the table saying this has to be looked at and has to go forward.

I think that has to happen again with industry

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sitting at that table along with that societal group.

In looking at that, as we start to look at least at what is happening today, I think in the United States especially, we have talked about the quality assurance programs that are on farm today, and this is for all our major producers, that we do have quality assurance programs that are really looking at preventive disease methods.

We are trying to get away from treatment, we are trying to prevent disease, and this brings in many things, biosecurity and down through.

Again, we need to do that in human medicine, and obviously we are not there yet, but talking about it, and that needs to move forward. At the same time we have been doing that, we have been looking at the health concerns, and we then, working with our colleagues -- and I think that is what has to happen here, too -- is to start to work with people that are dealing with other environmental issues.

Our group now is working very closely with our agriculture environmental management, which is looking at, at least other waste problems, be it nutrients, be it pesticides, be it other toxicants, and trying to relate these two as to how we control that.

Becoming very primary in that is the pathogens,

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and I think as we look at watershed studies -- and I am involved with one in New York City -- we have all of a sudden seen that basically, yes, we have pointed fingers at farm animals, and they are a part of the Crypto and Giardia problem there, we have done some very good wildlife studies now, and they are also part of the problem, but so are the humans.

We are doing a lot of work now with filtration plants, runoffs in communities. There is the parasite again. So, the same thing with this, we need to look at the complete societal situation.

So, I applaud you at least as saying let's try to increase our monitoring and let's try to look at the background that would be there, and try to get education to the full public on the use of antimicrobials.

DR. TOLLEFSON: I would like to make a brief comment, if I could. There is a lot of confusion on this drug-specific issue versus a national monitoring program, and part of the problem with that is that because of the approvals of the fluoroquinolones, we are linked to drug-specific monitoring programs, but that was an initial attempt on our part to gather some sort of information, and we have learned from those that it is not an expedient way

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to either get information or the maximize use of resources.

I also agree with you about the diagnostic labs, and we have started adding sentinel sites, we are calling them, in the national antimicrobial resistance monitoring system, and we hope to expand that every year, because it does give different information, but it certainly gives valuable information.

I certainly don't want to underestimate the success of the national antimicrobial resistance monitoring system because it was landmarked even in the attempt to gather collaboration not only across department lines, but several agencies have been involved in that, and it is very helpful.

In many ways, the human side of the program has benefitted from the experience of the hospital infection control programs that started a decade ago and, you know, gathered information and then tried to control it all in their little ecosystem, and I agree with you, Don, that we need to look at all aspects of it.

DR. STERNER: Dr. Fletcher.

DR. FLETCHER: I need to ask Dr. Miller to clarify something for me. If you have already answered this, I apologize for asking it, but in the current pre-approval

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process, review for me again what is required relative to pathogen load.

DR. MILLER: For antimicrobials administered in feed for more than 14 days, they do a Salmonella shedding study, and in the Salmonella shedding study, in addition to looking at resistance, you look at quantity, prevalence, and persistence of Salmonella in those animals.

DR. FLETCHER: So, Salmonella then is the target organism in those studies.

DR. MILLER: Right. The animals are artificially infected.

DR. FLETCHER: And that is only for antimicrobials given in feed?

DR. MILLER: For more than 14 days.

DR. FLETCHER: Okay. But now do I understand in the framework proposal or what you said yesterday would extend that to look, in other words, the question being what potential human pathogens might be increased in number as a result of antimicrobial therapy? Is that part of the proposal?

DR. MILLER: The framework document calls for pathogen load studies. What the framework document does is it separates out the resistance studies from the pathogen

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load studies, and the Salmonella shedding, it was tied together, we have separated them out, and the threshold for needing a resistance study is a human health concern.

The threshold for looking at pathogen load is an exposure-based concern. In other words, if I have excess pathogens in just one animal, I am not going to have a public health concern, but if I have increased the pathogens in a whole flock or, you know, 10 herds or 100 herds, then, there is an impact on the public health.

DR. FLETCHER: I was trying to get some feeling for the level of complexity at which one would look, for example, at the first level being an increase in resistance to those specific human pathogens of concern, Salmonella and Campylobacter maybe being the primary two at the moment, but then the next level being what happens to changes in the microbial flora that might change the potential exposure and also change maybe the potential exposure to organisms that might become resistant. That is an added level of complexity it seems to me in a regulatory process.

DR. STERNER: Dr. Angulo.

DR. ANGULO: Many of the speakers yesterday spoke in support of increased monitoring or increased surveillance, making it more robust and enhancing the

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surveillance.

Very few speakers were in favor of tying any corrective actions to what was detected, and if we were to increase or continue the same level of surveillance, my question would be to a historian from FDA or perhaps legal counsel, the historical question is has there ever been an instance where we have withdrawn, we, FDA, has withdrawn an antimicrobial off the market, and that is an historical question, and the second might be to legal counsel or to someone else from FDA, if we were to detect with this increased or the same level of monitoring an increase of resistance that is a public health concern great enough to want to withdraw that drug from the market, let's just imagine, for instance, with the poultry fluoroquinolone product, if we were to reach levels of fluoroquinolone resistance in Salmonella associated with poultry, that is a public health concern.

Let's say 10 percent of all Salmonella in the country is fluoroquinolone resistant, much of it coming through poultry, if we were to demonstrate that to be the case, if we wanted to pull the poultry fluoroquinolone product off the market, if we wanted, how long would it take to do that, and would we have the legal authority to do

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that, how could we do it, and if it were done, how long would it take from the time of noticing this public health concern under the current legislation?

MS. DAWSON: I will try and answer that. To my knowledge, I am not aware of any antimicrobials that have been withdrawn from the market -- nitrofurans, and that was for?

DR. STERNER: No, they have been banned from use.

MS. DAWSON: They weren't resistance issues. I am not aware that any of that had been withdrawn based on resistance issues. You know, we did have proposals to withdraw certain sub-therapeutic uses. Those proposals are still pending, and have been pending since the mid-seventies.

In terms of the withdrawal process, what is required is that the agency make a finding that a drug is no longer shown to be safe based on the information that we have. At that point, it would issue a notice of opportunity for hearing, setting out its proposal to withdraw the approval, as well as the grounds for the approval.

At that point, affected parties could request a hearing. The second step in that process would be to issue a notice of hearing if there are factual issues, at which

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time that hearing would take place, and then the agency would make a final determination on whether to withdraw the approval.

In the context of other approvals that have been withdrawn, it is quite a lengthy process. I am not sure of the exact time frames, but my sense is that process can run for several years because of all the due process procedural requirements that are available.

There is one particular provision in the Act which allows the Secretary to suspend a use if it is determined that a use presents an imminent hazard, and that particular standard is quite strenuous. That determination can only be made you the Secretary, it is not delegated down to the agency.

I am not aware of a drug that has been suspended based on imminent hazard, but there may be someone else who has. But that is a short, that is a quicker method.

DR. STERNER: Richard Geyer has a comment to add to that.

MR. GEYER: I was just going to point out that there has been just one drug that has been removed on the imminent hazard provision in all of the years of the Food and Drug Act, and that was a human drug.

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DR. ANGULO: A follow-up question would be the company could continue to market the drug during these years or many months and perhaps years of discussion about imminent health hazard, is that correct?

MS. DAWSON: In the case of imminent health, the marketing is suspended right away. In the case of other withdrawal proceedings, you are correct, that the company can continue to market the drug until the agency makes a final determination with regard to the withdrawal after going through the due process procedures. That is the current statutory structure.

DR. STERNER: I might add, Dr. Angulo, as a practitioner, however, there is another mechanism that stops the use of it, and that is the immediate banning of use in diethylstilbestrol and nitrofurans, nitroimidazoles, all come to mind as products, chloramphenicol, whose use was immediately ceased.

Dr. Langston.

DR. LANGSTON: Simply, a big concern, of course, that we have heard is the effect of these regulations in new drug approval, and your need to establish safety pre-approval. Your comments on pathogen load helped clarify that aspect somewhat. I wonder if Linda or Peggy would give

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us a synopsis on resistance, establishment of safety pre-approval.

DR. MILLER: I think I addressed that yesterday in my talk. I realize there has been a lot of water under the bridge since then. We are looking to engage in a public process to get a lot of scientific input on how those studies should be designed.

I outlined how, in my mind, some of the changes that need to be made to the existing 558.15 studies in order for us to get some data to do a risk assessment or a safety assessment, whatever you want to call it, in order to get data that has predictive value.

We would like to have, depending on how these proceedings come out, before we come up with a final protocol, we would like to have lots of public input, but we understand that we are going to have to probably make some decisions in the interim, and so we will probably not get it right the first time.

DR. LANGSTON: So, it would be safe to say that those are truly not established.

DR. STERNER: Dr. Barker.

DR. BARKER: This is for Dr. Tollefson. I am a little confused. Anyone who knows me, knows that is a

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common state of mind. I think I called Dr. Sundlof Gary yesterday, he has such an uncommon first name.

The on-farm monitoring program, as I understand it right now, is not to be drug specific, is that correct, it is to be species specific?

DR. STERNER: The answer was yes?

DR. TOLLEFSON: Let me explain something about that because we can't dictate how it would be done.

DR. BARKER: But, obviously, your intent is to make it species specific.

DR. TOLLEFSON: That is our advice.

DR. BARKER: Right. That is my point. You are asking private industry for the approval of a specific drug to monitor potential resistance development on individual farms that may be using a variety of different drugs and may be using a variety of different farm practices where there may be a potential for individual farm workers to actually expose animals to resistant bacteria.

I don't see the reasonableness in that given that they are getting their approval for a specific drug, but they are going to be monitoring resistance development perhaps in a very complex drug use including feeding antibiotics in a variety of species.

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How do you reconcile that with what appeared to be, as expressed by a number of the different speakers, the concerns of private industry in trying to conduct that kind of study on farm?

DR. TOLLEFSON: You have brought up some real good points. What they would be looking at is risk factors that would be a wide variety husbandry practices, different drug uses, non-drug, non-antimicrobial drug uses, all types of things.

I guess that is worth discussing and talking about, and worth giving guidance to the agency as to whether you think because of those inherent difficulties, it would not be wise of us to ask for that in the framework document. We have laid it out as a series of, you know, here is what we would like for pre-approval, here is what we would like for post-approval.

You have valid arguments here. You are asking a drug-specific sponsor to buy in, if you will, to a program that is beneficial to a lot of -- yes, I agree, we have been struggling with this for a long time. We don't have an answer.

DR. STERNER: Richard Wood was seen last with his hand up.

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MR. WOOD: Several of the commentators or presenters yesterday from particularly the animal drug industry were saying that this framework would, in their mind, place any new approvals all within Category I drugs.

That has led me to try to figure out in my own mind, looking at current approvals, where they might fall within the various categories, and I was wondering if someone might identify examples of where current approvals might fall within these categories, particularly dealing with either residue, particularly at the residue level, and in that regard, if you could also identify, I assume and from reading this document, that sub-therapeutic uses also would fall in the same framework, if you could provide an example in that regard.

A related question is that I understand that this document is only prospective, but if a current approval moves within any of these frameworks or any of these category levels given the results of a NARMS study, would they at all be involved in this framework?

DR. SUNDLOF: Let me just answer the last question that you raised, Richard. It is on page 7 of the framework document, in the footnote, it says, "FDA anticipates that the framework, if finalized and implemented, will be part of

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the approval of new animal drug applications and as resources permit will also be used for reviews of uses of antimicrobials for food producing animals."

Again, as resources permits will allow us to take a risk-based approach, such that if we saw something in the NARMS program that caused us concern, we would direct whatever resources were available at that particular risk rather than trying to go back and do a big global reassessment of all the antimicrobials. It would be a risk-based decision.

DR. STERNER: Dr. Flamm.

DR. FLAMM: Something that you had said earlier that implied that it is very simple for FDA to ban the use of antimicrobials, I found somewhat confusing, and I was wondering if either Joy Dawson or Dick Geyer could clarify for us the process involved.

DR. STERNER: Joy.

MS. DAWSON: I didn't quite understand what Dr. Sterner was referring to when he was about banning a drug.

DR. STERNER: The extra-label use essentially is what happens when an imminent hazard is determined, and the most recent antibiotic one that I can think of -- well, I guess there were a number of them that kind of fell all in

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at the same time -- but chloramphenicol comes immediately to mind in use in food animals.

What you are referring to is does the statute allow for certain approved drugs to be used extralabely; that is, for uses that are not labeled indications? The statute also allows us to prohibit uses when we think it presents a public health risk.

For fluoroquinolones, we did issue an order of prohibition. That does not mean the drug is banned from marketing. It just means that the drug cannot be used extralabely, legally. So that is a somewhat different list of drugs.

MR. GEYER: Also, I think there was another idea expressed in there. You mentioned chloramphenicol. That was a drug for which we did withdraw an approval. It was for a non-food use and I think that product had been used extralabely. That was one of the reasons for withdrawing the basic approval.

That withdrawal of approval, along with all of the other withdrawals of approval, whether it be the nitrofurans or DES or whatever, did take a considerable length of time. The length of time depended upon whether or not the sponsor requested a formal administrative hearing. If there is that

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request, there is a statutory opportunity for a formal administrative hearing and that process takes a considerable length of time.

So the drugs whose approval we did withdraw did take anywhere from several years to a decade or more depending upon the circumstances involving each particular one. Some were antimicrobials but none were withdrawn for resistance reasons.

MR. WOOD: I didn't quite get an answer to the first part of my question. Can I try that again.

DR. STERNER: I got the footnote answer. I wonder if I could get the front end.

DR. TOLEFFSON: Most of the current antimicrobials would fall into category II.

DR. GALBRAITH: About risk assessment. Industry clearly sees risk assessment as a viable alternative to the framework and cites a lack of data as a reason for opposing the framework. In the setting of default assumptions in risk assessment, clearly they are there by definition because there is a lack of data.

If default assumptions are going to be reasonably protective of public health and meet the reasonable certainty of no harm, you are going to have to make a

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decision with lack of data. Doesn't the whole process just bog down when you get to that to continue the statement of lack of data supporting action?

DR. McEWEN: I guess the point I was trying to make in a separate statement yesterday afternoon was that my personal opinion, and this is where I am talking about U.S. policy which is probably out of place given my origin, but I would suggest that it would be a misuse of risk assessment to use it as a way of delaying decisions for public health benefit, that there is a gradient of risk assessments, in my view, looking at the way it has been used in other areas, that the simplest one could be done using the information that is in the framework document where you would outline the four categories with a narrative describing scientific information, summarizing it, with an analysis in a qualitative sense based on expert judgment.

And then the characterization step would be, perhaps, a categorization of risk in terms of high, medium and low and then judgment would have to be used on whether or not that warrants regulatory action or not.

I guess what I was suggesting in my talk would be a possible way of using a formal risk assessment would be to have a tiered approach, that initially a qualitative

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approach would be used because decisions have to be made about public safety now. But provision would be made in the future for incorporating more sophisticated techniques, incorporating more data as they became available, as confidence grew, as expertise became more widespread.

Also, in the interest of using resources wisely that a qualitative approach would be used as a screening method. If that, using the default assumptions you have mentioned, showed that there was very little risk, then you would stop there and there would be no problem.

But if the use of the conservative approach showed that there were grounds for concern, then, perhaps, industry or other interested groups should have the opportunity to try to further refine the critical points in the assessment that are driving the concern and then attempt to refine that through gathering more data, conducting more studies, what have you, and that the agency could reconsider that in a sort of iterative fashion.

DR. LEIN: Coming back to Linda or Margaret or Steve, basically as we look at the framework and you go forward, if it is accepted, in putting together at least how that is going to be managed, you mentioned that you are going to use outside expertise.

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How would that be composed, say, for the preapproval or the postapproval, and is there going to be a industry representative? Is there going to be a AVMA representative? Is there going to be a public-health representative? Is there going to be at least the group effort to get all the connections that I think would be important in that?

DR. SUNDLOF: Of course, we have to work within the law which is the Federal Advisory Committee Act. Some of the deliberations would be taken on solely within CVM but then taking it to outside experts for review. It is the way we have to do business.

But, yes; we would seek input from the public at large and specifically from those stakeholders who would be impacted by the decisions.

DR. LEIN: If I could follow up on that a bit. Would there be at least any symposia that would be worked around this so there could be a broader context for people to have comment?

DR. SUNDLOF: Yes. In fact, that is how we plan to address some of these challenging scientific issues is by having symposia and trying to make sure that we have the best expertise available in order to help us with our

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decisions.

DR. LEIN: Would there also be an effort in that to look at existing programs that have been initiated now to help at least cut back on pathogens in the food, HACCP, certainly, which is just instituted in the last year, and processing plants, herd-health assurance plans that are just going forward at this point? Would those be attempted to at least look at those as ways of reducing some of this problem or as a checkpoint for this problem of at least antimicrobial resistance?

DR. SUNDLOF: I think, initially, we would be focussing on the specific areas for which we need additional expertise and those would be things like designing a preapproval study to give us a predicted value for the emergence of resistance on the postapproval side, how to design studies or monitoring systems that adequately capture the kinds of information that we need, having symposia where we address the issue of setting monitoring or resistance thresholds.

I think those three would be the ones that we would focus on initially. Anything that will help the reduce the pathogen load in animals as they are processed for food would help us refine our risk decisions on the

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exposure assessment.

So we are certainly interested in all of these different things that are happening; competitive exclusion products, HACCP, irradiation. A lot of the things that can reduce the pathogen load will have an impact in refining our exposure assessment.

DR. GERKEN: I have a question. It is not obvious to me who is going to triage the drugs into the different categories. If company Y has drug X that they are thinking about developing, is it your intent that they should come to you and justify what category it should be in and then you should approve that? Or you should make the recommendation with the--I'm nor sure whether the chicken or the egg comes first here.

So what was the background for that, if you could elaborate, please.

DR. SUNDLOF: In terms of determining the importance to human medicine, we would ask for a consultation with CDER. CDER may, in turn, ask for a consultation outside of the agency such as with CDC or other groups who they feel has knowledge that would have a bearing on ranking it as to importance in human medicine.

So largely that decision would be based on

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information in consultation with the Center for Drug Evaluation and Research. The exposure estimate would be determined by CVM in collaboration with the sponsor so that we would hold meetings with the sponsor, try and determine exactly how the drug was going to be used, try to get an assessment of what the incidence of the disease is that the drug is going to be used to treat so we have an idea of how many animals may be exposed to the drug and, through that process, determine the ranking of high, medium or low.

DR. GERKEN: I have a subsequent question to that, then. As you well know, as the drug goes chugging through the system, it is kind of a long period of time. Once that classification would be decided, would it be held in that classification during the time that that is chugging through the system or is this a moving target and can change during the time that it is chugging through the system, thereby increasing the burden or, in the rare case that we just realized that it might decrease the burden--I doubt that that is going to happen very often--but increasing the burden to industry while it is chugging through?

DR. SUNDLOF: We would do our very best to try and give the best guidance we could at the time but recognizing that things do change. We had a recommendation for the

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approval of the drug Synercid. If that would have occurred during the time that we reviewing virginiamycin, that may have changed things.

I am not saying that it would for sure, but as issues come up, there may be a need to reevaluate the classification. We try not to do that unless we felt that there was a clear need. It is our intention to discuss all issues of the approval process, the approval requirements, with the sponsors early on in the process. Unless there is some compelling scientific need to change the agreements, we honor the commitments that we make up front.

DR. GOLDBERGER: If I could just also comment on that. I think that, as far as thinking about the categorization of human drugs, as a practical matter, hopefully some of this can be dealt with on a class basis; that is to say, that, once the agency, for instance, has considered a fluoroquinolone, a penicillin, a macrolide, as examples, one would normally expect, taking into account issues of cross resistance, et cetera, that subsequent products that came in in those same classes would normally get the same ranking.

I think that the consistency is an important issue. There may be circumstances where, for instance, a

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company may claim, on the basis of data they have collected or had experts look at, that cross-resistance may be less of an issue or there may be certain other properties of the drug which would warrant some sort of different classification.

I think that those, certainly, would pose a little more in the way of challenges. The other issue that will produce a challenge, but I think that it is appropriate that it does so that we come to the best decision, is what happens when the first antimicrobial of a genuinely new class comes in.

I think it is legitimate that, obviously, that receive more attention. I think everybody would agree with that. The exact process of how we would do that, I think, remains to be worked out. As you noticed in the classification system, I think both during my presentation and in a little more detail in the actual document, drugs with a unique mechanism of action at the moment have a default into category I.

But, obviously, that is an area where at least there ought to be some discussion. I think those two types of issues, a genuinely new class which only will occur for the first product, normally, of that class and a drug from

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an existing class that, for whatever reason, for instance, industry might believe has unusual properties, might be the exceptions to what we hope would be a relatively consistent way to classify drugs.

DR. FLETCHER: Just a question maybe for Steve. How feasible is it, or is this an opportunity to put together a surveillance monitoring system that incorporates multiple approaches as opposed to being focused solely on the industry as an industry responsibility.

I am thinking of the FSIS HACCP programs within processing plants, quality-assurance programs by producer groups as well as the NARMS system and that type of thing. Is this an opportunity to put together some kind of a national approach that is more comprehensive than even proposed in the framework?

DR. SUNDLOF: That is a good question, Oscar. It would be my hope that we could do something like that, that there could be a national program that addressed the issue of having a very robust system for monitoring resistance as it occurs out there and that that could be supported by whoever has the money.

If it is a government-funded program, I think it would be certainly in the interest of the public health to

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do that because it is a public-health issue. With the Food Safety Initiative, there is an effort in the U.S. to look at food safety from farm to table. I think that there are a number of opportunities within the Food Safety Initiative to put together some comprehensive programs that could be used to monitor resistance and other foodborne issues that occur on the farm.

DR. WACHSMUTH: Just to reiterate from USDA's point of view that we are already participating in and would like to even increase participation in this kind of monitoring system. We are testing close to 200,000 samples in support of HACCP. This is for Salmonella testing. We won't have that many positives, hopefully, but we are feeding a certain of those already into the NARMS system.

We are beginning to test for Campylobacter this month. So we are going to also send those organisms into the system. In envisioning some of the discussions about on-farm and monitoring of clinical isolates, I see this as a sort of nice doable place in the food chain to detect something prehuman, a problem, that could focus on farm studies, if we can do it in real enough time, and I think, possibly, we could do that.

