

# TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR VETERINARY MEDICINE

VETERINARY MEDICINE ADVISORY COMMITTEE

Pages 1 thru 239

Gaithersburg, Maryland  
January 26, 1999

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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  
Two Montgomery Village  
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.  
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## PARTICIPANTS

Keith Sterner, D.V.M., Chairperson  
Richard Geyer, Executive Secretary

## MEMBERS

Frederick Angulo, D.V.M.  
Steven Barker, Ph.D.  
George Cooper, Ph.D.  
Oscar Fletcher, D.V.M.  
Wanda Haschek-Hock, B.V.Sc., Ph.D.  
Robert Holland, D.V.M.  
Vernon Langston, D.V.M., Ph.D.  
Richard Wood

## CONSULTANTS

Peter Galbraith, D.M.D., M.P.H.  
Diane Gerken, D.V.M.  
Donald Lein, D.V.M., Ph.D.  
Carl Norden, M.D.  
Thomas O'Brien, M.D.

## FDA and USDA

## CVM

Stephen F. Sundlof, D.V.M., Ph.D.  
Linda Tollefson, D.V.M., M.P.H.  
Margaret Miller, Ph.D.

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Albert P. Sheldon, Ph.D.

## Office of Policy

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## DHHS

I. Kaye Wachsmuth, Ph.D.

## Office of the Commissioner

Jesse L. Goodman, M.D., M.P.H.

## Office of Chief Counsel

Joy Whetstone Dawson, Esq.

## GUEST SPEAKERS

David Bell, M.D.  
Sherwood Gorbach, M.D.  
Patricia Lieberman, Ph.D.  
Scott McEwen, D.V.M., D.V. Sc.  
J.M. Rutter, D.V.M.  
Abigail Salyers, Ph.D.  
Lyle Vogel, D.V.M., M.P.H.

C O N T E N T S

PUBLIC SPEAKERS

Dr. Jim Jarrett, American Association of Bovine  
Practitioners

Dr. Ran P. Smith, National Cattlemen's  
Beef Association

Questions from the Committee and from the Floor

Presentation of Awards

Committee Deliberations

P R O C E E D I N G S

1  
2 DR. STERNER: Good morning. I will now convene  
3 the second day of the VMAC Committee dealing with issues of  
4 antimicrobial approvals and antimicrobial resistance.

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

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

11 Dr. Jarrett.

12 Public Speakers

13 Dr. Jim Jarrett

14 DR. JARRETT: Thank you, Mr. Chairman.

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

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

20 DR. JARRETT: Right now. Next sentence.

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

24 I am a veterinarian. I am a former dairy owner,  
25 part owner of a 1,000-cow dairy. I practiced for some 30

1 years in a dairy practice and still do some practice. In  
2 fact, we will be on the farm one day later this week trying  
3 to explain the proceedings of yesterday and today to a dairy  
4 client .

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

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

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

20           We know that in the United States, food from  
21 animals is purchased by the consumer on a voluntary basis.  
22 To think that any producer would do anything to discourage  
23 or endanger that voluntary purchase is to abandon all sense  
24 of reality.

25           We agree that there could be a problem associated

1 with the use of antimicrobial in animals, but to use the  
2 vernacular of the day, is it a high crime and misdemeanor?  
3 We don't know for sure.

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

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

18 As an organization and as individual members, we  
19 have a great concern over this issue. This certainly  
20 includes the concern for the health of the human consumers  
21 of the products produced by our clients. We are dedicated  
22 to the maximum safety of these products through the health  
23 and well-being of the animals we treat.

24 To reach that goal, we from time to time need  
25 tools such as antimicrobial to treat, control, and prevent

1 disease. As an organization, we reached early on a  
2 consensus and an understanding that this matter can have a  
3 great impact on the way we practice and the service we  
4 render.

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

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

15 We are a part of the financing of the database  
16 project that Dr. Apley mentioned. We are a part of the AVMA  
17 Committee on its judicious use principles, and other  
18 activities which I will discuss later.

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

23 We fear that the adoption of this proposed  
24 framework document as it is written would further restrict  
25 the availability of products needed by the cattle

1 veterinarians to reduce and control pain and suffering in  
2 the animals we treat.

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

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

13 I feel this issue to a great extent may be based  
14 on what may have happened in the past, and not the way  
15 antimicrobial are currently used on farms today. The  
16 practice has changed, and as a dairy practitioner I can  
17 attest to that. We do not use antimicrobial in the ways on  
18 farms that we did 10 or 20 years ago.

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

25 As to specific comments regarding the document,

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

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

12           Monitoring, the third question. Certainly some  
13 monitoring could be helpful in determining any changes in  
14 the susceptibility of microbes to antimicrobial compounds.  
15 There is an old practice axiom that I use constantly that  
16 says, "If you can't measure it, you can't manage it."

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

24           The fifth question relates to on-farm testing and  
25 monitoring. This sounds good, however, when and where and

1 how will these samples be taken? What will be the impact of  
2 management on individual farms as relates to the outcome of  
3 the testing on these samples, and the concern regarding the  
4 fact that these samples will be taken a long way from the  
5 consumer, and could they just as well be or include samples  
6 closer to the consumer.

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

11 I would point out some of the areas of extra-label  
12 drug use as an example of some of these concerns.

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

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

25 This lack of understanding has led to a

1 polarization of two groups that should have the same goals  
2 on this issue.

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

9 I think we can agree on the fact that the exposure  
10 of microbes to antimicrobial can, not always does, can lead  
11 to some reduced susceptibility in the area of treatment. I  
12 think we can agree on the ways and the fact that the ways we  
13 have used antimicrobial in agriculture does need some  
14 changes to minimize the development of antimicrobial  
15 resistance.

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

22 I would urge that you deliberate your  
23 recommendations regarding this document, that it continues  
24 to allow the involvement of the professional practicing  
25 veterinarian in this effort. Please try not to restrict the

1 tools of modern technology needed to relieve animal  
2 suffering and assure the wholesomeness and safety of the  
3 products of American agriculture.

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

6 I mentioned earlier that I would discuss one  
7 additional area of AABP activity in this area. In an effort  
8 to improve the understanding on both sides, in the past year  
9 we have arranged some visits to livestock operations by CDC  
10 personnel.

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

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

19 Thank you.

20 DR. STERNER: Thank you, Dr. Jarrett.

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

23 DR. SALYERS: This is a comment on a number of  
24 talks in the same general direction. It is something that I  
25 am a little confused about. I have heard a lot of comments

1 of concern about suffering of animals and treating animals,  
2 and it seems to me that the reason that confuses me is it  
3 seems to me that one of the things that this guideline would  
4 do is to help to reserve some compounds for later treatment.

5 No one seems to be concerned about the fact that  
6 the first victims of agriculturally causes antibiotic  
7 resistance are likely to be the farmers or rather the farm  
8 animals themselves.

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

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

25 DR. JARRETT: As I understand the question, are we

1 in veterinary medicine, food, animal veterinary medicine,  
2 particularly concerned on-farm as it applies to out activity  
3 about the development of antimicrobial resistance, and the  
4 answer is certainly yes, and in that regard we feel it is  
5 the activities we are taking so far, as an example, in AABP  
6 and in AVMA, coming up with guidelines, recommended  
7 procedures for use of these compounds to help reduce that  
8 capability.

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

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

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

22 DR. STERNER: Further questions for Dr. Jarrett?

23 [No response.]

24 DR. STERNER: Thank you, Jim.

25 Our final public speaker of the morning represents

1 the National Cattlemen's Beef Association, Ran Smith.

2 Dr. Ran Smith

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

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

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

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

22 For example, in the area of food safety, in 1985,  
23 the National Academy of Science recommended the U.S. meat  
24 inspection system move to a hazard analysis and critical  
25 control point approach to inspection.

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

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

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

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

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

23 In order for drugs to retain their power over  
24 pathogens, they must be used in a responsible manner in  
25 human, plant, and animal treatment. NCBA recognizes that

1 the use of feed additives and drugs and antimicrobial  
2 aerosols are a necessary tool in efficient production of  
3 livestock.

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

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

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

19 We encourage livestock producers to use animal  
20 drugs and additives in conformity with dosage directions,  
21 requirements, and withdraw periods. Through the efforts of  
22 the industry's beef quality assurance education initiative,  
23 producers commit to using sound animal husbandry and  
24 preventative practices to limit the need of antimicrobial.

25 NCBA recommends and participates in long-term

1 producer and veterinary education on the prudent use of  
2 antimicrobial in food animals. The beef quality assurance  
3 program is being expanded currently to include greater  
4 emphasis on proper drug use beyond the current focus of  
5 residue prevention.