I also haven't spoken up to date, but I do want to

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express our support for this framework document and the hard work that CDC and FDA are doing to try to harmonize some of the different issues.

DR. STERNER: My compliments to Dr. Wachsmuth because Dick Geyer and I were just talking about asking you your opinion on that very question. So thank you for your commentary.

We are five minutes into the break. We will break for fifteen minutes and reconvene.

[Break.]

DR. STERNER: We are going to change the schedule just a little bit here and afford--it is obvious to me that we have a great deal of collective wisdom in the assemblage in the audience. I think that, given that this is a public forum and a public meeting, I am going to allow questions from the floor for a twenty-minute period.

I am going to ask that the questioners be very brief in their question and that the respondents be brief as well. We are going to employ the traffic light again and we will allow a total of two minutes at which time I am going to go ahead and stop and recognize a new questioner and responder.

So, with that in mind, I think we have enough

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people assembled here. If there are questions from the floor, the floor is open for questions to invited speakers at this deliberation.

MR. GEYER: We would ask that each of you come to a microphone, one of the standing microphones, in order to ask your question.

Keith, would this include comments or are you just looking for questions at this point?

DR. STERNER: It can be either. If you wish to take your time and make two minutes worth of comments, that's fine. However, I think that you may wish, for purposes of clarification for VMAC, itself, to ask questions.

MR. GEYER: Also, if you would identify your name and affiliation, too.

DR. STERNER: In waiting for a few more people to come in, I will give VMAC members an opportunity to respond to any of the invited speakers.

DR. LEIN: I just wanted to follow up from the last question that we were talking about at least looking at antimicrobial resistance patterns and monitoring in saying that, certainly, if we look further into that, and I think this was following Dr. Fletcher's question of whether this

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could be a broader use.

Certainly, as we have worked in the labs and worked with industry, this has gone forward to trying to standardize at least the methods in the labs, and this has been somewhat through NCCLS but also through accreditation that we are seeking, with NVSL, to try to meet at least OIE standards at this point and to become at least compatible with ISO standards, then, to at least try to get consensus at the National Institutes of Standards Technology that what we are doing in the laboratories would be accepted as a national standard.

This becomes important as public health has with the CLIA laboratory accreditation, basically, that we can get national recognition because of world-trade issues.

What we are talking about today is a health issue as we talk about antimicrobial resistance problems, but it will, at some time, I'm sure, become a trade barrier, too, if we have a problem within an industry.

We have seen this before so it is very important as we go forward at least to have these monitoring systems and try to prevent these conditions from happening, and to have at least the laboratory credibility that will be accepted worldwide.

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DR. STERNER: Did you with to have anybody respond to your comment?

DR. LEIN: I think this was a statement, but if they want to respond, that's fine.

DR. STERNER: I will make the offer one more time that initially I did and that is, since this is a public forum, I will open the floor to questions of any of VMAC members or invited speakers. If you would come to the microphone to ask the question, state your name and affiliation and there will be a total of two minutes allowable from the start of the question to the end of the respondent at which time I will recognize a new questioner.

Dr. Thornsberry?

DR. THORNSBERRY: Thank you very much. This is Clyde Thornsberry, MRL Pharmaceutical Services. I wanted to make a point that I dwelt on yesterday. And let me say up front that I am not sure that trying to guess whether or not we will create a resistant and a patient would get infected with that resistant is a very difficult thing, I think, in a drug-approval process.

But assuming that you did that and that somewhere down the line in your postmarket approval, you found out that an organism such as Salmonella was resistant to the

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newest fluoroquinolone, if, at that point in time, you decide to remove the drug, you have got to remember--let's say it is Salmonella DT104.

You are not just removing a fluoroquinolone. You are removing every fluoroquinolone. And you will have to remove every aminoglycoside, likely at least streptomycin. You will have to remove chloramphenicol. You will have to remove sulfa. You will have to remove trimethaprim. And you have to remove chloramphenicol. I think I got them all in.

I would also remind you that if you go back in the history of Salmonella, in the '60's, I think it was, there was a pandemic of Salmonella infections in Latin countries and South America. And guess what the resistances were; chloramphenicol, sulfa, streptomycin, ampicillin.

We survived all those. That is not to say that we should close our hands, but to remind you that Salmonella is that kind of bug. It comes, it goes, depending on the type that it is.

But my main point is that you cannot, where you have multiple resistance, just dwell on one of the newer drugs. You are talking about a whole lot of other drugs.

DR. STERNER: Thank you, Dr. Thornsberry.

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DR. WALKER: Dr. Walker, Michigan State University. If we take ourselves back in time a few years, say, in the 1940's and we were having this meeting, and we look at penicillin, would penicillin fall into categoryÊI? It probably would.

Yet if you look forward, now, fifty years and you look at the problems with penicillin in the animal world versus the human world, we don't have a problem with penicillin resistance in the animal population. Our staphylococci are less than 70 percent penicillinase producers. MRSA is not a problem.

The problem with penicillin resistance is in the human arena. So I think we need to keep something like this in perspective as we move forward.

DR. STERNER: Thank you.

MR. GEE: Good morning. My name is Julian Gee. I am with Pfizer on the animal health side but, in my capacity on the animal health side, I also sit on various of our bodies that look at human pharmaceuticals as well.

Interestingly, the point about penicillin, if you look at Pfizer and its current renown for Viagra, as we move into our sort of 150th year of existence, the involvement in penicillin and the discovery and development of penicillin,

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is probably one of the issues about which Pfizer is most proud.

As I look at this debate that has taken place here, and certainly some of the issues raised this morning about categorization of drugs--as you look forward and look at the discovery and development process, much of what we do now in the cutting edge of the discovery process pushes us almost inevitably in the direction of category I drugs.

To invest in a discovery and development program means that you have got to have a first-in-class product coming out at the other end. As soon as you have a first-in-class product, the chances are two things are going to happen.

One of those is that it is going to have a different mode of action. The second is that it is going to be developed for human medicine. And that pushes you almost inevitably towards category I.

To respond to the points made by Dr. Bell yesterday, I think there would be great benefit to the industry, to CVM and to CDC to try and get some of the scientists from all the stakeholders involved here together to look at that process and look at, as we predict to the future, how this is going to roll out so that the sort of

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please made by Dr. Apley, Dr. Wages and the other veterinarians yesterday that what we don't do is move this in the direction where we won't have new pharmaceuticals.

Clearly, it is the same concern that we have that you have. I think that getting the two sides together would help to move it forward.

DR. STERNER: That is part of what we are here for as well.

DR. BARKER: This is a question for Dr. Bell. In terms of foodborne pathogen disease in humans, what risks are posed by imports and how many foodborne pathogen diseases have occurred and have been documented as having occurred from those imports and in how many of those cases was it due to bacteria that were antibiotic-resistant?

DR. BELL: I ask the chair to permit Dr. Angulo to respond to that. That level of detail, I just don't know.

DR. ANGULO: I heard two questions. One is the extent that imported food contributes to human illness in the United States is very much a hot topic. We do recognize imported food and, in particular, imported produce as a burden of foodborne disease in the United States.

We are in the process of trying to understand that more fully. We do not know precisely what proportion of

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foodborne illness in the United States is caused from imported food. We do recognize, though, a significant proportion of foodborne illness in the United States is due to domestically grown food.

The next question was about antibiotic resistance. I think that an important feature about the is in terms of support of this framework document, as you know, CDC is in charge of the human surveillance portion. We have begun an initiative to interview all people who have certain types of resistance of public-health importance through the National Antimicrobial Resistance Monitoring System.

One of the key questions that we are asking them is if they had traveled before they became ill because we want to be very sure that we try to eliminate the effect of increasing resistance due to international travelers.

We are also interviewing them about whether they took antibiotics before they became ill so we can try to control for that factor. But what is very difficult to control is we will not be able to ascertain if we know that they were not international travelers and we know that they didn't take antibiotics before they became ill, we would assume that they became ill from eating a contaminated food, although we cannot eliminate the possibility of a companion

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animal contributing to illness.

But if they became ill, the likelihood that they became ill from eating a contaminated food, we will not able to determine whether that food was domestically raised or an imported food.

But, as you know, being familiar with meat and poultry in the United States, there is very limited, in general, there is very--

DR. STERNER: Dr. Angulo, exercising the two-minute rule and the prerogative of the Chair, thank you for your comments.

DR. ANGULO: In all fairness, let me finish the sentence. There is very limited meat and poultry imported into the United States as a general rule.

DR. STERNER: Dr. Burkgren, you had a question?

DR. BURKGREN: I would like to return to Dr. Toleffson's comments as far as educating companion-animal owners. I guess I would like the FDA's view on things like pork-quality assurance where there has been demonstrated results from education of producers. Food animal owners, also.

DR. TOLEFFSON: What I meant by that comment was to try to differentiate between a known hazard where an

owner is giving a pet animal an antimicrobial versus the I will call it risk through food where the consumer of the food is expecting that food to be free of resistant pathogens.

So the link between the veterinarian and the owner of the pet animal is direct and is a means to let the human know that there is a risk associated with giving that small animal, that companion animal, an antibiotic. That was my only point.

DR. STERNER: Further questions?

DR. LEIN: Just to follow up on that a moment, too. I agree with you but keep in mind that that may have not happened on the farm. It has the continuum of being added all the way through the processing and at the home.

DR. BARKER: I would like to return again to imports for just a moment because I don't think my question was answered and that, in itself, may provide the answer that I was looking for. We are asking to consider a framework document that addresses CFR 52 170.6, reasonable certainly of no harm.

As part of the calculation of determination that there is harm, we are basing this on statistics from foodborne pathogen disease in humans. I would like for the

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CDC to tell us, if possible, and perhaps this is not possible, what percentage of these numbers that are part of the statistics are derived from non-meat production, that do involve, perhaps, other forms and perhaps do come from imports.

If we cannot distinguish between disease factors arising from imports and disease factors arising from the farm, how are we to really assess this reasonable certainty of no harm requirement and, of those foodborne pathogen diseases that have been identified and deaths have occurred, how many have occurred from antibiotic-resistant bacteria.

I would prefer to get this answer from Dr. Bell, if possible.

DR. BELL: Perhaps I should clarify the roles that Dr. Angulo and I have at CDC. I work in the Office of the Director of the National Center for Infectious Diseases. I coordinate CDC's efforts to deal with the problems of antimicrobial resistance.

I do not have all the expertise, myself, in any of the numerous areas that CDC is confronting this issue. Dr. Angulo is CDC's subject-matter expert on the issue of foodborne zoonotic pathogens and the resistance that is associated with them.

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It is his branch that conducts the scientific studies. So I don't know this information. I would respectfully request that Dr. Angulo be permitted to answer because he is the expert and I don't know.

DR. BARKER: Then, in as brief statements as possible, how many of the foodborne pathogen diseases leading to death are known to occur from antibiotic-resistant bacteria whether of U.S. or foreign origin?

DR. ANGULO: Could you restate it?

DR. BARKER: How many of the foodborne pathogen diseases that have led to death in humans have been identified as foodborne pathogen diseases and were the result of antibiotic-resistant pathogens either of U.S or foreign origin?

DR. ANGULO: There appear to be a couple of questions in what you are asking.

DR. BARKER: No; there is only one. How many?

DR. ANGULO: We estimate that there are thousands of deaths of foodborne illness each year in the United States. We are developing more precise estimate of that. Many of them--

DR. BARKER: I am sorry to interrupt, sir, but I

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am really just trying to get a very simple answer. Perhaps this has already been answered. I believe that some others have stated that there are not any deaths on record that have occurred from antibiotic-resistant bacteria in foodborne illness; is that correct?

DR. ANGULO: That is not correct.

DR. BARKER: Could you identify--

DR. ANGULO: I will give you just an anecdote and I would be glad to show you the data. Just last month, we investigated a fluoroquinolone-resistant Salmonella outbreak, the first fluoroquinolone-resistant Salmonella outbreak in the United States.

There were seven patients ill, three of whom died, two of whom died due to fluoroquinolone resistance because they were treated with fluoroquinolone. This data has been presented in an abstract at the Epidemiology Intelligence Service at CDC.

That is one instance. I could cite--

DR. BARKER: That is sufficient. Was that of U.S or foreign origin?

DR. ANGULO: It was an instance in which the clinical consequence of antibiotic resistance resulted in the death of the patient. It was a foodborne pathogen. In

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this instance, as far as our epidemiological evidence is able to show, it was an instance where the infection was acquired in a foreign country. The initial case was in a foreign country.

We had another case, to give you the last anecdote, at the end of last summer in a child of a veterinarian in the Midwest. That child had only a gastrointestinal illness, did not have an invasive illness, was resistant to all antibiotics approved for use in children in the United States.

Had that patient had a blood-stream infection, which occurs in a certain proportion of Salmonella infections--had that child had a bloodstream infection, it would have been an untreatable infection in that child.

DR. STERNER: Further questions from the floor? Speak now or forever hold your peace.

MS. LISTERSON: Sarah Listerson at Agriculture Committee. There have been a number of comments about incorporating the progress that we have made in HACCP and the opportunity for irradiation of food into a bigger picture about the threat that is posed by antimicrobial resistance, I just want to add what might be a counterpoint to try to balance that.

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Using the example of our School Lunch Program, the School Lunch Problem is required, by mandate, to purchase disproportionately from small meat plants. While we are hoping that we get the same performance in pathogen reduction from them that we have from the large plants, we don't know yet the performance of that sector of meat and poultry processing industry.

In addition, the School Lunch Program doesn't have the funding to purchase meat or beef that is either steam pasteurized or, in the future, irradiated. So I am a little bit concerned. I am going to add additionally that we already know that people and children who live on farms or who have visited farms are at a higher risk of infections from the so-called foodborne pathogens presumably because they are at risk both from food and from more direct contact with the animals.

I am a little bit concerned that we not justify HACCP as a reason to make it okay that we increase the environmental contamination of resistant pathogens, the ones we call foodborne, because we may be shifting the burden of illness to rural and otherwise medically underserved populations.

So I would suggest that, as we look at the

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performance of HACCP, we also need always to keep our eye on FoodNet and PulseNet and listen to what it is telling us about who becomes ill, who truly is becoming ill and, to the extent that it can, why they are becoming ill.

Thanks.

DR. BARKER: This is probably my last question. No guarantee. This has to do with categorization. Under CFR 521 70.6, reasonable certainty of no harm, we have had a good bit of testimony about how bacteria can transfer resistance from one strain to another between different pathogens.

Given that that is the case and the very fact that any antibiotic selects for resistance, would not all antibiotics be expected to surpass the reasonable certainty of no harm criteria and be expected, at some time in the future, to produce resistance and perhaps be considered unsafe?

Whether it is in category III or category II, it could possibly pass along by some as yet unknown mechanism or even known mechanism resistance to category I, that the categorization of antibiotics into three different categories and then subdivision into nine categories is a somewhat artificial categorization, that the reasonable

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certainty of no harm criteria should apply equally to all antibiotics given the possibility of transference of resistance.

DR. STERNER: Who in the agency or elsewhere would like to respond to Dr. Barker's comment and question?

DR. SUNDLOF: That would be counter to our premise that there is a risk associated with certain antibiotics for which the risk is not as great as for others. It is true that resistance will increase over time. The idea of setting resistance thresholds on a compound-by-compound basis was intended to be commensurate with the risk of the loss of that antimicrobial to human medicine.

It is a bug-drug, so it would be a specific antimicrobial and a specific organism that would be what reasonable scientists would be consider to be below what is reasonable certainty of no harm.

The passage that you referred to, 570.6, also says that, "It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety must be determined by scientific procedures or by general recognition of safety."

What that says is that the standard is not based

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on no possibility of anything bad ever happening. It is by reasonable scientists who can get together and agree upon what they think, in their best scientific opinion, represents a reasonable certainty of no harm.

DR. BARKER: Does that data current exist?

DR. SUNDLOF: I would say it does not. In fact, part of this process--if it is agreed to that the framework should move forward, then we would have to go to the next step which is defining, on a drug-by-drug basis, what is the reasonable certainty of no harm of resistance for that particular drug.

That would be part of a preapproval decision, would be to set that standard for what is a reasonable certainty of no harm. I think in the framework document we looked at a category I drug and we said that resistance in Salmonella to fluoroquinolones would cause us concern. Right now, under the NARMS system, we have not picked up any resistance to fluoroquinolones in Salmonella.

So there is an example of a drug, at least based on those criteria, Salmonella and resistance, that, at this point in time, that drug meets the criteria of reasonable certainty of no harm if we were to apply this standard.

DR. GOODMAN: Just one other minor clarification.

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The way the framework is written, in response to your question; a drug is called class III or class II if it is not known to induce resistance to a class I or a class II drug. So it wouldn't be in that category if it was felt that it was going to induce resistance to a higher-class drug.

Therefore, the feeling is that the standard of reasonable certainty of no harm could be met at some level of resistance occurring because of the availability of alternative therapies. So I think there is a clear distinction between those essential drugs for which there is no alternative in those other drugs.

Now, if a new drug comes along and it is in class III and in vitro and in vivo studies show this induces resistance to glygopeptides through some unique cross-resistance manner, then I think, to be protective of human health, you are absolutely right, the framework, as it is constituted, would say essentially that is a class I drug.

DR. STERNER: Since we have usurped via VMAC questions here the last of the time for floor questions, Dr. Walker, we will give you the opportunity of the last floor comment or question.

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DR. WALKER: I have three. Number one is I would like to thank CVM for acknowledging the need for a national-wide on-farm monitoring system. I think that if such a system were in place, we would have an answer to a lot of these questions that are taking place; how prevalent is antibiotic resistance in bacteria isolated from animals.

We wouldn't be guessing. We would have hard data to document that. The second statement is in regards to categories of antibiotics. One of the big things we are talking about today is the fluorinated quinolones. There are studies underway now where they look at mechanisms of resistance of bacteria to the fluorinated quinolones.

Because the fluorinated quinolones are totally synthetic, chemical modifications can be made to those drugs that bypass these resistant mechanisms. There are studies going on today where they are specifically looking at these mechanisms of resistance, making modifications to counter those mechanisms of resistance.

At the last Interscience Conference on Antimicrobial Agents in Chemotherapy, they were talking about the Son of Cipro. This is a modification of ciprofloxicin that will address these resistant organisms.

The third and last thing is directed to Dr.

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Miller. In the drug approval process, it seems like we have two diabolically opposed factors that we have to deal with. One is the residues issue. In order to minimize residues, we want to use the minimal amount of drug.

But, in order to do that, we maximize the potential for resistance. On the other hand, to minimize resistance, we want to kill to organisms. To kill the organisms, we want to use the maximum amount of drug. Studies clearly show that there is a relationship between concentration of drug and MIC.

If we have concentrations of eight to ten times the MIC, we end up with dead organisms. Dead organisms are not resistant. So, in the approval process, which takes precedence, resistant or residues?

DR. MILLER: I have heard that a lot, that the problem is that food safety is prohibitive. But I just don't think it is true because we have a very valuable tool which is called the withdrawal time. Provided an ADI is anything reasonable, the product, if we just wait, the animal metabolizes the drug and it is excreted into the environment.

So I don't see that there is this problem here. Whatever the tox study says is the ADI is the ADI. Whether

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you have to wait three days or fourteen days--and that is the time period we are talking about--really doesn't make much difference.

DR. O'BRIEN: To the second question, the possibility that a modified fluoroquinolone would evade the resistance mechanisms to an earlier fluoroquinolone, I think the answer to that is there has been a lot of experience with that kind of thing in the beta lactam family of antibiotics which has been a succession of resistance mechanisms pursued by a succession of new classes of beta lactams each of which was successful as a therapeutic agent until the next generation of resistance mechanisms emerged.

The fairly simple way, I think, that that was managed everywhere, by susceptibility testing and I would guess by FDA regulation as well, is that they were considered a different class of agent and were treated as such, a different category for resistance testing.

I am sure--I am not sure, but I would imagine that the FDA would make that distinction.

MR. GEYER: The answer was "probably?"

DR. MILLER: We think we can.

DR. GOODMAN: The distinction is made in the framework in terms of generations of cephalosporins, for

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instance, and their importance to human medicines, I think, where they are distinct classes. Of course, it is nice to remind people also that when quinolones came along and were first marketed, there was going to be no resistance to quinolones because they were a new class of agents with a unique chromosomal mechanism of resistance that had a very low frequency. Of course, that turned out rapidly not to be true.

DR. STERNER: That concludes the opportunity for two-minute commentary. That dragged a bit longer but that is the way of these meetings.

I would like to afford an opportunity to the VMAC panel at this time to conclude their questions of they might have of invited speakers. I will just go ahead and start right around.

DR. COOPER: I have a question for Dr. Sundlof. In responding to Dr. Barker's earlier question about the category of drugs, I think you indicated that you probably don't have the research sophistication yet to provide a response to all of the questions.

My question is why do we need to subdivide the three categories by three subcategories and what do we gain by doing that at this particular stage. If we look at the

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research needed to justify this, if you were in either category, then what will you get from the sophistication of dividing it into three subcategories?

DR. SUNDLOF: I am going to ask Dr. Toleffson to answer. Actually, at one time, we had twelve categories so we are getting better.

DR. TOLEFFSON: What we anticipate is that the different exposure categories will allow different types of mitigation strategies that the sponsor could submit to us on a preapproval basis that would give us more assurance that the product will be safe preapproval. So you are right in that the requirements are going to be similar.

Say you have a II-H drug versus a II-M with the exposure categories being high, medium and low. But they can be managed in very different ways.

DR. COOPER: What would you gain from that process? I guess if you look at the level of sophistication, will there be any value gained?

DR. MILLER: I think we have that in the framework document although there have been so many refs, it is hard to remember what is in what. But we talked about it, and I mentioned it yesterday, that if you have a high-exposure scenario, so you do your worst-case scenario, and that ends

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up to be not a problem, then anything that is a lesser-case scenario can be covered by establishing the safety of your worst-case scenario.

So if you have a high-exposure drug and a species that has a high pathogen load and you are able to determine that you can establish safe conditions of use, that can, then, be applied to the other species that have a lesser--a formulation that is going to be used less frequently and in a species that has less pathogen load.