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

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

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

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

24 We believe such data and other research will over  
25 time assist the production sector in making accurate

1 scientific-based decisions.

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

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

15           Perhaps an alternative to the action listed in the  
16 proposal would be to work to establish a strong system of  
17 national monitoring for trends in antimicrobial resistance.  
18 If trends indicate the number of resistant bacteria are  
19 increasing, APHIS and ARES could work together to perform  
20 epidemiological studies of these bacteria in order to  
21 pinpoint the cause of such changes.

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

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

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

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

14 Thank you, Dr. Smith.

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

17 [No response.]

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

20 MR. GEYER: Did you have a question?

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

23 DR. STERNER: Thank you, Dr. Angulo.

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

1 support.

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

6 DR. STERNER: Do you have any financial interests?

7 DR. SMITH: I do not.

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

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

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

20 P and U supports the CVM initiative to develop an  
21 appropriate risk-based framework to address the human health  
22 impacts of antimicrobial used in food animals, however, P  
23 and U contends that there is no evidence for an imminent  
24 hazard from the use of antimicrobial in food animals that  
25 would demand immediate changes in the pre-approval process

1 for new animal drugs.

2           They would prefer to have a complete risk analysis  
3 performed before implementing any changes in regulatory  
4 policy affecting animal drugs. P and U commended CVM for  
5 putting forward concepts of risk characterization and  
6 exposure assessment, but believes that the resulting nine  
7 categories, such as IH1M, and so forth, overly simplifies  
8 the process.

9           P and U recognizes the need for an expanded  
10 surveillance system to gather more data. P and U supports  
11 systematic monitoring of drug susceptibility patterns and  
12 zoonotic pathogens from animals at the time of slaughter,  
13 but emphasizes that such data is insufficient to set  
14 monitoring and resistance thresholds.

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

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

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

25           Dr. Lechtenberg recommends focusing resources on

1 four things: first, continuing the process of risk  
2 assessment; second, educating consumers and meat industry  
3 workers and veterinarians; third, increase support for the  
4 national antimicrobial resistance monitoring system; and,  
5 fourth, development and implementation of judicious use  
6 guidelines for veterinarians.

7 That concludes the summary of the written  
8 comments, and while I am on my feet, let me introduce a  
9 couple of people who are at the front table in the first row  
10 here who did not speak yesterday, and they are available  
11 today as resource people to us for the benefit of the  
12 committee and consultants.

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

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

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

25 Thank you.

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

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

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

19 DR. STERNER: Thank you, Dr. Cooper.

20 Questions from the Committee and  
21 from the Floor

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

1 to come to a microphone.

2 I would like to open the questioning, exercising  
3 again the prerogative of the Chair, the questioning to Joy  
4 Dawson, having to do with some comments that Dr. Vogel made  
5 in the AVMA presentation yesterday regarding the authority  
6 for regulation of microbial contaminants as a food additive,  
7 and could you give CVM's position on that. Thank you.

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

13 Unfortunately or fortunately, the statute does not  
14 provide flexibility in this area. If the substance results  
15 from the use of a drug in the animal, it must be considered  
16 under Section 512, which is the new animal drug provisions.  
17 The only way to get it under Section 409, which is the food  
18 additive provisions, we would have to establish or it would  
19 have to be established that the resistance was not a result  
20 of the use of the drug for treatment, that it was separat<sub>e</sub>  
21 and apart from that.

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

25 MS. DAWSON: When you say risk-benefit, do you

1 nean the risk to humans versus the benefit to humans or to  
2 animals?

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

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

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

16 DR. STERNER: Dr. Barker.

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

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

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

1 of developing a framework document.

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

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

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

20           We recognized very early on that this was not just  
21 a CVM issue, that this issue had broader ramifications, and  
22 so it was important that we involve people outside of CVM,  
23 but within the FDA, and those included individuals from the  
24 Center for Drug Evaluation and Research, and Mark Goldberger  
25 was the primary contact person from CDER. Al Sheldon also

1 participated.

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

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

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

21           If I can just go on a little bit further because  
22 it is apparent that our intentions in writing this are maybe  
23 not well understood. The intention was to develop a  
24 document by which we felt we could make a determination  
25 prior to approval that there would be reasonable certainty

1 of no harm, which is the only legal basis that we have for  
2 making the determination of approval.

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

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

18 How you make a determination of reasonable  
19 certainty of no harm when there appears to be a great deal  
20 of scientific uncertainty surrounding this issue\*. We have  
21 heard the concerns of many that we haven't done an adequate  
22 risk assessment and that an adequate risk assessment is  
23 necessary, I can tell you that we have attempted to develop  
24 a risk assessment. We are still doing that. We have under  
25 contract one of the world's authorities in risk assessment

1 who is assisting us with the issues, but in the end, we  
2 don't believe that the data exists out there to be able to  
3 determine the specific impact of resistance on public  
4 health, and we don't want to get to the point where we have  
5 data that will allow us to make that decision. Once we have  
6 gone there, once we have hard data that shows that  
7 antibiotic resistance as a result of animal drug use has  
8 caused harm to people, then, we have gone beyond the  
9 reasonable certainty of no harm standard, we have surpassed  
10 that.

11           So, we have to rely on surrogate endpoints in  
12 order to make the assessment of reasonable certainty. of no  
13 harm. In this document, the surrogate endpoints that we  
14 were considering were surrogate endpoints regarding  
15 resistance thresholds. Recognizing that those are going to  
16 be difficult to establish, but we felt that it would be  
17 possible to get scientists together who could address the  
18 issue and make a determination of what they thought was the  
19 best available knowledge was a level of resistance below  
20 which there is reasonable certain of no harm.

21           Making that decision prior to the approval, so  
22 that we could stay within our statutory framework, so that  
23 we can establish what consider a priori before the approval  
24 to be the reasonable certainty of no harm standard, and we  
25 had a basis for regulating to that standard, and the basis

1 would be using our monitoring programs both in animals and  
2 humans to look at the development of resistance and use our  
3 reasonable certainty of no harm standard as the trigger  
4 point for taking additional regulatory actions.

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

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

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

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

11           That, the agency has already determined. We have  
12 determined that there is a need for assessment, that there  
13 is a need to comply with the standard of reasonable  
14 certainty of no harm when making an approval decision.

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

25           We use laboratory animals as a surrogate model for

1 humans, and we apply exaggerated uncertainty factors which  
2 we call safety factors in determining what an acceptable  
3 daily intake is, and we don't look at that in the light of  
4 how many people are adversely affected.

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

8           When we do risk assessments, and there are cases  
9 where we do use a quantitative risk assessment in the  
10 evaluation of animal drugs, and those would be in the case  
11 of carcinogens, and in those cases we use a model, a risk  
12 assessment model, which is based on giving rats and mice  
13 generally the maximally tolerated dose of the product which  
14 is suspected to be a carcinogen over the lifetime of the  
15 animals, and the top dose is the maximally tolerated dose,  
16 and there are some other doses in between, and then  
17 extrapolating well, well below the data to determine the  
18 risk of a one in a million chance, an increased risk of one  
19 in a million that an individual may develop cancer.

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

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

8           So, where there is scientific uncertainty, then,  
9 we have to interject policy decisions, and this framework  
10 document once again was an attempt to establish through both  
11 science and policy a regulatory structure that would allow  
12 certainty, stability within CVM in the regulation of these  
13 drugs.

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

18           DR. STERNER: Thank you, Dr. Sundlof.

19           Dr. Holland, I saw your hand next.

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

23           DR. GOLDBERGER: Well, I think that several  
24 speakers asked yesterday, I think both some of the prepared  
25 presentations and some of the speakers during the open

1 public hearing about the issue of what is happening on the  
2 reman side as opposed to this initiative on the animal side.

3           As you can imagine, this concern about the  
4 development of antimicrobial resistance and its implications  
5 for the treatment of infections in human beings has produced  
6 concern more widely within the FDA than simply within the  
7 Center for Veterinary Medicine, and we within the Center for  
8 Drug Evaluation and Research are obviously quite concerned  
9 about it.

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

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

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

1 for instance, to that given antimicrobial.

2           So, that's an initiative that we are currently  
3 working on. Another initiative that we have been working  
4 on -- and, in fact, this was part of a large public advisory  
5 committee meeting that we had in this past October -- is  
6 how, for instance, we might facilitate the development of  
7 products that are referred to as narrow spectrum products,  
8 that is, new antimicrobial which are more likely to be  
9 active against some of the resistant organisms that we are  
10 concerned about, but otherwise don't have the same broad  
11 spectrum that drugs, for instance, like the fluoroquinolones  
12 have that might encourage these products ultimately to be  
13 used in more selective circumstances.