So you go with your worst-case scenario. If that's safe, then the rest falls out.

DR. COOPER: Would this be viewed on the part of the sponsor as an objective assessment or would it be a subjective assessment once you determine the category? And would all sponsors have to meet the same criteria if you look at the three subcategories of either category?

DR. MILLER: Yes. All sponsors would need to meet the same--I mean, I think we would try to have transparent--we tried to do this, lay out a points-to-consider document that would direct a sponsor so that they would know. But it just got too complicated as a first-brush cut.

But I think that we would be consistent in our

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categorization and I would propose that a sponsor run through a points-to-consider document. I think we left in there points that you would consider to categorize your drug, then come in and discuss it with the agency as to why you came up the way you did.

DR. GOLDBERGER: I think that, and many people have touched upon this, the issue with the categorization of antibiotics is not actually with the categories per se. It is with the implications that will ultimately come from being in a certain category. That is really the bottom line.

I think that, of course, it would have been possible to have no categories and just, on the one hand, either say that all new antimicrobials would have to do, for instance, what is proposed for category I, which I think a lot of people would object to, or, alternatively, all new antimicrobials would have to do what is proposed for category III which a lot of people, although probably other people, would object to.

This is an effort, I think, to produce a differential set of requirements depending on the given product. Whether it is entirely successful or not, I think that is an open question and I think, obviously, without

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knowing what these implications are, it is hard for people to have a real feeling for it.

But it needs to be looked at like that. It is a goal so that the requirements are not the same for all new products coming in.

DR. GOODMAN: We have heard a lot about the concern that there sort of be some risk assessment end to this. In essence, this second categorization that makes for the nine categories that you referred to. The high, medium and low exposure categories is a qualitative risk assessment of then not only how important is that antibiotic but what happens to it and is that likely to result in problems.

For instance, as in the document, an exposure of huge numbers of animals with lots of foodborne pathogens over long periods of time qualitatively results in a high risk assessment. That subcategorization of H would have more stringent requirements on the sponsor than for treatment of sick animals specifically, individual animals.

So, in a way, it affords sponsors an opportunity to use these drugs in ways that are safe without having to necessarily go through all the hoops that they would have to go through for higher risk uses. So it is, in essence, an attempt. FDA is really looking for input into what is, in

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essence, a qualitative risk assessment embodied in those categories.

DR. FLAMM: To amplify what already has been said. On the exposure estimate, the main difference in terms of preapproval studies would be in the pathogen load requirements. So low exposure wouldn't have the pathogen load requirements preapproval studies as high and medium exposures would.

So there is an automatic distinction if you fall into one of those categories. Regarding the categorization up-front as to the high, medium or low importance, we have already had some discussion of how we intend to do that and that is should be in a transparent process.

We didn't go, in the document, much into process and how one would accomplish these things largely because this is supposed to be the first go-around and we want input. But one of the things that we have considered is that we would do rulemaking to establish the criteria by which a drug would be considered high, medium or low importance for human medicine.

Rulemaking, obviously, is a notice and comment procedure that gets input and provides for input from all interested parties. Assuming we were to go this route,

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there would be a regulation that establishes the criteria by which a drug is judged as to high, medium or low. And then, perhaps, one might have guidance documents that would be referred to in the regulation that would actually list drugs or drug classes and where they are.

The reason we would contemplate doing that aspect in guidance as opposed to regulation is because of the issue that circumstances change and then a drug might move into a higher or lower category. And it is much more difficult to change regulation than to change guidance.

So the ideal would be that there would be a very transparent process to establish the criteria and, based on that criteria, a transparent process as to how we use that criteria and then sponsors would know, assuming they are developing a drug that falls into one of the classes that has been categorized, they would know up front where it is.

Now, granted, things can change and things may move, but that is just the way it is. That is not something that we can modify. To some extent, there is a moving target to the extent that the science changes and the uses of drugs change. But we are trying to make it as limited a moving target as possible and as transparent and as consistent a process as possible.

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DR. O'BRIEN: Do I understand that exposure, then, means anticipated volume of use--this is two-sided--anticipated volume of use in animal care and/or anticipated volume of use in the care of humans.

DR. FLAMM: Peggy and Linda should answer this, but, essentially, we are talking about exposure in the animal use.

DR. O'BRIEN: Okay. This implies some kind of ongoing measure of what that exposure is, and that is mentioned in the document. That appears not to have been controversial. At least, we didn't hear much. It was scarcely mentioned in the discussions of the last day and a half.

I don't think it is clear how it will happen but at least the idea that there should be some monitoring of volume of usage of different agents in animals is an implied part of the process. Am I right?

DR. TOLEFFSON: Yes. The exposure categorization is really trying to get an assessment of a prediction of the exposure to humans of the resistant pathogens. But the way we determine that is based on the use in the animal. Then the requirement for use data submitted in the drug experience report is more to validate that and also to help

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us predict in the future.

MR. WOOD: I think I have one final question. Antibiotics, of course, are one tool, particularly for therapeutic use, for use in treating animal health. Yesterday, there were several presenters that raised the concern that this framework document did not address animal health and, as it was interpreted to us this morning, or today, the document is intended to focus on no harm to humans.

Does the document exclude consideration of animal health and, if it does, it does not exclude that consideration in the normal drug-approval process; is that correct?

DR. SUNDLOF: The issues that we are dealing with here are how do we satisfy the human food safety requirements of an approval of an animal drug for food-producing animals. In making a food-safety assessment, we do not take into consideration any benefits that may accrue to the animals. It is purely a risk-based decision.

In determining the benefit effects of the drug in the animal, there is a separate determination in which the drug has to be safe and effective for the animal for which it is intended. But this document that we are talking about

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here today is strictly concerned with the food safety issues.

Some of the other questions that have come up, and unless you understand that that is really what we are dealing with, it can be confusing; why aren't we applying similar kinds of constraints to companion animals. The reason is because there is a different standard for companion animals, a statutory standard, that we are dealing with a food standard and, for that reason, companion animals don't fall into that.

DR. STERNER: Generally, given certain cultural considerations.

DR. LEIN: I have two. One is the mitigation. Of course, it is not clear how that is going to be set. As we look at that, are we looking at increased resistance in at least the monitoring of the human side or do we look at it on the veterinary side. If it is increasing in the human but staying low on the veterinary side, what happens with that, versus maybe higher on the veterinary side and not quite yet at the human side.

I can see where I would look at it but I am wondering what the concerns of FDA are with that.

DR. TOLEFFSON: I will try to answer that. You

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are really talking about resistance thresholds.

DR. LEIN: Right.

DR. TOLEFFSON: Or monitoring thresholds. Of course, that is going to depend on--

DR. LEIN: How is that going to get pulled and where is the triggering level for that.

DR. TOLEFFSON: What we envision, although we really don't have any answers--that is going to require probably quite a bit of public input and many more meetings. What we envision is tiered thresholds so that we would start thresholds on the animal data simply for the animal issues. If you reach a certain level that is agreed upon, some sort of mitigation would need to be implemented, such as an education program, whatever.

And then, maybe, possibly another level, again on the animal side. That struggle we have really been going through--we could design all kinds of scenarios that would be most beneficial for the animal side of the equation. The ultimate threshold, if you are speaking of one that we would request withdrawal from the market or restricted distribution, that sort of thing, would probably need to be linked to the animal data.

Here, I am speaking as an epidemiologist because I

believe that the human data are much more robust and we can control for that. Dr. Angulo mentioned the case-control studies that are already ongoing. I have more confidence that the human data are more valid. So there would be several thresholds.

DR. LEIN: That bothers me because there is not the direct avenue of from farm to table. You have always got the problem of where is this coming in, basically, as we look at that processing.

DR. TOLEFFSON: That is why it would be beneficial to the sponsors to have on-farm studies where they could identify where it is coming in.

DR. MILLER: That is it not coming from the farm.

DR. LEIN: That is why I say if it is low at the farm level, you cannot see it, but it is high at the human level, how would that be looked at? I suppose it depends on the quality of that monitoring, that is what you are trying to say.

DR. TOLEFFSON: Correct.

DR. LEIN: My other question is to Dr. Vogel. Being a veterinarian, I am very interested how he sees AVMA, if we go forward with this framework, being involved in at least helping FDA come to, hopefully, the conclusions that

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are going to make this successful for veterinary medicine and for human medicine.

DR. VOGEL: In my discussions yesterday, I did bring you up to date on the current activities of AVMA in forming a steering committee to develop judicious-use principles and to guide the profession forward in developing continuing education programs and developing information sources for veterinarians to make wise therapeutic choices.

The AVMA has several advisory bodies that guide the profession in these areas. There is a Council of Public Health and Regulatory Veterinary Medicine which, from its title, you can tell emphasizes public health, food safety, those aspects.

There is another Council on Biologic and Therapeutic Agents which advises the profession on the wise use of drugs and biologics. So both of those advisory groups would help AVMA in developing policies, positions and advice for the agency. I think AVMA would welcome the opportunity to enter into any sort of dialogue with the FDA, with CDC, with any other groups to help us move forward in this issue.

DR. LEIN: Would this include industry support, then, too, Dr. Vogel?

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DR. VOGEL: The steering committee does include liaisons from the producer organizations. We have invited liaisons from the American Society of Microbiology, the Infectious Disease Society of America. There is a liaison from the animal-health industry.

So I think our steering committee has the broad representation of all the stakeholders in this issue.

DR. LANGSTON: You have probably noticed I keep coming back to establishing resistance thresholds. Both the document and several people have acknowledged that that is not now possible. My question, then, becomes is it possible.

Steve mentioned that you have a risk-assessment consultant. In a sidebar, did I hear--not with you but with someone else--that there is at least a preliminary model although it is not validated that would give some correlation, or at least an association, between animal drug use and a human health outcome?

DR. MILLER: Yes. I think one of the things is should we be doing thresholds, which is the question for this group. But, certainly, if you look back in history about how people have established thresholds, and we had this conversation, the first way we do it is what is out

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there now. We say, okay, that's the threshold and then we go ahead and do some further investigation to establish whether that is too high or too low and make adjustments there following that.

That is what we did in HACCP and the FDA has done that repeatedly in the past. We have gone ahead--and the way I view this is there is a burden of pathogens and resistant pathogens in the animal, and there is a pipeline, which people have talked about, through food processing, to the consumer and then the consumer gets sick.

What we have is a model which is saying we agree that there are all these things like dose. But those are all beyond our purview. And so we have simplified the risk model to what is the burden at the slaughter plant and then what does that translate into in sick humans.

Then the assumption that we are going to make is that resistant organisms travel down this pipeline or though this slope at the same rate as susceptible organisms. Then we will model. We will say, let's say resistance is 1Êpercent in the humans; how does this translate back into a resistance load at the slaughter plant.

Once we have that level, then we will go back and make some prediction about how much you could have on a farm

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to reach that threshold in the slaughter plant. That is where we are at with the process right now.

DR. LANGSTON: The second question relative to that, then, is if that may be possible, since we are talking about requiring these thresholds preapproval, can it be done before the drug is released, or is that strictly a postapproval process?

DR. MILLER: We will build the model--is going to be on how does Campylobacter travel from a chicken carcass into getting somebody sick. And then the model will take into account--assume that the resistance is 1 percent in humans--we will have to have some discussion about what would be acceptable in humans--how does that translate back to what I can allow at the poultry facility.

That can all be done because that is just assumptions.

DR. LANGSTON: So, admittedly, your initial threshold may be somewhat--I hate to say arbitrary, but at least a SWAG--and then it will be refined. SWAG is better than WAG, I guess. And then it will refined as the model becomes clearer and gets more and more data.

DR. MILLER: I don't think we have come to a final decision yet of how we would set the thresholds, whether we

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would go out and monitor for what is the existing level of resistance now and we would work from that, whether we would work off of our pipeline model. I think those are open for discussion.

One of the questions I think we had in there is should we look at the level in humans, should we base it on the level in animals. Maybe that is an issue for a subsequent meeting about how would we go about setting these thresholds.

DR. STERNER: Editorial time. While I laud the detail of the answers, in the interest of completing the rest of our VMAC members' opportunity to ask their questions, please be as concise in your responses as you possibly can so that we can get through the entire panel.

DR. GERKEN: My question is for Dr. Angulo. Does CDC have antimicrobial resistance data from processing-plant environments and/or from humans in those plants and, if you do, what are the results of those data.

DR. ANGULO: The short answer is no. The explanation is that we participate in the National Antimicrobial Resistance Monitoring System and the USDA has data on antimicrobial resistance in slaughterhouses. We do not collect samples from healthy people in terms of the

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current NARMS. We do not collect samples from people working in processing plants.

DR. GERKEN: Then I have a second question. Do you have a concern in that area? I think there are some other people who do. And do you have any plans to do this?

DR. ANGULO: We have begun some studies, piloting some studies of healthy individuals looking at enterococci from healthy individuals. It is not a high priority to focus on processing-plant individuals because it is our impression that the feces of processing-plant individuals don't frequently get into the food that they are processing and so we don't think that they would serve as a reservoir for antimicrobial resistance to any great extent.

DR. GERKEN: I wasn't implying that the feces from those humans was contaminating it. But the environment, you are saying that that is USDA and USDA has the information on the antimicrobial resistance in processing-plant environment; is that correct?

DR. ANGULO: I may have misunderstood you; not the environment but the finished product. The slaughterhouse samples is part of HACCP that are collected. They have those samples. There is not sampling being done in the environment of a processing plant that I am aware of. It is

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not a part of NARMS.

DR. GERKEN: Do you believe that there may be some contamination, some environment issues, in the processing plant that may or could be responsible for this human food contamination rather than the animal that comes from the farm and that this may be an important issue in trying to decrease this antimicrobial resistance?

DR. ANGULO: I fully agree that antimicrobial-resistant organisms can enter the food chain anywhere along the line. But there is strong epidemiological evidence of where the primary source of introduction of contamination in the food supply is.

The environment does not recognize it as an important reservoir for such contamination and, because of that, the HACCP regulations implemented by FDA FSIS did not focus on the environment in processing plants.

DR. GERKEN: So that data is based on the DNA typing or is it based on your epidemiological data?

DR. ANGULO: It is based upon the wealth of data available from epidemiological field investigations, sporadic case-control studies, molecular fingerprinting, episodes--it is well established in the literature where the primary source of foodborne pathogens which enter our food

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supply are from.

We fully recognize that there are exceptions to this dominant role. We recognize that sewage effluent from a human treatment plant could contaminate and enter the food supply. We recognize that as a possibility. But it is not the dominant source of contamination in the food supply.

DR. HOLLAND: I have no further questions.

DR. HASCHEK-HOCK: I have two questions. One relates to on-farm monitoring. The proposal is for monitoring by the sponsor with FDA giving advice to the sponsor. I am wondering is that going to lead to uniformity of data and, if it does not, whether that data would be useless to be considered in evaluating further resistance levels.

DR. TOLEFFSON: We would prefer one study, not a sponsor-specific or a drug-specific study. We could attempt to standardize the protocol such that the data would be about as uniform as we could hope for. Actually, Richard Wood asked this question and I neglected to answer it. We would have to put into place some kind of validation procedures, quality control.

DR. HASCHEK-HOCK: The other question deals with therapeutic and subtherapeutic use of drugs. This has been

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addressed to a very small extent at this meeting and I am wondering is it proposed that the categorization of drugs takes into account these uses by the high, medium and low exposure to humans?

It seems like there are other considerations as well; for example, that subtherapeutic use is not under veterinary control and we have heard about the judicious use of drugs being established for the veterinary profession. But, obviously, this would not be in place for subtherapeutic use.

DR. SUNDLOF: The document really doesn't distinguish between therapeutic and subtherapeutic uses although, because of the exposure assessment, subtherapeutics pay a penalty. Their use would not be limited to that segment of the population that is ill from a specific bacterial disease. All animals in the population potentially would benefit.

They are generally used for long periods of time and so the exposure assessment picks up that. The issue of regulating therapeutic and subtherapeutic drugs differently is an issue that really doesn't fit within the FDA's purview.

We do not make value judgments on specific uses.

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The criteria that we have is that the drug be safe for the animal and the environment, the user and the public, that it be effective, that it does what it claims to do and that it meets certain quality standards.

The agency does not have the authority to make value judgments as to which use is a good use and which use is a less than good use or imprudent use. I think you can understand that a number of the products that FDA regulates are controversial in nature, are offensive to some people for various reasons.

Yet, that is not the type of decision that I think you want a bunch of regulatory scientists making, making those kinds of value judgments about what should be approved and what should not be approved. If there are issues that deal with values, those are better dealt with outside of the FDA scientific regulatory process.

DR. FLETCHER: Steve, a question about timing. You mentioned, I think, yesterday that the end of public-comment phase was April 6. What do you see in terms of a time frame on this framework moving toward implementation? What would happen after that public-comment period ends and by what time--or do you have a time in mind in which you would expect that this is when we would

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implement this.

DR. SUNDLOF: After the comment period concludes, in fact we will be looking at the comments as they come in and trying to address the comments--a lot of the comments will say the same thing so we will address those as a group. Some of them will be individual comments and we will try and address all of the comments and make a conclusion as to what we think the advice of this committee was based, on the comments that you make in this venue and also the comments that we receive from the public.

Based on what we interpret as the directive on the document, if it is go forward, then we need to start immediately dealing with the specific issues of things such as how do you design a proper preapproval study, how do you set monitoring and resistance thresholds, what kind of surveillance system would be most appropriate?

We want to do these just as rapidly as we can so that we have a stable regulatory environment and so that drug-company sponsors can come to the agency and know fairly specifically what is going to required of them if they decide to go through the approval process.

We have made this the Center's number-one priority.

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DR. STERNER: Any further questions?

DR. GALBRAITH: Just one question. There has been some suggestion that surveillance data, if it raised issues concerning current uses, that the framework would be utilized. Does FDA plan to get the statutory authority to withdraw drugs? Should that be indicated?

DR. SUNDLOF: We do have the statutory authority to withdraw drugs. Generally, when we move to withdraw a drug because of a public-health problem we get into long and extended debates just as we have with the resistance issue as to what is a public-health threat, when does it rise to level of harm to the public that would require us to take action.

Those issues are never very clear-cut and there are always debates on both sides of those issues. Drug-company sponsors do have the rights to exert their due process activities in protecting their products and so we get into long scientific debates.

With the framework document, the establishment of preapproval thresholds will allow us to make a determination up front whether or not these products have exceeded what has been agreed upon prior to the approval as the point at which it no longer meets the criteria of reasonable

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certainty of no harm which should greatly expedite the removal of the drug from the market with much less debate than we usually consider.

That is why we think that is a very critical issue. So, taking drugs off the market that may rise to that level I think would be much more clear-cut once we have a standardized policy in place in which to be able to evaluate those.

DR. GALBRAITH: So you believe your authority is adequate as it stands currently.

DR. SUNDLOF: Yes.

DR. STERNER: Dr. Barker, you indicated that you might have placed your last question but I seriously doubt that. The floor is yours.

DR. BARKER: You know me too well. We are dealing with a framework document. I think it would be worthwhile to underscore that in our deliberations. It is obvious from the comments made from private industry and from the agency that, clearly, this is a cup that is both half empty and half full.

I think both sides agree that the cup is half empty of adequate science, details, specificity. Industry may also see it half full of unknowns and regulatory

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horrors, but I think the FDA sees it half full of promise, of also addressing, perhaps not finally but at least to some degree, this issue of antimicrobial resistance and their requirement to provide safe, effective and reasonable products to the market.

Either way, this cup is apparently full of somewhat bitter drink and we will have to find some way to sweeten it. I have upheld my promise that that was my last question. I just had a comment.

Thank you.

DR. NORDEN: That is difficult to follow. Sitting next to Dr. Barker has been an education. That's a compliment. I have, really, one point of substance which is a question for the FDA and a couple of comments. I will keep them brief.

I am particularly concerned on page 14 under microbial safety, there is a sentence that says, "Given our current understanding of mechanisms of resistance, FDA believes that generally it would not appear biologically plausible for resistance to be transferred from animal enteric pathogens to the human respiratory pathogens."

I think that Dr. Salyers' comments and presentation yesterday, and other data, would give pause to

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that. I would be happy for the FDA to respond. But my concern, and I think the concern of those of us who are taking care of patients, particularly in nosocomial settings, is not so much with foodborne pathogens, although I would hate to see multi-drug-resistant Salmonella epidemics, obviously.

Our concern is with Staphylococcus and with Pneumococcus right now, and VRE to a lesser degree. I think it is very clear that resistance can be transferred from enteric organisms to non-enteric organisms, Pneumococcus being the best example of it right now.

So my suggestion would simply be that I don't think that passage or that paragraph should remain in the document for scientific reasons.

My other concern, and I think Dr. Hock raised it and it is appropriate, is that--and maybe it is not the FDA's purview. I understand about subtherapeutic use, but subtherapeutic use is the best way I know in the test tube or in vitro to induce antimicrobial resistance.

If you take an organism and repeatedly expose it to a low contamination of antibiotic, you induce resistance. I would see that that may well be happening in animals and, therefore, since antimicrobial resistance is the subject of

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this meeting and what we are all trying to deal with and reduce, I would suggest that subtherapeutic use may be an important issue.

Finally, just as a general comment, I have found this an absolutely fascinating meeting and this is not an abstract comment on my part because we deal with this. I keep hearing the terms "human" and "animal" medicine expressed as though they were exclusive.

They are not. Human is all of us in this room and outside this room. These are very real issues. The animal part may be a very small part of the resistance problem. Again, I will acknowledge the role of physicians in this problem is huge, myself included. But I don't think we should be talking about human and animal medicine as though they were separate.

DR. STERNER: It is said, "He who laughs last laughs best." Dr. Angulo? It is your opportunity to laugh and make the best statement.

DR. ANGULO: Thank you. I have three short questions which follow up very nicely, I believe, with Dr. Norden's points. The first question is I have serious concerns about what is written on page 14 about the possibility of recategorization. CDER has explained an

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elaborate procedure for establishing the categories. But then there appears to be an option to recategorize a categoryÊI drug to a category III drug based upon a subjective opinion.

To phrase this as a question, it is a question to Eric Flamm. Would this recategorization, if this were to go forward--would this be part of the regulatory framework that you pointed out and the guidance documents that you have pointed out so that these considerations would be in that process or would it be after that there would be a recategorization later on downstream?