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

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

1           The other thing, just as an aside to mention, is  
2 there is also an interest in seeing what we can do to help  
3 facilitate the development of newer diagnostic tests that  
4 might make it easier to identify and organism earlier in the  
5 course of an infection, and therefore, tailor antimicrobial  
6 therapy more specifically to that organism.

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

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

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

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

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

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

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

21           DR. STERNER: Dr. Tollefson.

22           DR. TOLLEFSON: I would like to add to that, that  
23 the FDA feels also that when you are treating a companion  
24 animal with an antimicrobial, there is an education element  
25 which is very easy to transmit from the veterinarian to the

1 person, to the owner of the pet, recognizing that there is a  
2 risk from the disease in the animal.

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

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

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

19           My concern is once again although food animals are  
20 a major contributing factor to the food-borne problems, they  
21 are not the only problem, and I think we need to also bring  
22 up -- if you are going to make a broad statement, then, we  
23 need to look at all factors, and not just one factor  
24 perhaps.

25           DR. ANGULO: We recognize fully that Salmonella

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

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

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

16 Dr. Hock.

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

19 Could you just briefly summarize the current  
20 regulations in force for determination of pathogen load and  
21 resistance and what the proposal is for this framework, how  
22 to alter that?

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

25 DR. MILLER: Yes, I am really the pre-approval

1 person. Currently, the microbiological safety studies that  
2 I discussed yesterday, which are the Salmonella shedding  
3 study and the coliform study, which have both a component of  
4 resistance and patient load, are required for all  
5 antimicrobial administered in the feed for more than 14  
6 days .

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

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

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

17 DR. MILLER: In some cases, that would be the  
18 case, yes. SO, for an ionophore, for example, now they  
19 would have to do the whole 558.15 studies, whereas, under  
20 the framework document, they would only have to look at the  
21 pathogen load component of those studies.

22 DR. HASCHEK-HOCK: Thank you.

23 DR. STERNER: Dr. Lein.

24 DR. LEIN: Steve, in a way, the last antibiotic  
25 for a food animal being Batril for beef cattle has started

1 into this process, and we are looking at again a post-  
2 approval monitoring program.

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

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

13 DR. TOLLEFSON: To discuss the first question, the  
14 Batril 100 approval last August of feed lot cattle does have  
15 a voluntary post-approval monitoring program associated with  
16 it. We have not yet received any results on that. We can't  
17 discuss that in a public forum anyway. Those data are all  
18 owned by the sponsor.

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

25 We can get you more information about that.

1 Actually, the awarded programs are on our home page. We try  
2 to support as much as we can on the research end, but are  
3 very limited by resources.

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

9 DR. STERNER: Richard Wood.

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

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

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

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

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

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

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

23 The national program is a good start, but it is  
24 chronically underfunded. We cannot expand it to the level  
25 that we feel would make it robust enough to be able to

1 detect a problem should it exist, let alone -- I know a lot  
2 of concern is expressed about identifying little pockets of  
3 resistance and going out and doing some kind of regulatory  
4 action based on that, but in reality, that is not the  
5 problem with the system.

6           The system is limited by the amount of information  
7 we can collect on each of the species, the number of  
8 pathogens we can collect, the number of antimicrobial we  
9 can screen for, and it is really a matter of not having a  
10 lot of confidence in the data, that if a problem is out  
11 there, we are able to detect it, and that has to do with the  
12 representativeness of the sample, as well as the number of  
13 samples being taken.

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

21           Does that answer your question? Okay.

22           DR. STERNER: Dr. Lein.

23           DR. LEIN: Following Up on that, this sounds a  
24 little different than what was presented or what I  
25 anticipated, because it seemed like it was drug related to

1 the drug that was going to be brought up for at least  
2 approval for licensing.

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

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

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

21 This brings up the idea that we need to look at  
22 this as a society. I think the last NCBA statement here  
23 about societal needs to look at this become very important.  
24 I think when we first started to talk about antimicrobial  
25 resistance and monitoring, which goes back some years now, I

1 know I sat in that room and I was excited from the  
2 standpoint that we had human medicine, veterinary medicine,  
3 and at least universities, government, others sitting at the  
4 table saying this has to be looked at and has to go forward.