DR. FLAMM: To some extent, it is premature to say how it would work. But, certainly, my concept of how it would work would be it would be up-front and it would be part of the criteria of how one establishes the criteria for categories I, II and III and then the drugs would be put in the guidance documents listed where they are.

I cannot envision any process that FDA would use that would ever be simply we meet with the sponsor behind closed doors and something is shifted and there is no explanation and no one knows what happened or why.

DR. ANGULO: I think we have very clear parameters on how to categorize based from CDER. But this paragraph

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implies that there is some other unknown parameter that could be worrisome.

DR. FLAMM: Just to clarify there. That was one of our considerations of how we might categorize drugs. Based on comments, we will review whether that concept should remain. Again, it was intended to be used in specific circumstances where we thought a specific drug/bug combination was such that it might not cause a drug that otherwise would be category I to be category I.

This is not supposed to be some secret mechanism by which we change categorization of drugs.

DR. ANGULO: The next question was the framework document asks for additional detailed drug sales information through the drug-experience information. Isn't the drug-experience information currently confidential and would it remain confidential in the framework document?

DR. TOLEFFSON: Yes; it would remain confidential.

DR. ANGULO: So there would be detailed drug information but not available to consumers.

DR. TOLEFFSON: That's correct.

DR. ANGULO: I would disagree with that process. The last point is the categorization--I actually have greatest concerns on how we categorize category III drugs

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because I just foresee a controversy in the future and that is if category II drugs are categorized such that they are those little used in humans or not used in humans, we will forever debate what little used means, or also other questions about little importance.

I would strongly encourage, and I would like to ask if you have considered this, strongly encourage that either we have a fourth category that is drugs not used in humans which we could all agree to put ionophores in and we could set ionophores aside and eliminate them from the debate, or to take category II and have two parts to category III, those of little use and those of no use.

Have you considered having a category of drugs not used in humans?

DR. TOLEFFSON: We did consider it. We thought we somewhat took into account your concern by our recognition that this document or the categorization of drugs would be dynamic so that as new drugs came on the market--and it would require a great deal of interaction between CDER and CVM as to what is in the pipeline.

A subcategorization of category III is a way that we could handle this and we will take that comment into consideration like all other comments. But our idea that

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this could in no way be a static document I think is worth considering.

DR. ANGULO: My final commentary is I think, in the interest of trying to have a vision of coming in line with what is occurring in Europe in terms of growth promoters, it would be very prudent to have a category of no use in humans because they, of course, have a category of drugs which are not used in humans.

I think that we could try to adopt what they are doing in that categorization. So I would strongly encourage having such a categorization because ionophores just shouldn't be included in the same debate as Bacitracin or some of the other drugs which are used in humans.

DR. STERNER: We are at exactly the noon hour when we are scheduled to break. I will afford the panel members one last opportunity for any burning question that they need to have answered in order to address the five questions posed from VMAC.

DR. WACHSMUTH: One last question. USDA does run the Residue Monitoring Program although FDA enforces any residues above the allowable limits. Your comment about chloramphenicol struck me in that setting particularly. Why was the chloramphenicol banned and what was that process?

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DR. STERNER: Because of its ability to induce fatal aplastic anemias in humans who may have been exposed to the drug. And the second part? Why was it banned?

DR. WACHSMUTH: To me that is even more of a dire situation than the emergence of a resistance at that level. So then it was very easily banned?

DR. STERNER: Yes; Lester Crawford just said, "You can't use it anymore. And that was it."

MR. GEYER: It wasn't quite that simple.

DR. STERNER: You can tell I'm a practitioner.

MR. GEYER: The drug was approved for use in small animals and it was being misused extralabely in calves. There was the aplastic anemia problem that Keith mentioned. But we did have to offer the sponsor an opportunity for a hearing. They did not elect to pursue that opportunity so we were able to remove the product from the market fairly expeditiously perhaps in a year or so from the time we first started the process.

But we did need to provide an opportunity for the sponsor to exercise their due-process rights.

DR. ANGULO: I know things have changed dramatically in terms of food safety in the last several decades, but there was a chloramphenicol-resistant

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Salmonella outbreak following the ban or use of chloramphenicol and it was traced to dairy farms in California that were using chloramphenicol.

Our branch did do a survey of dairy practitioners anonymously in California and found a significant amount of chloramphenicol use following the prohibition of chloramphenicol.

Again, things have changed dramatically but the prohibition which took a period of time did not immediately, of course, cause the immediate withdrawal of the product from usage. That data is in the New England Journal of Medicine.

DR. STERNER: I will editorialize for just a moment and say that that very well exemplifies one of the potential negative consequences of regulations that limit the approval of new products.

With that, we stand adjourned until 1:00.

[Whereupon, at 12:00 p.m., the proceedings were recessed to be resumed at 1:00 p.m.]

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A F T E R N O O N S E S S I O N

[1:00 p.m.]

Presentation of Awards

DR. STERNER: At today's meeting, we would like to recognize three of our distinguished members for their contributions to the Veterinary Medicine Advisory Committee. I will just start and go sequentially around the table.

On my left, Dr. George Cooper has completed his term. Dr. Donald Lein has completed his term. You have set the mark very high for chair of the committee. I hope to at least follow somewhat in your shadow. To my immediate right, Dr. Diane Gerken has completed her term.

Dr. Sundlof, are you available to make your presentations?

DR. SUNDLOF: We have some plaques and other assorted paraphernalia for our outgoing members. Time goes by so fast and it just seems like you get on the committee and three years is up and you are gone. Diane, would you come on and accept your award.

This is in appreciation for all the hard work you have done and coming back and pulling extra duty.

DR. GERKEN: How could I resist with topic of discussion? Thank you. [Applause.]

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DR. SUNDLOF: Dr. George Cooper, come on down. This is in appreciation of your years of service to the Veterinary Medicine Advisory Committee.

DR. COOPER: Thank you. [Applause.]

DR. SUNDLOF: And for our outgoing president, Dr. Don Lein. We have a special award for you. You get the certificate of appreciation.

DR. LEIN: Thank you.

DR. SUNDLOF: And, in addition, you have a special gavel with your name engraved on it.

DR. LEIN: Thank you very much. [Applause.] I just want to mention one thing and that is that Keith has superseded himself. Handling this is going to be, I think, a very important thing that he has done and he is doing very well.

DR. SUNDLOF: One more, and we don't have a plaque as yet, but I want to recognize Dick Geyer for his years of service as the executive secretary for the Veterinary Medicine Advisory Committee.

DR. STERNER: How about a standing ovation.

DR. SUNDLOF: I think that is even better. [Standing ovation.]

MR. GEYER: I am surprised. Thank you very much,

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Steve, and thanks to all of you. It has been a great time and I have really enjoyed it. My best to all of you in the future. Three more hours and I am really retired.

DR. SUNDLOF: Dick was my mentor when I was on the Veterinary Advisory Committee. So it is sad to see you go, Dick. We really do appreciate all the efforts you have gone to.

Thank you, Mr. Chairman. I will turn the meeting back over to you.

Committee Deliberations

DR. STERNER: I have just a few editorial comments to make and we will proceed with the questions. I think that it is clear, listening to the speakers of yesterday and the commentary and questions of today, that there are very strongly held views on this issue and we bring many different opinions to bear on this issue.

I would recall the words attributed to a cowboy philosopher of an earlier time here in the United States and those were the words of Will Rogers. "It ain't so much what people don't know; it's what they do know that just ain't so."

I think that when we look at the interpretation of scientific data it is very clear that people from different

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perspectives in industry and regulatory and practice see these issues vastly differently. I didn't mean to ignore consumer-interest groups as well. We all bring different baggage to the table here. To quote Dr. Bell a bit from yesterday, it is time to move on.

With that as a preamble, Dr. Sundlof stated when he first came to chair the Center for Veterinary Medicine as Director that it was CVM's goal to have more new animal drug approvals rather than less so that veterinarians and the issue industry had safe and effective products to use and that the public health was provided for and protected by products that had gone through the approval process.

I think we need to keep that goal in mind as we structure our recommendations, as this committee structures its recommendations, to the Center.

I would also remind the committee that our charge here is not to debate the issue of antimicrobial resistance. That item, that philosophy, has been published in the Federal Register last November. The time to comment on that or to debate that issue with the Center. The 30-day comment period was passed with regard to the CVM position on that.

I see a head shaking, but that is a done deal. That is correct, Steve? So the issue rather deals with the

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framework document, I think, as an initial starting point and to give advice on where the agency or whether the agency should proceed.

It is obvious from the presentations made yesterday and the questions asked that most of us have looked at the framework document and drawn widely differing conclusions as to its suitability in correcting the issue much less the need for it in the first place.

In reviewing the comments, certain salient points seem to surface again and again; among them, and to name but a few, the ability to consistently define resistance in animal bacterial populations as it affects human health.

Two, the need for an expanded and enhanced NARMS or similar program that, over time, helps to provide a database for scientific public-policy decision making as it applies to veterinary drug approvals. The pitfalls and challenges here are daunting and, clearly, there will never be a unanimity of agreement on the validation of such a monitoring program.

The anticipated economic costs of the current framework-document proposal and uncertainties associated with the future approvability of an NADA cast serious doubt on future veterinary antimicrobial compounds ever being

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submitted for an NADA with a food-animal indication.

Dr. Sundlof has further elaborated in his comments the need for timely progress on this framework document in the light of the November Federal Register notice. In the interim, I will draw the conclusion of the inference that there will be no new antimicrobial approvals.

Underlying the whole issue of antibiotic resistance is the issue of subtherapeutic and growth-promotion issues which, while viewed as intrinsically bad by many, serve to obscure the more critical issue of most stakeholders with regard to therapeutic uses. We must weight carefully our deliberations so that our recommendations, no matter how well intended, do not result in unintended diminishing of the public health status of our human and food-animal populations.

There are numerous historical examples of attempts to address one wrong that have resulted in an even greater one being created. I think that the members of this committee are capable of evaluating their own objective biases and coming up with what is best described as the right thing to do with the information at hand. We will never have the complete answers.

We have a document before us and all that remains

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are the details and the devil is in the details. With that, Dr. Sundlof, I turn the floor to you to ask the committee the questions.

DR. SUNDLOF: Thank you, Mr. Chairman. I appreciate those opening remarks.

The first question--we will go through them and I will read the question and then turn it back over to the chair--there it is right up on the screen. "The FDA's goal is to protect the public health by ensuring that the efficacy of human antimicrobial therapies is not compromised due to the use of antimicrobials in food animals while providing for the safe use of antimicrobials in food animals."

The question to the committee is, then, "Do the concepts laid out in the document entitled 'A Proposed Framework for Evaluating and Assuring Human Safety of Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals' provide a sound scientific basis for achieving this goal if implemented?"

DR. STERNER: The floor is open for comments from the Veterinary Medicine Advisory Committee. I would like to canvas the members. How many of you have a comment to make with regard to Question No. 1? Just a show of hands. In

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that case, I am not going to canvas every member and I will just start to my left since I happen to be looking in that direction.

Richard, I think that you were first.

MR. WOOD: When I raised my hand, I didn't want to be first. We applaud FDA and CVM for taking this step and establishing this framework document. The framework document, overall, has us all nervous which is probably a good thing. Because it is a framework, it is not as specific as any of us would like to have.

But, in a way, that is a good step because that means it is a transparent process and that we have been brought in at an early point in that process to provide input and direction. So we also applaud that step not only of establishing the framework but allowing us all to be a part of the early formulation of that framework document as well.

We would hope that that kind of transparent process would continue through the ensuing steps that follow today's meeting. The scientific focus of placing the framework around human health implications from a lay perspective looks to us as sound. But from a consumer perspective, I think I need to say that we, as consumers,

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read the newspapers and then we sit down and we feed our children or, in my case, my grandchildren from time to time--as of Saturday, one more.

Our concern is not first and foremost has good science brought this food safely to my table but simply is the food safe. We, as consumers, are aware of what is happening out there in terms of what we read in the headlines. So what we bring to this table is a sense of urgency that we do move forward in policy, regulatory policy, in developing some response to the realities of antimicrobial resistance that is out there.

We are concerned that it be based on good science organizationally but, as consumers, we want forward movement and at least some framework by which to address those concerns.

Regarding risk assessment from the experiences that we have had in that light, we applaud the need for having risk assessments but often find them to be a delaying tactic or, not necessarily, a tactic but a process of delay. In another area, we have worked as an organization very long and hard on Salmonella testing of shell eggs. As some of you may know, the risk assessment leading to that rule which still is not in place has been a long one.

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Others can point in other areas where some risk assessments have not been enabling but rather have been disabling processes. In that regard, we appreciate the way in which risk assessment is incorporated into this framework where it evolves as the condition and need evolves. And we support that kind of relationship.

Thank you.

DR. LEIN: My statements won't be long but my interest is saying, scientifically, is this a good framework. I think the framework, if the implementation follows good science--what I meant by that, when this is put together--we have talked about a lot today but I think it needs to be repeated again that outside council should be sought and that the science needs to be good for this to be scientifically sound.

So, in putting this together, I think working with the industries, working with, again, other government agencies, universities, down through where the expertise is, along with your expertise, should be utilized in putting this together.

DR. LANGSTON: I would just like to say this has been a complex problem. As was said earlier, I don't think anyone on one side is either trying to penalize the animal

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health industry or agriculture nor, on the flip side, would any veterinarian honestly put the public at risk in their own mind.

Having said that, we do have two totally opposing viewpoints, it seems, one saying that there is no proven problem so why ask me to solve something that may not exist which, from a scientific viewpoint, I tend to agree with for the most part that we do need more research and risk assessment.

On the flip side, the idea that for certain illnesses and drugs, the stakes are simply too high to wait for a proven human effect--i.e., a human fatality--and that possibly that hasn't occurred because either it is very hard epidemiologically to prove and, to a certain degree, up until now, we have been able to discover new drugs to supplant the ones as resistance developed; for example, the fluoroquinolones to replace chloramphenicol.

So I am torn between wanting to protect those drugs vital to human public health while not willing to endorse a system that relies somewhat on thresholds that tend to be, at best, guesses.

To me, I think the scientific basis of it is what causes me some concern. I would probably, since I have to

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make a decision for some form of very strict definition of category I such that diseases that are life-threatening or have serious residual injury associated with them and there are no other legitimate choices in their treatment would be so designated and those would be relatively few.

Regrettably, that may have some impact initially on new drug development. Also, since we do not have a method of firmly establishing thresholds for those drugs, there will have to be some best guess made with the realization that those will be changed as things go along.

For category II and III, I do appreciate the concept of the category. I like that but I do not know that thresholds should be established for that. I think simply setting a background level and monitoring trends that would be reviewed by the agency or an outside blue-ribbon panel would be most appropriate.

DR. GERKEN: This document and this problem has caused me a tremendous amount of angst in the last two days. I must say that it seems with every minute, I learn either more or remember less of what I--something like that. But even at lunch, I learned more new information that changes perspective.

I guess I view the document as kind of a straw man

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to put out there for discussion. What was brought out this morning was that it was actually a composition of many organizations within the government getting together and deciding what to put in this. I think that is really good.

I would think that you should go one step further and bring advisory committees together. I know that sounds like a whole lot of hooey-hooey, but if nothing else, of all these different groups, it brings it out into the public so much more discussion can be had so that much more communication can occur and education can occur of the other perspectives.

We all come in with a certain perspective, not necessarily really emotionally involved, but certainly with a perspective. My perspective has been influenced by a lot of different things in the last two days. So I think that I would like to suggest that there be more joint meetings among the three or four groups, CDC, USDA, FDA, and have them be more publicly oriented.

There were probably things that could have been discussed in the last two days that weren't such as where the European community is with this and how we compare. My concern right now is that we will not have any new drug applications for food-animal use and that if we go back and

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review the ones that are currently being used, we may not have any of those.

Without having any drugs, that kind of bothers me as far as the veterinary oath is concerned. I don't know the solution to that. I think this is a foregone conclusion that some of this document is going to survive. I guess the best guess here is to continue to try to work with all the agencies to understand all the perspectives and to work out an agreement and try to get as much public communication and education as possible involved in that process.

DR. HASCHEK-HOCK: I would like to echo pretty much what other people have said. I think the FDA should be commended for their innovative approach. In answer to this question, I think that part of the question is does it provide a sound scientific basis for achieving this goal if implemented.

At the moment, I think it provides a scientific basis. The "sound," I think, is still to come. I think there is as lot more information that has to be gathered. I would especially like to encourage a rapid identification of areas where information is missing so that this could be gathered so that a more sound decision-making process can ensue.

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I think that, certainly, this committee--it has been a difficult task for this committee. We come from all different backgrounds and, certainly, I think experts, which you have already approached for information but, as you move forward, you need to make use of the expert information available in the specific areas that need to be addressed for this to be a sound scientific basis.

DR. FLETCHER: I have reservations about whether the framework provides a sound scientific basis. I think the comments we heard yesterday from various groups reflect that concern. I think that what I would say is that there is an opportunity that I am sure the agency would take advantage of to engage in further dialogue with those various concerned parties.

I think the question is providing for the safe use of antimicrobials in food animals. I just want to reflect that concern that we still have opportunity for safe use of antimicrobials in food animals.

The other response to that question I would make is it obviously depends on where you sit and where your view is as to whether or not it provides a sound scientific basis or not. The trick is to try to bring together enough of a consensus to be able to move forward in this whole arena and

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address the critical issue and that is what can be done to minimize the risk to a level that allows the agency to meet its statutory requirements.

I would have to say, Steve, I didn't fully appreciate that until you made the comments this morning about what the statutory requirements are which put a little bit of a different context that I think we have to wrestle with.

I think there may be, as we go through other questions, some sections that seem to me to be on a less sound scientific basis than others, pathogen load being one, perhaps establishing a threshold. But I think that that can be done probably picking the target organisms that would be a basis or logical reason for doing that.

So just looking at the general overview, the other comment I wanted to make is I think we need to be sensitive to the fact--and realizing that you can find in the literature whatever you want to find to support your point of view--but in the presentation of the document, it comes across as a selective identification of references to support the agency's point of view.

I'm sure that those who wrote it realize this, that there are other peer-reviewed references that can be

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cited that go counter to some of those approaches. So I don't know that that necessarily helps make any progress but there needs to be at least an acknowledgment that there is that difference of opinion supported by whatever one would choose to be able to find in the literature to support that point of view.

But the sensitivity to the availability of appropriate antimicrobials for veterinarians to use in protecting the health of food animals is critically important because that does have, in a broad sense, an impact on public health as well.

DR. GALBRAITH: I think with all its problems and complexities that the framework is, indeed, an innovative approach and provides a sound scientific basis for action. I think FDA should be complimented for the framework even with all the challenges that remain. I think waiting for a body count simply is not an option.

The alternative, which seems to be proposed, risk assessment, I think, is, perhaps, an issue for tomorrow and not an issue for today. I think you will get into the same problems coming up with default assumptions that you have for not accepting this framework and going ahead and setting threshold.

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I think FDA does not have in place now an adequate framework to protect public health and I think it would be irresponsible if they did not move ahead. If history is any guide, just within the last ten to fifteen years, state health departments tend to act when the federal government does not act.

Don Lein's need for good science which I back up, that is not a good omen when you have ten states going in ten different directions. This is not an issue that is on the horizon, on the radar screen of public-health officials right now and the public, but I think it could become one very easily.

I think one could argue that FDA is not moving aggressively enough on the current issue, on the current use issues. It is not at all clear that the existing statutory authority is adequate. Assuming you had justification for removal of a drug, with all due respect to what Steve said earlier, I think it could easily be a two-to-three-year process.

So I think FDA is to be complimented and encouraged to go ahead with this framework.

DR. BARKER: Does the framework document provide a sound scientific basis? It depends on what kind of

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framework is being perceived as being created, in part. Is this a framework for a Gothic cathedral or a framework to build a parking lot?

Some would like to have it just be flat and a parking lot and others would like to bring to it much more than, perhaps, needs to be present. Some of the supports that we have in our framework are missing. They may be essential parts of the frame that would help keep up the metaphor that I am going to continue with.

The frame may be missing lintels and lallies. It may be missing a major support wall. It is missing some scientific support. It is missing industry support. It is missing some decisions that need to be made. But, clearly, the frame in which this is going to be placed is a solid foundation.

The FDA has responsibility to meet its requirements of assuring safety and effectiveness. The foundation is sound. That is not the question. Should we build a Gothic cathedral or should we build a more modest home in which we can all live more comfortably. Once we get to that point, let's bring in the interior decorator and start picking out colors.

An awful lot of the details are left to be filled

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in and, to a large extent, I think that has created the controversy. No one is clear exactly what we are building here. Hopefully, in the process of our discussions and deliberations in which we take up each of the individual questions, we will be able to do that.

Is there a sound scientific basis as the others have already described? Certainly, we would be satisfied with more science, with more foundation, with a sounder framework.

DR. ANGULO: I am very encouraged. But as I think back on the discussion yesterday, and trying to think of what the main comments people said against the framework, there were some what I kind of view as peripheral statements such as that there would be no new drug approvals or that there would be antimicrobials available for food-animal practice, even, although not stated but perhaps even implied, that there would be no FDA/CVM if that would be the case.

I don't think any of those are actually true. It is certainly not the intent of the framework document. I think that it is not as dire as those pictures paint.

One of the things, though, that I did understand and a critique well taken was the statement that some

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thought that the background information provided in the framework document did not adequately defend the need for the framework document. There have been many statements made about the lack of data or the uncertainty of the data.

Perhaps that was an error on the public-health agencies part because we did not present at this meeting convincing data that there is a risk or the trend is increasing or why it is so essential to move forward now.

We have presented those before at meetings and we thought that including them in the background documents would be sufficient. Suffice it to say, we do believe that there is strong evidence of a risk and that the trend is rapidly emerging and that we do need to act now.

So, in closing, I think that I am very excited and encouraged by this document. I do believe it is the way forward. I think it is a visionary document by the FDA and, as a member of the U.S. Public Health Service, I am very proud to be a sister agency of the FDA for them to have put forward such a thoughtful and visionary document.

DR. STERNER: I have asked our previous chairman, Dr. Don Lein, to be our wordsmith for a moment. I think I heard a unanimous consensus that the answer to the first question is yes with caveats.

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Have you distilled the comments that you heard into additional sentences of instruction to the agency that this advisory committee would recommend.

DR. LEIN: I will read that and then, certainly, the committee should add or delete or whatever they want to do. "The proposed framework to protect public health by ensuring that the efficacy of human antimicrobial therapies is not compromised due to the use of antimicrobials in food animals while providing for the safe use of antimicrobials in food animals provides a basis for achieving this goal.

"But the sound scientific basis must be put together with a diverse group of experts from government, industry and academia to create this objective. This should be accomplished without hindering application for new antimicrobials that are in the process at this time."

DR. STERNER: Do any of the committee members wish to disagree or to add their commentary to the suggested wording?

DR. GALBRAITH: I think the statement is a good statement. I think, also, though it leaves it wide open for the debate to go on for another forty years.

DR. LEIN: What would you like to add?

DR. GALBRAITH: I think the consultation is

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absolutely essential but I think that there needs to be some affirmation that this is a reasonable framework to build on and move ahead with adequate consultation as you have pointed out.

DR. ANGULO: In the final clause of this statement which is just to suggest they should go forward with the old framework is nonsensical. That ignores the fact that we are in an emergent situation. If you endorse the need for the framework, then, obviously, you shouldn't continue business as current business.

If you acknowledge we need to change things, then we should change things not go on--

DR. LEIN: Let me debate that a bit. Basically, if you were a company and you come in all good faith to FDA and you start a proposed antimicrobial to go through. It was accepted. It was put together. It was en route and all of a sudden someone said, "No; we've got a new game here today. We are going to stop now and wait."

Do you think that is fair? Do you think that is the way business should be done? What if this does take a great deal of time and veterinary medicine is withheld from possibly getting an new antimicrobial that we all feel is important?

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DR. ANGULO: That final statement is encouraging continued debate because what it is saying is that we are going to continue doing things the way they are now until we get the framework the way that everybody likes it which, for everybody who likes the current situation, it is in their best interest to never come to consensus because, if they never come to consensus, they will stay with the current way that business--it doesn't make sense.

It is not a question that was asked of this committee and I don't endorse that clause.

DR. BARKER: I couldn't disagree more strongly. We are involved in a process of creating a framework document simply. It has been completed by the consensus of this committee, I believe, that there is presently, and as stated by most of the people who put the document together, just not enough information to, at this time, and perhaps not for six months, a year or longer, have the information that is really necessary to make decisions.

I think it is relevant to the question how this should affect current applications when it has not been clearly demonstrated that there is, indeed, a problem. I would endorse this statement as presented.

DR. STERNER: If I may, let me editorialize here

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or suggest that what you are talking about is grandfathering and that for those applications, there may be plenty or there may be none in the pipeline, that they be grandfathered under the previous rules and that new applications, before you would consider them, would have to undergo the scrutiny of the new framework document as it comes to bear on new animal drug-applications.

DR. TOLEFFSON: Could Dr. Lein repeat the statement?

DR. LEIN: The last part or the first part? The whole thing? "The proposed framework to protect public health by ensuring that the efficacy of human antimicrobial therapies is not compromised due to the use of antimicrobials in food animals while providing for the safe use of antimicrobials in food animals provides a basis for achieving this goal.

"But the sound scientific basis must be put together with a diverse group of experts from government, industry and academia to create this objective. This should be accomplished without hindering application for new antimicrobials that are in process at this time."

DR. ANGULO: I understand your concern. My request would be that you divide that into two statements.

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The first statement up until the final clause I would endorse fully. The second clause I would, whatever is my priority here, not endorse.

If you throw that all into one clause, then it doesn't seem--just make two statements and then we could discuss them separately.

DR. STERNER: We have four more questions to deal with. Dr. Langston?

DR. LANGSTON: I want a point of clarification relative to new drug approval. Didn't I hear Dr. Sundlof say that basically, in its present form, they weren't satisfied with the approval process and probably no new drugs would be approved if we stayed with the current system?

DR. STERNER: If we stayed with. But he didn't say about those that are already in the pipeline.

DR. SUNDLOF: Let me address that since my name was invoked. When we approve a drug, it has to meet the criteria of reasonable certainty of no harm. If we have information that we think is necessary in order to make that determination, then we are able to ask the proper question.

What I mean by that is that if there are specific questions that we have regarding the safety that have not

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been satisfactorily addressed, we always reserve the right to ask the companies for additional information or additional studies.

I think, in this case, there may be certain pieces of information that would be helpful for us in making that determination that would not require a lot of additional work by the sponsor. So, for instance, if we needed some kind of information on the preapproval side that would help us make the determination that those drugs could be safely used, even knowing that we don't have the whole system in place, I think that we would want to have the option of being able to request that.

DR. GALBRAITH: I think the recommendation that you had would make sense. I think that Fred's point is well taken. Perhaps if the statement contained something to the effect of, "encourage FDA to look at current uses and any new applications that are--" go ahead with the existing system, leave it in place until a new framework comes on line, but encouraging FDA to look at current uses as data becomes available.

Then you can have the two existing systems go ahead and there is a commitment to look at those under the new framework when it comes along.

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DR. BARKER: My consideration of that logic may be faulty, but if we extend it a little bit, we are saying that new drugs in the pipeline are more of a threat than existing drugs that are already approved. Is there something wrong with that logic somewhere? If we are considering applying a very flexible, ethereal rather moving target for drug approval for new antibiotics when we already have a fairly large number of antibiotics that are in the market and are already assumed to be in category I or category II and a possible threat, then how is it that this will only be very specifically applied to drugs that are in the pipeline.

There is an issue of fairness in that as well as scientific soundness and a reasonable basis for proceeding.

DR. STERNER: My rationale for suggesting it was to merely put a focus on a date that everybody could understand. It would be at the end of the comment period, I think something like December 11 or 12, if November 11 and you had a 30-day comment period.

Just for ease of accounting, if it said that the rules are now different, the rules have changed, are in the process of flux and we, in the interest of at least seeming fairness, if you had an NADA in the pipeline by that time, then you would be looked at under the old rules. It just

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seems fair.

Further comments?

DR. BARKER: I actually would agree with that, that grandfathering of drugs in the pipeline and our existing drugs, until this can be better defined, is a reasonable thing.

DR. STERNER: The cutoff date would have been at the end of the comment period so any drugs, for example, that were submitted for an NADA today would be subject to the new rules and it just gave a focus to a time that everybody could relate to in the legal process.

Dr. Lein, have you done any wordsmithing?

DR. LEIN: Could you repeat what you said?

DR. STERNER: Dr. Angulo?

DR. ANGULO: My point is first, in the framework document, it talks about a risk-based approach where they would evaluate drugs as resources become available in a retrospective manner also. So that is already there. But my key point is that this issue is peripheral to the question that we are asked.

The question is do you support the framework in concept. Your point, I think, is a question of implementation, not of--it doesn't make sense to me why you

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would pick this one thing. If you are going to pick on this one point of implementation, why don't you talk about some of the other very worrisome parts of implementation. We could cite many examples of people worried about how this would be implemented.

Why do you pick this one point?

DR. LEIN: I think those will come up. I think what we were worried about is there is no time frame that we have seen for this to be accomplished. If it does take a year or two years, I think I, as a veterinarian, and thinking about at least animal health, we would like to see at least any applications that are in there for new drugs proceed, not be stalled waiting for a new system and proceed under the old system.

I have no problem with FDA asking for other requests to insure that this is going to be safe from the standpoint of human health. In a way, they have done that. We all know what happened with the fluoroquinolone, basically, that Bayer went forward with and there were things there that were asked above and beyond what other applications have had.

So I am sure that will take place. It is just that you don't want to see something sit and sit. I am

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thinking of industry now. I am thinking that, really, we want to promote industry to work with us but we also don't want to hinder our situation of discouraging them from their applications that they put into the pipeline because I think they have invested money into this.

They, again, are sitting with something that does take a year, a year and a half. I don't know what it is going to take. They are losing money on that, basically.

DR. ANGULO: So a compromise for consideration because your point, your clause that you want to add, is out of deference to the industry. I think we could balance that clause out of deference to public health by having another clause that is something along the line that of a strong desire to have finalized the framework document as rapidly as--some urgency of timeliness.

My concern of the clause is that it encourages stalemate because, if things are stalemated, everything continues the way it is. So you could balance your point with some urgency for public-health concerns.

DR. LEIN: But, still, to proceed with the applications that are in the pipeline.

DR. STERNER: Dr. Flamm? I am going to stop this because we have four more questions to go through and we are

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at a point where we have bogged down. You had a comment to make and then I am going to ask for the committee to vote on the statement as Dr. Lein has it and you are free to disagree, and we will note that.

DR. ANGULO: I am wounded because it is me against the world. I put forward a compromise. Would you consider the compromise and have some discussion? I think it is very unfair, because of time constraints, to move forward so rapidly at this critical junction.

DR. STERNER: Dr. Angulo, I have tried very hard to keep this committee on task and move through. We are going to move through. We will vote on your amendment to divide this into two sections.

Dr. Flamm, you had a comment to make?

DR. FLAMM: Yes. I am not that sure how critical the issue is because the question really, to the committee, is does this framework provide a sound scientific basis, not the implementation deadline. But I think the thing that is important to recognize is that the framework in no way changes our statutory obligation.

Whether we have this framework or not, we are going to be reviewing new applications. And the standard that the drugs will have to meet is a reasonable certainty

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of no harm. This framework is a way for us to--we are contemplating that this would be a way for us to establish that reasonable certainty of no harm.

Unless we can establish a reasonable certainty of no harm, no new drugs will be approved. So, whether it is by the old method or the new method, you can't approve a drug unless you can establish a reasonable certainty of no harm.

DR. STERNER: You heard Dr. Angulo's request of the committee that we divide the statement into two parts. I would ask for those in favor of voting that we divide the statement into two parts to signify by saying aye.

[Chorus of ayes.]

DR. LEIN: I did put in something with haste. Maybe you want to stay with taking your comment. Let me add that and see what you think of it. "The proposed framework to protect public health by ensuring that the efficacy of human antimicrobial therapies is not compromised due to the use of antimicrobials in food animals. While providing for the safe use of antimicrobials in food animals provides a basis for achieving this goal, the sound scientific basis must be put together with a diverse group of experts from government, industry and academia to create this objective

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with haste."

So we are saying let's do it quickly, period.

Second, "We encourage FDA to proceed with applications in progress and ask for additional information to accomplish--" I didn't finish this yet--"accomplish safe human antimicrobial therapies," something of that nature. I am trying to bring in that they could add to this at least those which they are going to do anyway to accomplish a safe public-health aspect.

So I will finish that off.

DR. STERNER: I will give Don just a moment to go ahead and wordsmith it so we do have something in writing to reduce it to.

DR. ANGULO: While we are wordsmithing that, because we are answering a question that wasn't asked, could I just ask CVM's impression of answering questions that they didn't ask us to answer?

DR. STERNER: Sure. Dr. Sundlof?

DR. SUNDLOF: We want answers to the specific questions but we are also open to comments, any comments that the committee thinks would be beneficial in helping us make any determinations on this particular issue.

DR. STERNER: There is an intrinsic sense of

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fairness about the rules as they apply, and the suggestion about a date or a time in which people could focus on seems the right thing to do in terms of not changing the rules capriciously or arbitrarily.

Dr. Lein?

DR. LEIN: "We encourage FDA to proceed with applications in progress and ask for those additional informations needed to ensure a safe human antimicrobial therapy."

DR. COOPER: There was a comment made early this morning. It does not relate to the question but it might help us as we go through this deliberative process. There was a question raised of Dr. Sundlof as to the authors of this framework document and why.

He made two statements that I think are significant in getting us beyond this. Perhaps as we look at the history of the decisions that we are making now, I am concerned about making sure that there regulatory process maintains some accountability.

The first statement he made is that this was in response to a legal dilemma that they had with a animal-drug industry in approving new antimicrobials. The second, he said that it proposed a regulatory framework that is

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consistent in the drug-approval process. And he said, and I might just say parenthetically, without disrupting the current process.

When we make this decision, if we aren't careful, for those of us who are outside of the process, if we don't have that preface, in terms of the basis, then the decisions that we make are sort of going in several directions. But as we look at how the revised document might be written, I think it would be important to have a preface just to establish that as a basis.

For those people who are not a part of writing the document or reviewing the document, if they review it, then they understand the basis from which this whole process started. I think that would, perhaps, neutralize the conflict that we have in having a No. 1 and No. 2. It sets the stage.

Then if we have any approval action from this point, then it has a referent from which we set the stage. It is not to disrupt the current process. But the comment that Dr. Flamm made is that we are assuring that whatever happens in this regulatory process is that there is a reasonable certainty of no harm.

I think that forms the basis of everything that we

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do. Having that preface statement, I think, will be somewhat useful in explaining the actions that we take here today.

DR. STERNER: Would you like to draft that statement?

DR. COOPER: I have my notes; yes. Basically, what was said was that in looking at the framework document, it was to help FDA in its regulatory role respond to a legal dilemma from the animal industry in approval of drugs. They were proposing this framework for consistency in the drug-approval process and, parenthetically, without disrupting the current process.

So it means that it can be different. It would assume that there will be some difference in this process compared to what is presently taking place. I can write it the way I said it if that would be acceptable.

DR. STERNER: Yes. We have not been exactly operating under Roberts Rules of Order here. We initially entertained a vote here. We will go back and address Dr. Cooper's comment here. We all are aware of that. But I think we are at a point where we need to look at the division of the statement and the willingness of the committee to divide it into two.

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Can I see a show of hands of those who prefer to see our commentary divided into two parts.

Those in favor of seeing it divided?

[Show of hands.]

DR. STERNER: And those opposed?

[Show of hands.]

DR. STERNER: It is 4 to 6. So it is divided into two parts. I said that backwards, didn't I? 6 to 4.

I am rushing you, Dr. Cooper.

DR. HASCHEK-HOCK: Could I make an alternative suggestion?

DR. STERNER: Yes.

DR. HASCHEK-HOCK: Perhaps what we should ask is that the CVM make a specific determination of how it handles current and new applications so that everybody knows how it going to be handled but that this committee not make the specific recommendation?

DR. COOPER: I would agree. I am not making a specific recommendation for setting a referent. I would agree with your statement.

DR. STERNER: All those in favor of that raise their hand.

DR. HASCHEK-HOCK: Does that mean it is place of?

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I am not sure whether I am phrasing this quite right but what I would like to do is that the committee recommend that the CVM state how it will handle current and future applications until this process is completed.

MR. WOOD: And that is a substitute to the second section?

DR. HASCHEK-HOCK: Correct.

DR. STERNER: All those in favor raise your hand.

[Show of hands.]

DR. STERNER: You will go ahead, then, Dr. Cooper and give that to Don who will, in turn, give it to Richard.

Any further comments on Question 1?

MR. GEYER: Just to make sure on where we are on this, is the committee adopting the first part of what Dr. Lein wrote?

DR. STERNER: The answer is yes.

MR. GEYER: And then they are substituting for the second part what Dr. Haschek-Hock stated.

DR. STERNER: That's correct.

MR. GEYER: Then I am not clear as to where Dr. Cooper's statement will fit into that. Is that a preface?

DR. COOPER: I was proposing it as a preface.

MR. GEYER: And there is consensus on that?

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DR. STERNER: Yes. Dr. Sundlof, we are ready for Question No. 2.

DR. LEIN: Before we go forward, are we going to hear their statement to the question, of how they are going to handle the applications in the pipeline?

DR. STERNER: Dr. Sundlof says, "Trust me."

DR. SUNDLOF: I thought that the idea was that a recommendation came from the committee that the Center should make public that information; is that correct?

DR. LEIN: Right.

DR. STERNER: The committee is recommending to the Center that they make that information public. That is just a recommendation.

Dr. Sundlof?

DR. SUNDLOF: Question 1. "Categorization of Antimicrobial Drugs;" and that says "for Human Medicine." I think what that probably would be better stated as, and please correct me, CVM people, if I am wrong, that it should be "Categorization of Antimicrobial Drugs Based on their Importance to Human Medicine." Okay. So if you could make note of that because it isn't clear. It sounds like we are trying to regulate the approval of human medicines.

"The agency is proposing that the categorization

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of antimicrobial drugs based on the importance to human medicine take into account the usefulness of drugs in both foodborne disease and non-foodborne infectious disease when evidence exists that the use of the drug may result in the induction of resistant pathogens or the transfer of resistance elements to human pathogens.

"This approach recognizes not only the well-known risk of resistance transfer through classical foodborne pathogens but also the threat of transfer of resistant bacteria or resistance genes from other intestinal bacteria of food-producing animals resulting in resistant infections of humans with other types of pathogens; for instance, resistant E. coli or Enterococcus.

"Does the committee agree with this approach?"

DR. STERNER: How many members of the committee wish to make comments to Question No. 2? Quite a few.

I will start with Dr. Angulo this time.

DR. ANGULO: The short answer is yes. Concerns are, again, on page 14, the way of once categories are being established, then recategorizing. And the example they give is the respiratory patient in humans. It doesn't match with this paragraph as stated. So I agree with this paragraph but not what was written on page 14, the recategorization.

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The last part is I think the category III drugs--or we should have a fourth category--but there should be a category of drugs which are not used in human medicine because we can all, I think, agree on more lenient policies on those that are not used in human medicine rather than being clouded by those that are "little used in human medicine."

DR. GALBRAITH: The short answer is yes. I agree with the characterization.

DR. BARKER: I believe the characterization is overly complex. It would seem to be a little bit simpler matter based on the statements that are made here to take a slightly different approach. Clearly, different drugs fall into categories that are of similar structure and mode of action as those used in human medicine could be considered to be most of interest.

Others, certainly, that have no use in human medicine may be of less interest. It is reasonable to have categories I, II and III. However, the statement, itself, says that when evidence exists that use of a drug may result. Until that evidence is actually present in the form of the monitoring program where resistance is starting to be noticed, should it then be determined whether it is of high

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risk, low risk, moderate risk and maybe move something from one category to the other.

I would like for the CVM and the people who put this together to try to find some method of combining both the simplification of the categories based on speculation and expectation but then underscore that with actual evidence collected from field studies, either from the NARMS program or as part of the original approval application where a company will examine, for labeling purposes, the effect of their antibiotic on a range of different pathogens into any further consideration about its category or any real risk.

DR. HOLLAND: This is the one item that I had some anxious moments over. I just didn't feel that data were presented to support some of the categories. I would like to see more information or more data presented to support the categories that have been proposed.

I also have some questions relative to considerations given to categorizing drugs for use in animals. We have major animals and then we have minor animals. Where would all the minor animals fit into this equation?

DR. STERNER: Could somebody from the agency

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address the issue of minor animals since it has not previously come up in discussion? Dr. Sundlof?

DR. SUNDLOF: I have three people beside me that want to answer it. That minor use would fit into the exposure category such that minor species--they are considered minor because they are not eaten very often or they comprise a small, very relatively small, proportion of the diet compared to beef, pork, chicken and turkey.

So, from the exposure assessment side, they would benefit, minor species would benefit from this approach as opposed to other species. The benefits would be greater for minor species just because the exposure would be less.

DR. STERNER: Does that answer your question, Dr. Holland?

DR. HOLLAND: Yes.

DR. STERNER: Further comments? Dr. Lein?

DR. LEIN: I was just trying to formulate what I have been hearing here. I think I agree with Dr. Holland and wanted to bring that up. How do we consider this. I think if we looked at fluoroquinolones and their use today and knowing what we know in the human and what is needed because of the class of organisms that are resistant and could cause death, you can see where it fits into categoryÊI

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before we know much about what it is going to do in animals.

But if you look at the rest of this, and I don't know how this categorization would work, then, are you looking at the concern of a drug as it starts to increase in resistance and whatever is going to be the warning point--I don't know if we know that at this point--and this is beginning to be seen in at least the human part as well, does that move it into the category, then, of I, basically, even though it might have been a II, something of that nature?

Does that change the category? I think that is where Dr. Holland was coming from, too.

DR. STERNER: Any comments from agency personnel?

DR. TOLEFFSON: We are not sure what you are asking.

DR. LEIN: Let's say penicillin started to show a lot of resistance in the food-animal industry. I don't know where penicillin would be today is your categorization? II? Medium? High?

DR. TOLEFFSON: It would depend on the use. An injectable form of penicillin would probably be low.

DR. LEIN: But if that got high in the low, would it move to a different category?

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DR. TOLEFFSON: No. The resistance, as it occurs, doesn't have anything to do--the categorization is based only on importance for human therapy.

DR. LEIN: Would this bother you, Fred, if it moved? Say we had 80 percent resistance--

DR. ANGULO: I think a point that is not clear to many people is the categorization is going to be heavily weighted towards category II drugs. There are going to be very few category I drugs and very few category III drugs which I think would alleviate a lot of people's concern. Most things are going to be wrapped up in category II and there are not that many that are going to be categoryÊI.

DR. LEIN: If we look at that--I have been driven back to Dr. Thornsberry's statement that we look at these multiple resistance situations and, in his mind, it puts all of them into category I. At least that is what I heard when I listened to him.

DR. TOLEFFSON: But he is not correct. Jesse, do you want to say something?

DR. GOODMAN: I think the intent here was to make category I drugs, as stated, those that are essential for treatment of serious or life-threatening diseases in humans where, in general, there is not an equally safe and

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effective alternative therapy available. That is the main category of drugs trying to be captured here.

It is also recognized that if a drug is a unique member of a new class or there is very little resistance to that drug that it would probably be captured in this category.

The issue you are raising about increasing resistance, actually that would tend to make the drug lower in category because it would tend to make it become less useful in human medicine.

DR. LEIN: As long as there is an alternative.

DR. GOODMAN: As long as there is an alternative therapy.

DR. LEIN: I think Clyde wants to defend his--

DR. TOLEFFSON: But it would have been a categoryÊI drug anyway.

DR. GOODMAN: Right. If there is not an alternative, it is not going to move up. Now it could become that, let's say, X drug, previously there were multiple alternatives to it but resistance develops to all those alternatives, a drug could move up in category.

DR. LEIN: Because that is all you have left.

DR. STERNER: The chair recognizes Dr.

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Thornsberry.

DR. THORNSBERRY: Thank you for letting me defend myself. If you look on page 9, if I read this right, it says any antimicrobial that can induce or select for cross-resistance for a category I drug would be considered a category I drug.

What I said was if you select fluoroquinolone as a category I drug because of resistance to DT104, then you also, based on that statement, have to make--Linda is shaking her head, but what does that sentence mean, Linda, if it doesn't mean that?

DR. TOLEFFSON: That is not what it means. What you are talking about is the multi-drug-resistant cassette. That would actually come into play for the threshold, for reaching the threshold, probably more quickly but it wouldn't when you first characterize that drug.

For example, if you are saying that automatically puts ampicillin into category I--correct?

DR. THORNSBERRY: Yes.

DR. TOLEFFSON: Because of DT104. That is not what we meant.

DR. THORNSBERRY: Yes; but that is what it says.

DR. MILLER: Let me tell you what I think we

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meant. We were thinking about something like if there is chloramphenicol resistance and, let's say, chloramphenicol was very important in human medicine and we had something that was a structural analogue of that and it didn't cross-react with chloramphenicol, then it wouldn't be a type I.

But if it did cross-react with chloramphenicol and selected for chloramphenicol resistance, then it would be a category I. That is what we meant by that.

DR. THORNSBERRY: That is what I just said, I think.

DR. O'BRIEN: I think maybe a distinction that will help you, the distinction between selection for a resistance gene by its product, by its gene product in self-selection, as opposed to coselection which is selection of that agent for other genes that happen to be linked to it.

Both are important but I think, for the purposes here, you are talking about selection only, not coselection.

DR. THORNSBERRY: But how do you separate the two because it doesn't make any difference. Fluoroquinolones, Tom, would be no more of a selective agent than would chloramphenicol or ampicillin.

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DR. O'BRIEN: The circumstance, I would think--DT104 would be a good example. If you now have DT104 which is reasonably prevalent in the United States and other parts of the world with its four or five drug resistance, whatever it is, if you now had a subclone emerge, which is what you are describing, a subclone that is also quinolone-resistant, then it is true that all of the agents still select for the DT104 but only quinolones will favor that subclone over its cousins.

DR. THORNSBERRY: No, no, no. Not true. The subclone would be selection by fluoroquinolone and ampicillin and sulfa and streptomycin and every one of those.

DR. O'BRIEN: Again, it depends what you select them against. If you have got a neutral population; yes. If you are comparing it to other DT104s, then only quinolone will make that subclone--

DR. THORNSBERRY: There is no case in what you are saying, Tom, where fluoroquinolone would be the only selective agent. When you add fluoroquinolone, you are adding one more to the five that are already there.

DR. O'BRIEN: Again, selection is always in terms of what the competing population is. If you put one of

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those DT104 organisms that has the quinolone resistance in a chemostat with other DT104s that don't have it, only quinolone would favor it.

If you put it in a chemostat with another Salmonella typhimurium that doesn't have any of these resistances, then any one of them would favor it. So I think that there is a difference depending on what the competing populations are.

DR. STERNER: We are proving, at this point, what Dr. Thornsberry predicted last night that this portion of the debate is the subject of microbiologists. Few of us here are microbiologists.

DR. THORNSBERRY: I expected the microbiologists to agree with me. That's all.

DR. STERNER: That points out the need, as we move down--in the future, as this document gets fleshed out, the need for those very arguments to go ahead and be self-satisfied. I think Dr. Thornsberry brings up a very valid point. The language says one thing, and he certainly interpreted it one way, and CVM says no, that is not what it means.

That is why Dr. Lein said, in our opening answer or caveat to question No. 1, that these groups do need to

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get together down the road and come to some reconciliation of these issues. It detracts from us as a committee answering these questions. Yet they are very, very important questions.

If the folks at the agency ignore this kind of debate, then a lot of what we spend our time on here is wasted. So take note of this. I trust that you will. It looks to me like the language needs some revision so that the microbiologists, at least, don't say that this document is B.S. End of discussion there.

I have further panel-member opportunities to comment on this question.

DR. COOPER: As I read the document, this was the one question I had this morning. I still think that, perhaps, this three-by-three concept is overly complex. But I accept the guidance that I was given this morning from the staff.

The encouragement that I make as you look at an implementation strategy, sometimes, I would encourage you to be on the side of the public, the people who have to use the regulation. Sometimes, you have to be simple in conveying the meaning of this complexity that you have here.

So, as you move ahead, I would encourage you to

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find ways to simplify this so that the public will have a better understanding of how this categorization is used for I, II and III and what you perceive as subcategorization.

I am convinced that, because you have already moved it down to a three-by-three from a larger factor, that you will consider that as you move forward. I would just give that as guidance. It is one thing to have regulatory responsibilities. It is another thing to convince the public that you know what you are doing in a way that they understand what you are doing.

DR. STERNER: Thank you. I heard comments starting with Dr. Angulo and I would ask the committee to look at page 14 and the language in the middle of the third paragraph that says, "Given our current understanding of the mechanisms of resistance, FDA believes that generally it would not appear biologically plausible for resistance to be transferred from animal enteric pathogens to the human respiratory pathogen."

I believe your move was to strike that sentence?

DR. ANGULO: Yes.

DR. STERNER: How many would agree with what Dr. Angulo had to say? Show of hands in favor of agreeing that we strike that sentence from the document.

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[Show of hands.]

DR. STERNER: It looks like the "ayes" have it. So that sentence is recommended to be stricken from the framework document.

DR. BARKER: To follow up on Dr. Cooper's statement, I think it would also be quite beneficial, and it would appear that at least some of this information is already in the minds of the framers of this framework document, to provide examples of existing drugs that are already approved as to which would be in category I, which would be in category II, which would be in category III, which ones are already considered to be high-risk, low-risk, medium-risk.

It would have been very helpful for our deliberations had that been provided earlier on. But I think, at this point, certainly for the guidance of private industry to understand where their new drugs may be going, certainly where the approved drugs may already stand in the mind of the FDA, would be quite useful.

DR. STERNER: Dr. Angulo indicated that he also would prefer a fourth category, a "no human use" veterinary category.

DR. ANGULO: Either a subcategory III or a fourth

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category.

DR. STERNER: I will, just for purposes of complexity, suggest that a fourth category of no human use be proposed in this framework document. Those in favor of a fourth category signify by saying aye.

[Chorus of ayes.]

DR. STERNER: Those opposed, the same.

[No response.]

DR. STERNER: Then we would recommend a fourth category or whatever you wish to incorporate into the document. Don, you are recording this?

DR. LEIN: Yes.

DR. STERNER: We heard several comments from many members regarding simplification of categorization. I am not sure that I heard any clear-cut examples as to a proposal, but our charge to you would be that, if possible, in working out the details in future seminars, you, to the extent that it is possible, attempt to simplify.

I emphasize the word "attempt" because that may simply not be possible.

DR. BARKER: As part of the simplification, I think what makes this complicated is that right now people don't understand what the criteria really will be to put

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them in the categories that do exist. One of the reasons that it seems extremely complex is because we don't know what we are dealing with just yet.

The guidelines, the criteria, for putting different drugs in these different categories, are not there. I would suggest that once that is clear, once those criteria are well defined and spelled out, that it is not really that complex.

DR. STERNER: Point well made.

Further comments? Is it the consensus of this committee that question No. 2, as it reads--does the committee agree with this approach with the provisions that we had with regard to striking the sentence on page 14 and recommendation of a fourth category, no human use, and simplification, where possible, be our recommendations to you.

All those in favor of question No. 2, or in agreement with, signify by saying aye.

[Chorus of ayes.]

DR. STERNER: Those opposed, the same.

[No response.]

DR. STERNER: Dr. Sundlof, the floor is open for question No. 3.

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DR. LEIN: Do you want a statement on this?

DR. STERNER: At the end of No. 3, I will assume you will be able to read No. 2.

DR. LEIN: I made it very short.

DR. STERNER: I will go back, then; Dr. Lein, if you just read it.

DR. LEIN: "Categorization of antimicrobial drugs for food animals, considering the importance of this antimicrobial drug for human medicine, is accepted by the committee as a workable category for the importance of antimicrobial resistance. A fourth category of only food-animal drugs be considered by FDA," or I could make it "not human drugs."

DR. ANGULO: Just in the first sentence, I would request that you also say--because it says importance of that drug. But actually there are concerns about cross-resistance of drugs of the same class. The framework document captured that kind of language, but if we want to be specific, I think we would include that language in your statement.

DR. LEIN: I was trying to leave out the working parts of it. But you think that is important to put it in, to leave it to the committee, just that categorization was

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going to depend on how important it was to human medicine, basically. Whether it crosses over or not--

DR. ANGULO: The way that statement reads, the categorization for virginiamycin would be zero. It would be the lowest possible because it is of absolutely no importance to humans. But Synercid is of extreme importance. So it is not virginiamycin that causes it to be important, it is an analogue.

DR. LEIN: Okay. So I will add that other part in.

Why don't you go on with 3.

DR. STERNER: We will revisit question 2.

DR. SUNDLOF: Question 3; "Monitoring Threshold Levels," which was contained on pages 15, 16, 18 and 20 of the framework document and has two parts.

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

The second part of that question is, "What organism or organisms should be the basis for the monitoring

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thresholds? In the interest of cost-containment, would a sentinel organism be designated or should foodborne pathogens be used?"

DR. STERNER: I guess I repeated twice to the left. Dr. Angulo, you are up again first.

DR. ANGULO: The answers to this question, in all honesty, CDC has not fully considered. I don't know what is best, whether to use animal data or human data. CDC will be looking at human data and we would hope there would be actions based upon what we find in human data.

But the first question really goes way down the road in kind of implementation. I agree there should be monitoring thresholds which do result in corrective actions, but what those monitoring thresholds are based on, whether it be animal data, human data or both, I would just hope to defer to another opportunity for us to more fully evaluate and have people talk about the surveillance systems and how robust one part is versus another part, et cetera, which we have not had much discussion about the intricacies of the surveillance systems.

Personally, quite frankly, we haven't answered this question yet.

DR. BARKER: Should multiple monitoring thresholds

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be established? Should they be based on animal data or human data or both? Clearly, I think that you will have to establish multiple monitoring threshold levels for different actions. So the first part of that question and the second part of that question, should the levels be tied to specific actions, need for further investigation, mitigation strategies, et cetera, would be incorporated into the need to do multiple monitoring thresholds.

Should that be based on animal data and human data? Absolutely. If we are mainly talking about the effect on human microbe antibiotic resistance or human pathogen antibiotic resistance, we would want to observe that as well as seeing it occur in animals.

So I would think that you would want to monitor both, that you would want to have multiple thresholds and that those thresholds would be tied to specific actions. What organisms should be the basis for monitoring? I am not of the opinion that it should be simply a sentinel organism. I think the development of antibiotic resistance and the transfer of this resistance between pathogens clearly requires that other, more important, foodborne pathogens also be monitored.

To simply do a sentinel and to miss the actions

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that would be occurring on the biochemical levels of other types of pathogens would be remiss on the part of the agency.

DR. FLETCHER: I think this is an area where there is a tremendous opportunity to partnership with several different approaches to monitoring. I would urge the agency to take advantage of that opportunity.

We heard yesterday from a lot of groups that are talking about the kinds of things that they are doing. I think it ought to be incorporated in this approach. I think it needs animal data and human data and there needs to be some comparison and some correlation.

This is also an area where there needs to be a lot of additional work in the next few months to answer some of these questions. We have been talking about Salmonella and Campylobacter. It was suggested yesterday that Proteus might be a sentinel.

I think there needs to be additional work done on what organisms should be the targets. But I see a tremendous opportunity to use multiple sources of information and tie it together in some kind of national database or national network. I would urge the agency to take into consideration the comments that various groups

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made yesterday and try to put that package together.

It goes, maybe, beyond what simple regulatory requirement would be and I don't really know who would play the lead role in that, but I see an opportunity here. I do not think that it should be the burden of the drug industry alone to do the monitoring.

So I think there needs to be sensitivity to that. There are the issues of who is going to do it and who is going to pay for it.

We have mentioned in our questions I think a number of different possibilities, the diagnostic lab network that already exists, the FSIS HACCP program within plants, the quality-assurance programs that the various associations are implementing need to be tied together in some way, in my opinion.

DR. HASCHEK-HOCK: I think the simple answer to A) is yes, both animal and human data should be used and the levels should be tied to specific actions. But, obviously, we don't have data here to make any more recommendations. And I don't think we have enough data, really, to make any statements about what organisms should be the basis for monitoring thresholds.

DR. HOLLAND: Again, I think the simple answer is

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yes, as well. But I have trouble in seeing how a lot of the mechanics of this will be worked out. We can only trust that the mechanics will be worked out.

I think that we should look at the animal data, the human data, the pet data, as well as the vegetable data because feces from most farms, as an example, just don't stop with the animal. It goes out into the environment at some place. So we have got vegetables and fruits that you may want to consider there as well. But that is not a part of this.

I think we need to be cognizant of the financial constraints that some of these studies may put on the pharmaceutical industries and look to government support or other supports to help finance these.

Regarding to organisms? Who knows? I think that is one that you really have got to get down and get dirty. When I say "get dirty," get out on farms and really look at what is going on. At Michigan State, we laugh about the epidemiologists. We tell the ones that work and the ones that work at their computers because they have dirty coveralls on. And they are the ones that you trust their data, by the way.

DR. GERKEN: I think this is one of the areas

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where a lot of us have a problem because of what we perceive to be animal data-gap, or the data being missing, and the missing link of making these things fit together in the underpinnings of this document.

At any rate, I believe, wholeheartedly, that the animal data need to be collected along with the human data in order to see whether this grand experiment really is going to be the way people think it will turn out.

I would like to see, at the end--or, not at the end but during this middle time, that this be revisited a little bit about whether there is actually the animal data to support the human outcome or whether there is no change in animal resistance patterns but there is change in human resistance patterns, that this may be made public so that we all could understand a little bit more about what actually is going on.

I just don't think the data is there. As far as the organisms, I think this is definitely a microbiologist field and I defer to those people.

DR. LANGSTON: Should multiple monitoring thresholds be established? Again, the short answer is yes. Again, the short answer, we don't know how to do it quite yet. Hopefully, it can be done expeditiously.

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Animal data, human data; I think you have to look at human data, obviously. But, because of the potential for magnification where undercooked hamburger in one pot of spaghetti may cause 100 cases, you absolutely have to have a animal data to correlate it with.

From what I know, I would argue more for pathogens rather than sentinels. But I think that would be a better question, again, for a microbiologist panel.

DR. LEIN: Yes. Again, both animal and drug data. Certainly, and I have said quite a bit about this already, but increasing the power of the national antibiotic group at this point in their antimicrobial resistance survey. Also, I think, utilizing the diagnostic lab data would be important if that can be standardized and put together.

I think a third component, and Clyde Thornsberry made reference to this, too, would be to have an independent group with a centralized lab that would at least be responsible also for some of the on-farm data that could be collected from normalized animals basically or normal groups.

The diagnostic lab data is, at this point, pretty biased toward sick animals so it would be good to have some monitoring of a sentinel-type system throughout the United

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States. Again, I feel that this should not all be left up to industry to support but needs a wide basis of support, both industry and, hopefully, government support for these initiatives.

MR. WOOD: Just briefly, as a lay person, I don't really feel equipped to deal with particulars of this question, but do support the establishment of thresholds. I most particularly want to say that as thresholds are created and determined and established that consumer groups have the opportunity to be a part of those discussions and particularly to review the decisions that are made because we also are stakeholders in this whole process and that kind of participation is important.

DR. O'BRIEN: I think yes, you do need some kind of thresholds to give it structure although I think exactly how those will be arrived at will have to be on a case-by-case basis because we can't anticipate--again, we can't anticipate what the bacteria will do.

The same is true for sentinel organisms. I don't think you can pick sentinel organisms in advance and, as much as you can afford, you have to look broadly. I think who would have guessed Enterobacter faecium would be the sentinel organism for avoparcin or who would have guessed

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Campylobacter for fluoroquinolones.

These things pop up at some time and they are very unpredictable. So I think you would have to look broadly rather than at a few sentinel organisms.

DR. COOPER: I have one question before I answer it. If you turn to page 15, third paragraph, where it says monitoring threshold, I believe the statement, "If a resistance threshold can be established," should not be there.

To me, if you read it for a category I drug, "The agency would establish monitoring thresholds for resistance development in animals to guide the postapproval monitoring program for these products." Is that so? Or should that statement be in?

DR. LEIN: Is that No. 4?

DR. COOPER: Yes; where it says monitoring threshold, on page 15.

DR. LEIN: Aren't we going to answer that in No. 4?

DR. TOLEFFSON: Dr. Cooper, it should be there. That would be established preapproval if we could establish a resistance threshold.

DR. COOPER: Okay. My assumption was that you

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would always establish a resistance threshold. That is not so?

DR. TOLEFFSON: We would. But if we couldn't--

DR. COOPER: But the reason I raise the question is when you look at the way this statement is written and you look at the same paragraph for category II and categoryÊIII, it is not written that way.

DR. TOLEFFSON: Correct.

DR. COOPER: So if that is the correct way, then I don't--

DR. TOLEFFSON: For category II and category III, it is not required at all. But for category II, we could define--we are assuming we could define a level, a resistance threshold preapproval that would be protective of public health.

For category I, we might be able to for some drugs. We may not be able to for other drugs. In other words, it would be zero for the ones we couldn't establish a threshold. That is the transfer of resistance from the animal to the human, that threshold.

DR. COOPER: That answers my question.

DR. STERNER: When in doubt, the answer is zero.

DR. COOPER: Okay. I would say yes.

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DR. LEIN: Could I come back to one more statement on this and that is I also agree that we shouldn't select an indicator organism or think of one organism. I think that came out again from our microbiologists that you need to look across a group of organisms for resistant changes.

DR. ANGULO: I agree. One of the weaknesses of our current system, of NARMS, right now is that it is all Gram-negative-spectrum organisms and there is not a Gram-positive. I would encourage that we move towards having some Gram-positive-spectrum organisms.

But I think, as I have heard comments, there is some confusion about what the monitoring thresholds are because there have been increasing statements that industry should not sponsor this alone. But my understanding of who is sponsoring the monitoring threshold part is that this is largely going to be the sponsorship of FDA through the existing National Antimicrobial Monitoring System and it would not be a major burden for industry.

Is that the vision of the--

DR. TOLEFFSON: Yes.

DR. ANGULO: My impression is that these monitoring and resistance thresholds, in my understanding, have no industry sponsorship. Industry sponsorship is

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called into question in question No. 5, the on-the-farm survey. My understanding is the on-the-farm studies are not part of the thresholds; is that right?

DR. TOLEFFSON: They could, actually, give us more information about approaching the threshold. But, no; you are right, Fred. Your concept is right that since we know we have the NARMS, we would use that to monitor, for the monitoring thresholds.

DR. STERNER: Implicit in that, however, is the ability to devote resources to a greatly expanded program as described here. We may or may not have those available through the Food Safety Initiative.

DR. ANGULO: The last clarification, with such a strong statement for the animal data, which I wholly endorse, I think there is agreement that the best quality animal data are the ones at slaughter because those are the closest towards to consumer. So we are very encouraged that FSIS is so supportive of this and has offered to make those HACCP or slaughterhouse samples more readily available.

DR. STERNER: Dr. Barker, you indicated a question?

DR. BARKER: Just to follow up on Dr. Angulo's statement. I think in any statement that we make about this

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question that it should be made clear that the monitoring will a part of existing programs and would not be expected to be part of the approval process for private industry.

DR. STERNER: So be it.

DR. LANGSTON: I simply wanted to echo what Dr. Lein said in that I think we are wasting a valuable resource in our diagnostic labs not only in terms of ability to track potential trends for public-health purposes but realizing when we are talking about judicious use, you are talking about empirical use.

It is imperative that you know the probable pathogen that is going to be isolated in a disease and its probable antibiotic, in a biogram. So I would strongly encourage AAVLD and NCCLS to get together and certainly USP has had an interest in this in our Vet Med Panel to come up with some way of implementing such a scheme.

DR. STERNER: The question to the committee is, in question No. 3, monitoring threshold levels. I will read this off in segments. I think everybody has had an adequate opportunity to comment at this point.

DR. LEIN: Could I comment? I just wanted to come back again to a couple of things. One is that I think we mentioned existing programs. There may be one beyond this.

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I had brought out that I almost think you need an independent center, basically, for the on-farm. I think the diagnostic lab data would be good. It is biased toward sick animals.

Some of the data in labs, because they will be doing some sentinel work, too, if we get into herd-health quality-assurance programs, could be important from the standpoint of random, normal animals.

But, to get that type of data, an independent group, if we had a centralized lab, could be helpful in support of that. We had talked about the concept some when we talked with the microbiologists here. I don't see a reason why that wouldn't increase our capabilities of understanding on-farm data.

The idea there is support by government--I'm seeing government as a very broad sense here--and industry. So it could be state governments. It could be federal, if we can talk USDA or someone else into some money. And industry could be the drug industry or it could be the animal industries, basically, that we are talking of in this.

So I am making that sort of broad by just saying government and industry if people agree with this.

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DR. GERKEN: Don't you think, Don, though, that the diagnostic labs are uniquely positioned to try to identify whether there is antimicrobial resistance in the animal population? In other words, if an antibiotic has failed on the farm, you are more likely, as a diagnostic lab, to receive that sample because there are deaths or there is some kind of continuing disease and, therefore, you could be able to determine whether there is resistance because that is where the failures are going to be, or some of the failures that we are going to come to.

So that data is really important. I agree we have to have the normal data but, for therapeutic failures, that would be good data to have.

DR. LEIN: I agree 100 percent. I am just going a step beyond that and say that there are a lot of organisms out there that don't kill animals that run around with antimicrobial resistance in them. I think Fred would agree with that. Could you pick that up by sentinel-type farm situations?

DR. STERNER: We have two more questions to deal with, but first we have to vote on No. 3. I will read through the two parts in segments. "Should multiple monitoring threshold levels be established and should they

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be based on animal data, human data or both?" I heard a consensus that it was both animal and human data. So let's go ahead and vote on that first.

All those in favor, raise your right hand.

[Show of hands.]

DR. STERNER: Those opposed, the same.

[No response.]

DR. STERNER: "Should the levels be tied to specific actions; for example, the need for further investigation, need for mitigation strategies, need for withdrawal of product from the market?" Any disagreement with that?

[No response.]

DR. STERNER: By consensus, then, we agree.

Under part B), "What organisms should be the basis for the monitoring thresholds?" I heard pretty unanimous consent that we need to look at a broad range of organisms and we weren't going to look at sentinel organisms, that was inappropriate.

Any disagreement with that? All those in favor of no sentinel organisms but looking at as broad a range as is practical within the resources of the monitoring program signify by saying aye.

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[Chorus of ayes.]

DR. STERNER: Those opposed, the same.

[No response.]

DR. STERNER: Mr. Director, we are open to question No. 4. Oh; one more time. I will retract. Are you ready with question No. 2 and the statement?

DR. LEIN: I have 2 and 3.

DR. STERNER: Okay.

DR. LEIN: 2; "Categorization of antimicrobial drugs for food animals considering the importance of this antimicrobial drug for human medicine is accepted by the committee as a workable category for the importance of antimicrobial resistance and transfer of resistant genes from other bacteria of food animals. A fourth category of only food-animal drugs should be considered by FDA."

DR. STERNER: We are in agreement with that?

DR. ANGULO: Just to wordsmith it. The fourth category shouldn't be only food-animal drugs, because you could have a companion-animal food-animal drug. It should be non-human drugs.

DR. LEIN: Thank you. That was the European--

DR. STERNER: No human use.

DR. ANGULO: Drugs not used in humans.

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DR. BARKER: Wasn't there something in our discussions about requesting simplification if feasible, possible?

DR. STERNER: That was duly noted by the agency. I don't know that it has to be a formal statement. You heard us loud and clear, didn't you, Dr. Toleffson? She is nodding her head, but not at me.

MR. GEYER: It is in record. It is in the transcript. It will be highlighted in the summary minutes. So I think it is covered.

DR. STERNER: Did you want to do a reading of question No. 3?

DR. LEIN: "Monitoring threshold level is the important tool for the proposed framework and assures the human safety of the microbial effects of new animal drugs. We encourage the use of both human, animal and other environmental data to be obtained for making these decisions. The committee feels the national program using NARMS, diagnostic laboratory data and an independent central lab for on-farm data using sentinel farms be supported. These should be supported by government and industry. A broad range of organisms should be used for monitoring antimicrobial resistance."

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DR. STERNER: Any disagreement the statement as read?

[No response.]

DR. STERNER: Seeing none, Mr. Director, QuestionÊ4.

DR. SUNDLOF: Thank you, Mr. Chairman. QuestionÊ4 is in regard to Resistance Threshold Levels. The issues are addressed on pages 14 through 16, 18 and 20 of the framework document.

"The agency has proposed the creation of different levels of resistance transfer to humans that would be acceptable based on the importance of the drug or drug class in human medicine. Category I antimicrobial drugs would require that the use in food-producing animals results in little or no resistance transfer to humans.

"Category II antimicrobial drugs would require that a predefined level of maximum resistance transfer be established prior to approval that would depend on several factors such as the existence of alternatives to the drug, the human pathogens of concern," et cetera.

"The level of resistance transfer must be low enough that there is a reasonable certainty of no harm to humans associated with the use of drug or the product in

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food animals. What criteria should the agency use to safely define the acceptable level of resistance transfer, if any, for antimicrobial drugs that fall into categories I and II?"

DR. STERNER: I am going to split and go this way and this way, so, Diane, be prepared after Dr. Cooper.

Dr. Langston?

DR. LANGSTON: I have significant concerns about the ability to do this. Presently, I don't believe that we can. I would say either that we delay this in terms of setting any sort of criteria until that can be established. If not, then those should be established for category I and anything in category II or III would simply be monitored and reviewed.

MR. WOOD: As the criteria are created, and I don't hear us ready to list them out now, I am continually concerned, as others have also expressed, about the existence of subtherapeutic use of antibiotics that may impact human therapies.

That use has been narrowed and defined a little further by our creation of a fourth category. Apparently, subtherapeutic drugs will be dealt with in the same light as therapeutic. I do appreciate the assurances that we received this morning that, regarding exposure questions,

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subtherapeutic use will receive the attention that it deserves.

I also want to again reiterate our concern about prior approvals. As we talked about grandfathering and making certain that we were only talking about new animal drugs, I still wanted to raise that question and to lift up how important the footnote is on page 7 that would allow for a risk assessment of prior approvals if funds are there.

DR. O'BRIEN: I think the questions about transfer--it is kind of a second-level question. You are monitoring levels of resistance. Now, a second level of examination is how much of that is due to transfer or can you measure transfer rates in between.

It is possible, and it is possible, probably, within the framework of a good surveillance system to find suspicious anti-biotypes and, now, increasingly easy, to do genetic markers to show that they are the same and to begin--CDC's work, of course, traces some of these lines.

So I think that it is good to have this in because it will be increasingly possible to do at least some studies like this. I think it would add another dimension. But I think, at the moment, you can't really say the extent to which you will be able to do this very easily right now.

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DR. COOPER: I don't have any comments. I will yield to my expert colleagues.

DR. GERKEN: You talked about it in the context of a monitoring program but the way I read this, this is something that would be established prior to the approval and speaks to the drug-approval process. I am not very comfortable with it. I agree with Dr. Langston. I am not sure that it can be done.

I don't understand it well enough to understand how it can be done as a preapproval. Those are all my comments.

DR. HOLLAND: I think this is the one that the microbiologists really need to work with from my perspective.

DR. HASCHEK-HOCK: Ditto.

DR. GALBRAITH: I am certainly not qualified to say how it should be done, but I think if the public health is going to be adequately protected, there has to be some reasonable level effect.

DR. STERNER: Dr. Barker, surely you have an opinion.

DR. BARKER: I am even less qualified than everybody else but I have never let that stop me. There is

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a small problem that I have with it. I would underscore what has already been said. It seems right at this point very difficult to understand exactly how this is going to be done.

But, clearly, even if you have a category III drug that demonstrates significant resistance, that that is also of concern, not just for the human medicine part but for the veterinary use, continued veterinary use, of that drug under your mandate to provide products that are both safe and effective.

If you prove that the drug is no really no longer effective, then you have to take some action, I would think, based on the information that you generate here. But, as far as being able to actually make resistant threshold levels at this point, I don't think it is possible. You simply have to start to generate the data for one, all the existing drugs that are on the market and start to look at how those impact the position of the different drugs in the categories.

One is how we speculate that they will today and how they actually come out. I would be very interested to see the result of that.

DR. ANGULO: I recognize this is a critical

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question and very difficult to answer but I hope it will be one of many and there will be much continued discussion to find a rational approach. But, clearly, my impression is that we do not want antimicrobial resistance to emerge in humans to such an extent that it causes a clinical consequence.

So, at the very least, we can put a conservative threshold in human data and we could even make sure that it was focused because we could--besides monitoring resistance levels in humans, we could also interview those humans that had a resistant infection and make sure, like I have said before, that they didn't travel and didn't take antimicrobials and, if necessary, we could follow that up with more analytical studies which would include interviewing people who were not ill and doing an epidemiological study to try to pinpoint what the most likely source of their infection is.

Nonetheless, I think the point is that we can make a threshold based on human data because we do know there would be a clinical consequence if a certain level of resistance should emerge in humans. So there is sufficient data, we believe, to understand what the clinical consequence to humans would be, for instance, if we were to

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have emergency of 1 percent fluoroquinolone-resistant Salmonella in the United States.

To the extent that we use animal data at all for this or the other questions I agree fully much additional discussion needs to be held but, at the very least, human data could be used to set a resistant threshold.

DR. O'BRIEN: One other point might be, if I understand it properly, that the information on transfer, if it were to become available, might be modulating in the thresholds. In other words, if you found that the level in humans of resistance to a certain agent had reached what appeared to be a threshold, but if transfer studies tended to exonerate an animal source or pinpoint an alternative source, it might be a way of keeping that threshold from provoking a remedy in the animal-food industry.

DR. ANGULO: To follow up on that, I think we do have a good example in the United States that, in 1991, we did surveillance on Campylobacter and we had zero fluoroquinolone-resistant Campylobacter in the United States. Now we are at 13 percent fluoroquinolone-resistant Campylobacter.

There was an analytical study done in Minnesota which demonstrated two important things; one, over half, I

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think almost 60 percent, of their infections were in international travelers mostly to Mexico which demonstrates the concern about international travel.

But the other 40 percent were domestically acquired which they followed up with retail studies and found the same isolates in poultry at retail, et cetera. So we can exonerate animal sources by doing further analytical studies if necessary. So I agree with the point that you made, Dr. O'Brien.

DR. STERNER: I think the committee has pretty universally said that we don't have enough information here so that is job security for some researchers. My own comments to this, and I feel this is a very critical question as well, were that the background materials and the invited speakers did not provide enough data or information on which to base a recommendation at this time.

DR. LEIN: I wrote something down as I was listening here. "Resistant levels for category I antimicrobial drugs would require that use in food animals result in little or no resistant transfer to humans. If resistant transfer is detected, a review by FDA with an expert group would review the data and discuss mitigation for the future use of this drug in food animals."

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DR. ANGULO: But it sounds post hoc instead of a priori. Before a drug is approved, we can convene an expert committee and decide what we are going to do if resistance--I mean, I don't think you need to wait to see it emerge and decide what to do.

If the decision as a category I drug should result in little or no resistance, then we should decide a priori before we approve that drug--

DR. LEIN: What I worry about in that is, again, this idea that we are going to consider only the human data, we are not going to look at on-farm data if we can get that to a point that may be meaningful.

If we are seeing now an increase in resistance in human data, we really don't see that in background on-farm data. It is a question I asked before; what are you going to do with this? Does this mean that it is definitely coming from the farm or is it someplace in that process chain?

I think that Dr. Toleffson mentioned this pipe situation where we look at both ends and we are looking at some of the materials in between from plants, from other places, talking about where this may be entering the system. What I am trying to do here is trying to spare the fact that

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we are going to pull a drug from the food-animal industry when it may not be required at that level but needs to be required at HACCP or some other level or treatment of humans.

DR. LANGSTON: Would you agree that largely we are concerned about category I drugs, Dr. Angulo? Really, it is not too much of an issue on class II. Given that, if they are going to be monitoring all along anyway, the question becomes, do you set a threshold preapproval that, when it reaches, you automatically do something.

My argument would be that yes, you can set a threshold but you really but you realize it is somewhat arbitrary on human data and instead of automatically triggering a mitigation or a withdrawal, the trigger would then be to a review panel.

DR. BARKER: Sometimes things are a little slow to dawn on me but it would seem that the driving force here really isn't where we place blame. It is not whether it occurred on the farm, whether it occurred from contamination in the environment, or whatever, that if we see in the human data a large increase in resistance to a particular antibiotic to treat a particular pathogen, that that takes precedence over everything else and that simple continued

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use of the antibiotic in animals would raise the risk that other further additional resistance would be passed on.

Am I wrong about that?

DR. ANGULO: I think you are missing just slightly. Just because on the human data, we detect an increase in resistance, we would not assume, necessarily, that it is a food-animal source without first interviewing the people and making sure they didn't travel internationally and make sure that they didn't take antibiotics before they became cultured for this organism.

Then we would look at the animal data. If the animal data shows that there is no change in resistance, then I think we would have to do a more in-depth analytical study to find--I don't think would have found the answer yet.

But that raises two points. The first point is it answers question No. 5 which is if you don't do an on-farm study, then when we see changes in human data, you don't have the data to refute--refute is too strong a word, but it is the truth--you don't have the data to refute the change. So you obviously need on-the-farm studies.

DR. LEIN: I agree with you 100 percent.

DR. ANGULO: The second point, though, is the

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point about arbitrary setting of human thresholds. True, it is arbitrary, but we can put in on the clinical threshold. It is arbitrary, but it is arbitrary to the extent that you are uncomfortable with having 25 people a year with an invasive Salmonella infection with fluoroquinolone-resistant Salmonella and in the first 48 hours while they await culture results, they will be being treated with fluoroquinolones, whether that makes you uncomfortable, or whether it is 2 percent or whether it is a half of 1Êpercent, and we will have a spectrum of uncomfortableness from different groups.

We can set it arbitrarily but we can put it somewhere. There should be some place where we could say 25Êpeople at risk is too high or 50 people is too high or 100 people is too high.

DR. GERKEN: Dr. Lein, the comment that you read, was that in summary of what I just heard us say around the table or was I in another world? I kind of thought Keith summarized it and then, out of your mouth, came something that I didn't--

DR. LEIN: Oh; I changed what he said. Yes.

DR. GERKEN: Okay. Now I understand what I didn't recognize it. Are you making a motion to change what the

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rest of us all said?

DR. LEIN: What I am stating is that we all feel like category I is a very important group if we are going to look at it as single-type agents that are available for human medicine and that this should create a warning, basically, if we see an increase in antimicrobial resistance and that, then, should provide for FDA and this expert panel, whoever that is going to be, to review that and, if we could, in the ultimate, have good farm data and human data, some decisions made as to where the problem is.

I think Fred explained it very well, if we had all the datapoints that we could look at, yhat would make a decision--at least, that is much more important to source of problem, whether it is at a human level or whether it is at the farm level or whether it is at an environment level.

DR. GERKEN: I guess I am not quite understanding. I thought that the rest of us said that this was a very complex--

DR. LEIN: It is. I didn't mention a threshold. I didn't mention anything.

DR. STERNER: If I may. We all are in agreement that category I antibiotics, that the threshold is zero or very, very low. The problem comes in category II in

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establishing resistance threshold levels and we simply didn't have enough data.

My statement was background materials and invited speakers did not provide enough data or information on which to base a recommendation. Therefore, it should be deferred to a later time at which point, hopefully, we will have better information to base a recommendation to the Center.

DR. BARKER: I would move to substitute that for the comments from Dr. Lein.

DR. STERNER: But, with regard to category I drugs, make no mistake that the resistance threshold levels would be effectively zero.

DR. LANGSTON: It sounds like we really have two parts to this. It is really saying that we don't have the information to set a threshold. The other part is that we may need a working threshold for a category I in the meantime. Am I misinterpreting that?

DR. STERNER: I am going defer to the agency here since you folks came up with this document and we are charged with answering it. I am not sure I have the insights to answer this. This is a tough one.

DR. SUNDLOF: I think we are asking you to think in the conceptual terms that we agree that it may be

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difficult to set one, set it based strictly on scientific evidence. But assuming that we had all of the information that we needed to establish these thresholds, conceptually, would these be a good idea?

DR. STERNER: For all three categories?

DR. SUNDLOF: There is none for category III.

DR. STERNER: Excuse me; categories I and II. I guess I will just speak for the committee, not seeing any heads nodding in the opposite. We agree with category I and more research is needed for category II at this point, more data.

Is there disagreement around the VMAC, in the interest of moving on? One of our members has an airplane before too long that he has to pay attention to.

Donald, would you wordsmith that. We will make it into two parts. Is there agreement? Okay.

DR. ANGULO: On category II, I am not sure we need more data. We just need more discussion. I am not sure we need to do a new study--I am not sure we are going to get any more new data to answer--I think we just need to come together and try to decide what the levels would be.

DR. STERNER: It was envisioned that there will be workshops and other meetings to more specifically address

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this, hopefully, with more expertise in the area, that can come to some agreement. You, the agency, are charged with, in fact, coming up with that if you would like us to make a recommendation there.

Nobody felt a comfort level at knowing at this point the right thing to recommend to you.

Mr. Director, question No. 5.

DR. SUNDLOF: Thank you, again, Mr. Chairman. The last question, question No. 5. refers to on-farm postapproval monitoring programs. The question is, "On-farm postapproval monitoring programs will be necessary for certain antimicrobials in category I and category II, high, and some category II medium products." That is referred to on pages 17, 19 and 20 of the framework document.

The question to the committee is, "Should on-farm monitoring be instituted immediately postapproval or should it be triggered by a change in the data generated from other sources such as NARMS?"

DR. STERNER: Dr. Sundlof, just for clarification purposes, the responsibility for the monitoring program on-farm will be on a case-by-case basis for the NADA applicant, or will responsibility for administration of this program like with the agency?

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DR. SUNDLOF: That has not been determined. I think everybody is in agreement that we would not like to see a drug-by-drug system put into place, that we should have a more global, comprehensive system. Where the funding comes from for that has not been determined. In terms of this discussion, we can deal with the funding issue separately. We are just interested in your thoughts on whether or not having such a program out there makes sense in light of the rest of the framework.

DR. STERNER: This on-farm monitoring, however, is so integral to this whole issue that who is going to pay for it becomes almost an overriding issue here. We can wish for a lot of things. We have all got a great wish list. But that resource pie, again, becomes a very critical factor.

Maybe I am speaking out of turn here. I will stop.

DR. FLETCHER: This is, in part, where I was making my plea earlier for some kind of coordinated effort. I would actually like to see on-farm monitoring even before any approval, as some kind of benchmark. I have a lot of problems with knowing how this is going to actually work. I understand what the agency is asking for and I support that in concept, but I am having difficulty knowing how a company

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is going to do this.

I think it does get back to a drug-by-drug basis. I think this coupled with--I did not appreciate that the monitoring thresholds levels was not going to be also a responsibility of the industry. It wasn't clear to me from the framework document who was going to have responsibility for that.

But I think here is an opportunity for the quality-assurance programs, perhaps, to provide some kind of information in a database that could be drawn upon as benchmark kinds of information and then you don't necessarily have to worry about immediately postapproval or triggered by a change. You have it ongoing.

How to work that into a framework regulatory mode, I don't know. But my plea is to find a way to do that because if the breed association groups are saying, "Look; we have got quality-assurance programs," and if the integrators say, "On-farm quality-assurance is important," then that ought to be able to be coupled with data that is coming from the slaughterhouse and from product and from what is happening in the human population.

That, to me, is the one compelling argument that I see for looking at this framework in a very positive way to

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say that could take us down the road as opposed to endless debate. But there needs to be some coordination about it.

DR. HASCHEK-HOCK: I guess when I see this--in response to one of my questions earlier, I was told that on-farm monitoring would be non-drug-specific and non-sponsor-specific. So where does postapproval come in? I think I would support what Dr. Fletcher says that we need continual monitoring, however that is going to be established, and that it would not be triggered postapproval for any specific drug.

DR. ANGULO: Obviously, resources are going to be restrictive. So if we were to prioritize the animal data, I think it is very clear, but worth reiterating, that the slaughter samples are paramount. And the more slaughter samples we can do, the better. And if we have limited resources, that is what we should do most.

So then should there be an on-the-farm component. That is a good question worthy of discussion. I realize that that could be very expensive for the industry. It obviously would be to industry's advantage to have on-the-farm studies so that they could help, if we noted a trend in human data, explain that.

But how extensive it should be on the farm, those

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types questions, I think the resources are going to direct--the more the better, but I don't think it is essential, not like the slaughterhouse samples are essential.

DR. GERKEN: I don't quite understand how this could be a burden of industry since, on the farm, they are going to be using probably more than one antibiotic regime. So you are going to get really a mixed message. If they were going to be using just one antibiotic for a whole year, you might say, well, that could be borne by the company.

But I don't think that is realistic. So you may have a whole variety of antibiotics used during a given period of time. I don't know how you can ask a sponsor of one antibiotic to be looking for drug resistance in other--I don't know. Maybe I am missing something but I have a concern about that.

MR. WOOD: I also support the on-farm studies either initiated postapproval or, as was suggested earlier, beginning as soon as possible. It was indicated earlier, as well, in terms of identifying where resistance might take place that if resistance monitoring began there and no resistance was found but it was found as it went into the plant, it would certainly help to clarify some issues at

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that point, too.

I think any kind of monitoring that would take place, though, needs to be coupled with other kinds of review of on-farm management practices and steps that are taken that would have to do with creation of pathogen load or creation of resistance levels dealing with stress or biosecurity or density of animal populations that would have an impact in both those areas.

Related to the on-farm studies, although they are one piece of the pie and even though it is not a question, I think it needs to be supported again that the drug-sale data needs to be another part of that pie as well as what we have talked about many times, the resistance monitoring, overall resistance monitoring such as through NARMS, that all those are part of the whole and they all need to be a part of an effective framework system.

DR. LEIN: I think there are two things that are present here, one already existing and I will come back to diagnostic lab data, as soon as new drug is seeking approval and it is available, even before, possibly, licensed, the diagnostic labs have the disc. They start to incorporate that in for that animal group.

They will start to look at background because a

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lot of the companies need background data before that is ever licensed. From there on in, we will be looking at that drug, basically, in whatever melee of animals come through as far as the diagnostic labs. So I think diagnostic-lab data is important again.

Second, I talked about an independent laboratory, a centralized laboratory, that has good QA, good QC, that is certified and basically it could even be CLIA certified. It could go that far to say it is into the human health part of it. And it would be looking at sentinel farm data again.

I think if you could develop that, that would work very well. I agree very wholeheartedly with Dr. Fletcher that our herd-health programs or animal-health program, quality-assurance programs, are going to be calling for this basically as we go forward.

Today, we do work with independently--not available to government agencies because it is done privately with industry--we monitor a lot of industries for bacterial background. That is done in the poultry industry. It is done in the semen industry. It is done in the embryo industry. It is done in some of the production units.

So that already has started, basically, in helping them determine what their bacterial load is and what their

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antibiotic use is and their problems within that industry. So I think our step towards quality assurance is going to be a monitoring program.

As we put together these programs, basically, and we are developing one in the Northeast, it is certainly going to be developed that way for the dairy industry or other industries as we go forward.

Now, who will pay for this? Basically, industry, I think, will be involved with paying for a share of this. Again, I would throw out government and I am using a broad statement when I say government, be it state or be it federal or other agencies, to look at this. So I think this will be important data for us to glean.

We are going to need it for world trade. I think that day is here. And for the production units, we are certainly going to need it. So I think we should say, yes, we are going to look at on-farm data, make a statement and go forward.

DR. BARKER: Is part of the approval process for a new antibiotic drug that the manufacturer, the sponsor, must generate a baseline set of data about the effectiveness of their drug so there are acceptance of isolates from a range of different diagnostic laboratories and other sources? As

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part of the efficacy trials, in many cases, isolates are taken from the animals involved in the study to verify that it is a particular type of pathogen and the MICs on those are examined.

So as far as implementing anything immediately, it would seem that the data are made available to the FDA in a reasonable form already as to what the MICs of these antibiotics are.

Is it reasonable to expect that one, a question of legal ability of the FDA to do this and, certainly, others know more about this than I do, but to have them go on-farm, first get permission to go onto a farm, and to monitor for general resistance on a farm that, perhaps, is not even using their drug.

Of course, it would not be reasonable for them to go ask to monitor on a farm that didn't have their drug, but it is so complex, the variables there are so difficult to get a handle on, that the data that comes through from that is part of their approval process, may be quite difficult to interpret.

I would suggest that there might be another way to approach this problem that might be more acceptable. Certainly, the baseline data must be generated. Private

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industry will do that anyway. We will know what the resistance patterns are in a very large number of animals prior to approval of the drug.

Part of the second question here is after a trigger--I certainly, after the product is on the market, if we start to see antibiotic resistance from the NARMS data, that suspicion will be raised as to what the cause of that is.

Slaughterhouse data is far more important to prevention of transfer of pathogens to the human than on-farm data, would be my position, that we would be far better served to recognize, one, that there is a problem, that resistance is occurring and then make the attempt to identify that through epidemiological approaches where a company may be invited to do another on-farm study that is controlled, where they would be asked to administer drug now to this herd of animals and examine the resistant patterns to see if they have changed rather than to mandate a continuous monitoring on-farm where the variables are extremely high and, for quite some period of time, what you will observe is no change.

DR. ANGULO: In terms of a public-health safeguard, the on-the-farm testing is not essential to

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establish adequate public-health safeguards. The adequate public-health safeguards would be in place, I believe, by monitoring slaughter samples and monitoring human samples.

But we do have the disadvantages of we have noticed different changes in those two surveillance systems. If we don't have on-the-farm data, then we will just have to assume that it came through on-the-farm if we are going to have an adequate public-health safeguard, which may be an unfair assumption.

From a public-health perspective, I don't have an opinion whether there is an on-the-farm study or not. I do see a huge advantage of having some on-the-farm data because if there is on-the-farm data, you could fine-tune the current prudent use guidelines that are being developed by the data that is being generated.

I just believe that getting the on-the-farm data is in the best interest of the animal-health community. But it needs probably to be done by a group basis rather than individual companies so I would strongly encourage the Animal Health Institute to take the leadership in developing on-the-farm studies, maybe through an independent center or not, but it seems prudent that the whole industry should support it rather than an individual company.

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DR. STERNER: Dr. Lein, for everybody's information, would you have any idea about what a problem, an on-farm monitoring program nationally might cost?

DR. LEIN: No. I haven't thought about it.

DR. STERNER: It is one thing simply to go ahead and say to the pharmaceutical manufacturers, "We ought to go ahead and do this," and we may no idea about the price tag attributable to it. I say that, if somebody were going to say, "It is a small problem for me," but they may not know what my circumstances are either.

DR. LEIN: I think when we say industry, though, we shouldn't be just thinking about Animal Health Institute. I think we are talking about animal industries, also, kicking in on this. That is what happens today in some of the bigger industries. The poultry industry is a good example of that.

DR. BARKER: I believe there is already a wealth of information out there that just simply is not being taken advantage of. A lot of the cases, and you mentioned this earlier, that are seen on-farm where there are treatment failures or where there is actually a development of resistance are seen by a lot of diagnostic labs.

That data is very important, that good

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documentation of those cases is made by diagnostic laboratories and that there are more standard methods applied there, that there is already existing a very valuable resource for examining certain aspects of this.

To add one more layer of this as proposed here, individual companies would be responsible for establishing monitoring programs which the FDA has cited they would really have no control over, so it is not clear exactly what they would be monitoring and how, just doesn't seem either practical or reasonable and, in the end, fair, particularly if you are not going to make it drug specific, you are just going to make it species specific.

DR. HASCHEK-HOCK: I think we would all like to see on-farm monitoring. I think the question is how much is it going to cost and how would it be implemented to make the data useful across multiple farms and multiple sources of information.

So I think maybe we should just say that slaughterhouse data is essential. Diagnostic lab data should be used because that is a wealth of information and there should be at least a mechanism to do on-farm monitoring once a problem is detected so that there would be ability to investigate.

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The other things, I think, would be nice to do but may not be absolutely essential at this point.

DR. ANGULO: I think, in terms of this independent center, one possibility, of course, is the Center for Epidemiology Animal Health at Fort Collins, part of APHIS, which is an independent science-based agency and does to on-the-farm surveys, and they could head such a survey as this.

Those types of surveys that Fort Collins does, although expensive, are not resource-prohibitive, I don't believe. A similar type scale of study could be done by Fort Collins.

MR. WOOD: I would hope, though, that as we deal with this question, we deal with it in the same framework or the same understanding as the other questions in that we are not, at the same time as we answer this question, trying to work on budget questions.

We certainly have to live within the realities of what might be feasible but, to me, I think we are being asked conceptually whether or not on-farm monitoring, either postapproval or triggered, makes sense to us.

What I have heard us say earlier is that, yes, on-farm monitoring does make sense to us although there may

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be some financial implications that would make it difficult.

DR. STERNER: I think you have also heard that the validity of the on-farm monitoring presents some logistical nightmares, particularly for an individual manufacturer when we look at category I or II-H in terms of being able to mandate that for a sponsor.

DR. BARKER: Just one quick question, legal. Do you think that it is legal for the FDA to require a sponsor to monitor resistance on a farm where it does not directly and specifically involve their drug as part of proof of safety and efficacy?

MS. DAWSON: I haven't discussed that issue with the Center. I certainly would have the same concern. I think, under the statute, the types of reports and information that we are allowed to get are to serve the purpose of determining whether the drug continues to be safe and effective.

In my view, there would have to be some connection between the sponsor's drug and the information that we require the sponsor to collect. But that is just my preliminary view.

DR. STERNER: Is there further discussion from the committee? Dr. Lein?

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DR. LEIN: Looking further at the herd-health quality-assurance programs, we are developing one in New York State. Similar programs will be developed in Ohio and Pennsylvania. We are looking at a regional concept for this at this point really for the Northeast.

That would look at modules that would be involved with monitoring. Some of this is disease-oriented. If we had a Salmonella outbreak, obviously, it is quite easy to diagnosis Salmonella. It only takes, usually, the one animal that is sick or has a problem for those that have illness connected with it.

But there might be environmental monitoring that we would be doing as well because of Salmonella. We do that today in the egg industry for Salmonella enteritidis. It is a routine procedure that goes on within our states and several states in the Northeast and further, all the way out to the California Coast.

But in this situation, basically, what we are looking at in the new type of herd-health quality-assurance programs is that once we have an outbreak of Salmonella on a farm, usually it is typhimurium or it may be DT104, or it may be something less than that, the difficult thing for the farmer and the practitioner is to manage that.

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In managing that, frequently what we want to do is give help to the farmer and the practitioner in providing at least a post-diagnostic test to show that his management strategy is clearing up this condition.

That means that you are going to be doing environment testing as well as animal testing because you are looking for source of that infection and where it is harboring. It includes also rodents and birds and other wild animals that may be involved or other species on the farm because the cat becomes a big problem in this, dogs at times, and could include people.

In our situation, we are also pulling in the New York Agricultural Medicine and Health Group which is really an arm, a research arm, that comes through a regional concept throughout the United States and has the ability to work on-farm with farm families.

In that situation, they can look at the farm family as well through a questionnaire but also through testing and provide help or local health departments. Peter has been involved in a few of these before, too, where they become the arm that is necessary to be working with the farm family as the veterinary group works with, basically, the animals and environment.

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So I think putting those two things together gives us a unit, really, to go forward to start to look at some of these problems.

DR. STERNER: To the committee, the question says, "Should on-farm monitoring be instituted immediately postapproval or triggered by a change in data generated from other sources such as NARMS?" Implement immediately or after trigger? You have heard enough discussion and, I assume, have been taking notes that you have a consensus.

DR. LEIN: Just see how this fits. "On-farm postapproval monitoring programs," and I didn't specify what category, "would be encouraged by the committee." This sort of doesn't say it has to be there for category I or II. It is just encouraged by the committee.

DR. STERNER: Would you specify ownership?

DR. LEIN: Yes. "Slaughterhouse data should be increased. Diagnostic laboratory data and an independent accredited central laboratory should be developed utilizing government and industry moneys to monitor sentinel farms."

DR. STERNER: What is the committee's comfort level with the statement as read? Comments?

DR. ANGULO: I like it, but the possibility of getting enough resources--I know we are not supposed to talk

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resources, but getting enough resources to develop an independent laboratory kind of weakens the statement. So I think it might be a good idea to have an independent center participate but it is not essential to the statement.

I don't know whether you want to include that.

DR. LEIN: I put it in because we put it in once before, basically, back someplace in the third one or whatever it was. It could be CAH, or it could be NVSL; a centralized laboratory. We don't have to make it independent.

DR. FLETCHER: I don't think it adequately expresses my feeling that there should be some partnership with quality-assurance programs, for example.

DR. LEIN: Good idea.

DR. BARKER: I don't think it expresses my feelings at all, but--no; it does. I think it is desirable, that the committee would consider it desirable, to have on-farm data. I think there are still issues about the legality of requiring it, certainly, in terms of public health, that there are, in that list of things that you gave, I would think, different priorities.

I think Dr. Haschek's description was actually a little more appropriate, that there are mechanisms to do

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these individual things with existing programs and that, at some point, after a trigger, that we should apply the on-farm testing under a more controlled manner than is described in the framework document.

DR. STERNER: I am hearing some rumblings of agreement.

DR. LEIN: I have added the on-farm health quality-assurance programs. I say, "On-farm postapproval monitoring programs utilizing health quality-assurance programs should be encouraged by the committee," or, "would be encouraged by the committee," and then go on from there to say about slaughterhouse data, diagnostic lab and a central laboratory monitoring sentinel farms."

DR. HASCHEK-HOCK: Could you read that again, because maybe what we need to do is put some priorities in there, what the priorities for each of those would be.

DR. LEIN: "On-farm postapproval monitoring programs using health quality-assurance programs would be encouraged by the committee." We are not saying it has to be done. We are encouraging that they be developed.

DR. LEIN: It occurs to me--I have a little bit of a problem with postapproval in on-farm monitoring programs because I would like to see monitoring programs on-farm

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without regard to approval.

DR. LEIN: I agree with you. Let's take it out, if everyone is in agreement with that.

DR. STERNER: I will ask for a show of hands at this time for removal of "postapproval." Those in favor of removal of "postapproval?"

[Show of hands.]

DR. STERNER: We have seven. We have a majority. So, "On-farm monitoring programs," is how you start out reading it?

DR. LEIN: Let me put in here, "antimicrobial resistance." "Monitoring programs utilizing on-farm health quality-assurance programs would be encouraged by the committee."

DR. HASCHEK-HOCK: Is that the whole statement?

DR. LEIN: Then, "Slaughterhouse data should be increased. Diagnostic lab data and an accredited central laboratory should be developed utilizing government and industry moneys to monitor sentinel farms."

DR. HASCHEK-HOCK: I guess I would like to see some priority starting off, perhaps, with the slaughterhouse as being absolutely essential, increasing that first, and having the ability to do on-farm investigation when

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triggered by a change in the slaughterhouse samples and then say that we would also encourage on-farm monitoring.

MR. WOOD: I am a little concerned with setting up a situation where we would immediately turn this over to quality-assurance programs, as valuable as they are. Quality-assurance programs do, in some areas, particularly with the pork producers and others, address--and we have heard from others today or yesterday--address this question on how they address resistance.

But not all of them do. Not all producers are a part of the quality-assurance programs. I am not sure that quality-assurance programs are in all commodity areas. I don't know about aquaculture, for example. So that would be an avenue, but I would not want to see it established that it would automatically be relied upon.

DR. LEIN: I think, in answer to your question, we are really not saying that this is mandatory. What we are saying is we are encouraging it. I feel that any production group of food animals today is into a quality-assurance program including aquaculture. I know they have started one.

I think this is going to become necessary if they are looking at any foreign trade. It might even be if they

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are looking at interstate trade. I will tell you today, if MacDonald's is buying it, it is probably going to be mandatory because they are asking for these things today as we go forward.

So I think we are going to see the consumer pushing the quality-assurance program. We may as well add to the push at this level.

DR. O'BRIEN: I don't understand all the ramifications of implementation but I think, beyond just encouraging the on-farm monitoring, I think it would be nice if we could thing of somehow getting enough resources to do some pilot on-farm monitoring, at least to have that as a firm recommendation to get some samples of data, to see how it would work, to explore it as a source of information a little bit more than we can now.

The examples that I know of are the studies of Wolfgang Witte and the ones that Stuart Levy did years ago. But I think the interrelationships between use and resistance in different species and in different kind of farming operations would be extremely valuable to at least have small samples of, either triggered by just exploratory, just trying something, to see what kind of information you could get and how such a program could be fine-tuned, and

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then keep it as a possibility for the regulatory process, as, for example, to be triggered by events at the slaughterhouse.

But I think not to wait for that, but to try to find the resources to pilot it so you have models as to how to do it in-hand and then think where it fits into implementation.

DR. LEIN: Some of that has been done already. The NAHMS Program, the National Animal Health Monitoring Service, and Dr. Angulo mentioned the Center for Epidemiology and Animal Health which is a USDA division for epidemiology out of Fort Collins, has done this type of monitoring with several different species, now, over the last seven or eight years.

More recently, now, with both beef cattle, some dairy cattle, where they take a different species each year and set up a program statistically to test an industry and would look at several states. New York has been involved with both the dairy cattle, the Western states more with beef cattle, but spread across those states of interest and have looked at Salmonella.

Certainly, all those samples have gone through the NARMS testing because that is some of the data that has been

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in there for Salmonella and looking at antimicrobial resistance. There will be one starting in poultry, I think, in another year. They are doing the horse right now and that is looking, again, at a set of that fecal shed, basically, that could be present.

So we are getting background data ready out of that system. All the testing is done out at the National Veterinary Services Laboratory out at Ames, Iowa. NARMS is doing the susceptibility testing. All the Salmonella are typed.

DR. STERNER: We are at the end of our agenda, here. Time flies because we are having so much fun. The committee needs to come to some recommendation with regard to question 5. You have some language that I would like you to read for the committee.

Before you do, are there any last burning points that any individual committee members need to bring to this discussion? Wanda, yours have been expressed. We will get an opportunity to hear them in a moment.

DR. ANGULO: To second what Wanda said, the slaughterhouse samples are so essential, I think we could take that sentence out first and just say that, and then the rest on the on-the-farm.

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DR. LEIN: I separated that out and simply said, "Slaughterhouse data must be increased."

DR. ANGULO: You could say even more. You could say--

DR. LEIN: "Slaughterhouse data is paramount to this--"

DR. STERNER: "Is of paramount importance." There is agreement. I am seeing head nods universally around here with regard to slaughterhouse data being of paramount importance. That is statement No. 1.

DR. LEIN: And we'll say to the postapproval data or to the framework.

DR. STERNER: The framework is here. We have all pointed out some of the shortcomings, potential shortcomings, of on-farm monitoring, period, postapproval in particular.

DR. LEIN: We will make that number one, basically.

DR. STERNER: Yes. On-farm monitoring, period, as being problematic and postapproval, perhaps, even more more so. The rest of the statement reads--

DR. LEIN: "Slaughterhouse data is of paramount importance to the framework. On-farm antimicrobial

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resistance utilizing farm-health quality-assurance programs would be encouraged by the committee and diagnostic laboratory data and development of an accredited central laboratory should be developed utilizing government and industry moneys."

DR. BARKER: We may not be sufficiently addressing the question as that is stated. It is specifically about on-farm monitoring and whether it should be implemented immediately after approval of a drug or after a trigger. What we state there is just that it is encouraged, but we are not saying encouraged when, if ever.

DR. HASCHEK-HOCK: I think, in my statement, I indicated that, in addition to the slaughterhouse sampling that there needs to be a mechanism when triggered for on-farm monitoring. So could we add that in between those two statements?

DR. ANGULO: Which I am comfortable with. It is just that it places the drug company at a disadvantage, or animal health at a disadvantage, because if it is not in place until a trigger, it may be too late to have a mature system in place to refute the evidence that is coming through the food supply.

But that is a tradeoff.

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DR. STERNER: I am going to take a little license. Dr. Carnevale, you have had an opportunity, or Mr. Mathews, to listen to this. Would you care to comment about the Animal Health Institute's view on this, speak for the industry? This is pretty critical to you folks.

Dr. Carnevale, could you come to the microphone and perhaps just let us know what a semiofficial feeling would be? I apologize for blind-siding you on this, but I think it is very germane.

DR. CARNEVALE: Thank you, Mr. Chairman. I guess, listening to the discussion, we clearly support, as we said yesterday, the focus of the monitoring being at the slaughter plant. I think we have always stated that. We felt that that was the best measure of exposure.

I think, as Mr. Mathews stated yesterday in his summary/conclusions, we felt that using that slaughterhouse data as an indicator of trends in resistance, that there be follow up, epidemiologic investigations done, to try to determine, if one can, where that resistance is coming from, what species and where, maybe geographically, that is coming from.

So, conceptually, I think we completely support that notion. We understand that there is some concern about

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increasing sampling in slaughter plants. We have to be careful about recommending that. But, to the extent that we can strengthen and continue to fund the basic component of slaughter-plant sampling being the real trigger for further action, I think AHI would support that notion.

DR. STERNER: Would you care to comment to Dr. Angulo's comments about a program that was already in place versus post-trigger?

DR. CARNEVALE: That is a bit troublesome. I don't think the industry ever had a problem with on-farm testing in and of itself. I think that the problem that industry has with on-farm testing was on an individual product-by-product basis being somehow managed by the individual drug sponsor.

If the federal government and other sources were able to set up some sort of monitoring system on the farm, I don't think that industry would have any specific objection to that. I think it was the responsibility being placed on the drug sponsor to manage this whole thing on their own, which is really what stimulated the concern we had for this.

So, yes; certainly it would be a good idea to have something already in place. The problem is, as a routine basis, it is very difficult for a drug sponsor to accomplish

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that on their own.

DR. ANGULO: But don't you agree that for the on-farm system to be most useful, the more robust it is the better and, therefore, the more sampling done, necessary. So it would be advantageous to the Animal Health Institute, or at least the whole animal-health pharmaceutical companies, to provide also sponsorship of the on-the-farm study to make sure it is robust.

Just the way resources are in the government, if you rely on the government to only do sponsorship to run the entire on-the-farm, it may not be robust enough to answer the questions that all of us would like to have answered.

DR. CARNEVALE: That may be the case. This is a very difficult area. We can talk about on-farm testing, but when you actually get down to it, it is a pretty big deal. I think what you ought to do is ask some of the producer groups in the audience, too, what their opinion is because, obviously, if we embark on something like this, it is going to have to be a cooperative effort.

MR. WOOD: That kind of survey probably does need to be taken. I know that with it being a trigger, that smells to me like traceback, then. I think that that kind of perception or phenomenon has not been taken to very

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kindly by a number of producers at least as I know as important as it is.

If there were postapproval monitoring, it would all be in place. All producers would be participating in it who were administering that antibiotic and so it would overcome the stigma of a traceback. Also, quite often, a traceback has some arbitrary qualities to it. So I would argue, again, for postapproval monitoring.

DR. STERNER: Don, are you ready to read the statement?

DR. LEIN: Yes. "Slaughterhouse data is of paramount importance to the framework." Now, I can make that I or II. "On-farm antimicrobial-resistance programs utilizing on-farm health quality-assurance programs would be encouraged by the committee to look at postapproval antimicrobial levels for high-category antibiotics. Diagnostic laboratory data and development of an accredited central laboratory should be developed utilizing government and industry moneys."

DR. STERNER: The committee has heard the statement. Anybody vehemently disagree at this point? Could I see a show of right hands for those in favor as it reads.

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[Show of hands.]

DR. STERNER: Those opposed, the same.

[No response.]

DR. STERNER: I see unanimous consent.

That brings to a conclusion the five questions. Steve Barker, you have a comment?

DR. BARKER: Oh, as usual. I want to commend the people that worked on the framework document for bringing forward what they knew people would take potshots at and that they would have to sit and listen to an awful lot of both complaints and approval.

As Dr. Bell brought out, we did need to get off the dime. This have to move forward. The FDA does have a responsibility to address these issues and, hopefully, that will be done.

But, at the same time, I would like to direct just a comment to Dr. Bell. All of this time that we have spent here and all of these efforts will be absolutely meaningless if the CDC and the government do not come down hard on the misuse of antibiotics in the human medical area.

DR. STERNER: Dr. Sundlof, I would invite you to add any concluding comments that you have from the agency. I wish to thank those in the audience for their very kind

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indulgence for this very long meeting. We have tried very hard to keep on schedule. We have met that goal but barely.

My apologies. I thought we could run a bit further, but this issue transcends the need for speed.

Dr. Sundlof?

DR. SUNDLOF: Thank you, Mr. Chairman. I just want to add my congratulations to the committee for all of the hard work and for all the long hours that you have spent here and the long hours you have spent reviewing all this massive amount of information in preparing for this meeting. I think we are very happy with the deliberations that took place in this.

I want to thank our consultants, Dr. Galbraith and Dr. O'Brien, for taking the time out of their busy schedules to come here today. I want to especially thank our outgoing members, Dr. Gerken, Dr. Lein and Dr. Cooper, and to Dr. Lein a special thank you for your years as chairman but for being such an able rapporteur for this session. That is truly a gift.

I also want to thank all of the special consultants who attended here today and yesterday for taking the time to come here and give us their insight and their expertise, and to the people in CVM who spent a lot of time

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staffing this meeting, making sure that it came off as well as it did and, especially, again a hearty thank you to Dick Geyer for all the years of service he has put in there.

[Applause.]

DR. STERNER: This meeting stands adjourned.

[Whereupon, at 4:00 p.m., the meeting was adjourned.]