5 I think that has to happen again with industry  
6 sitting at that table along with that societal group.

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

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

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

23 Our group now is working very closely with our  
24 agriculture environmental management, which is looking at,  
25 at least other waste problems, be it nutrients, be it

1 pesticides, be it other toxicants, and trying to relate  
2 these two as to how we control that.

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

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

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

19           DR. TOLLEFSON: I would like to make a brief  
20 comment, if I could. There is a lot of confusion on this  
21 drug-specific issue versus a national monitoring program,  
22 and part of the problem with that is that because of the  
23 approvals of the fluoroquinolones, we are linked to drug-  
24 specific monitoring programs, but that was an initial  
25 attempt on our part to gather some sort of information, and

1 we have learned from those that it is not an expedient way  
2 to either get information or the maximize use of resources.

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

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

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

21 DR. STERNER: Dr. Fletcher.

22 DR. FLETCHER: I need to ask Dr. Miller to clarify  
23 something for me. If you have already answered this, I  
24 apologize for asking it, but in the current pre-approval  
25 process, review for me again what is required relative to

1 pathogen load.

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

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

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

11 DR. FLETCHER: And that is only for antimicrobial  
12 given in feed?

13 DR. MILLER: For more than 14 days.

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

20 DR. MILLER: The framework document calls for  
21 pathogen load studies. What the framework document does is  
22 it separates out the resistance studies from the pathogen  
23 load studies, and the Salmonella shedding, it was tied  
24 together, we have separated them out, and the threshold for  
25 needing a resistance study is a human health concern.

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

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

17           DR. STERNER: Dr. Angulo.

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

22           Very few speakers were in favor of tying any  
23 corrective actions to what was detected, and if we were to  
24 increase or continue the same level of surveillance, my  
25 question would be to a historian from FDA or perhaps legal

1 counsel, the historical question is has there ever been an  
2 instance where we have withdrawn, we, FDA, has withdrawn an  
3 antimicrobial off the market, and that is an historical  
4 question, and the second might be to legal counsel or to  
5 Someone else from FDA, if we were to detect with this  
6 increased or the same level of monitoring an increase of  
7 resistance that is a public health concern great enough to  
8 want to withdraw that drug from the market, let's just  
9 imagine, for instance, with the poultry fluoroquinolone  
10 product, if we were to reach levels of fluoroquinolone  
11 resistance in Salmonella associated with poultry, that is a  
12 public health concern.

13           Let's say 10 percent of all Salmonella in the  
14 country is fluoroquinolone resistant, much of it coming  
15 through poultry, if we were to demonstrate that to be the  
16 case, if we wanted to pull the poultry fluoroquinolone  
17 product off the market, if we wanted, how long would it take  
18 to do that, and would we have the legal authority to do  
19 that, how could we do it, and if it were done, how long  
20 would it take from the time of noticing this public health  
21 concern under the current legislation?

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

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

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

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

14 At that point, affected parties could request a  
15 hearing. The second step in that process would be to issue  
16 a notice of hearing if there are factual issues, at which  
17 time that hearing would take place, and then the agency  
18 would make a final determination on whether to withdraw the  
19 approval .

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

25 There is one particular provision in the Act which

1 allows the Secretary to suspend a use if it is determined  
2 that a use presents an imminent hazard, and that particular  
3 standard is quite strenuous. That determination can only be  
4 made you the Secretary, it is not delegated down to the  
5 agency.

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

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

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

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

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

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

7 Dr. Langston.

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

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

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

25 We would like to have, depending on how these

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

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

8 DR. STERNER: Dr. Barker.

9 DR. BARKER: This is for Dr. Tollefson. I am a  
10 little confused. Anyone who knows me, knows that is a  
11 common state of mind. I think I called Dr. Sundlof Gary  
12 yesterday, he has such an uncommon first name.

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

16 DR. STERNER: The answer was yes?

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

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

21 DR. TOLLEFSON: That is our advice.

22 DR. BARKER: Right. That is my point. You are  
23 asking private industry for the approval of a specific drug  
24 to monitor potential resistance development on individual  
25 farms that may be using a variety of different drugs and may

1 be using a variety of different farm practices where there  
2 may be a potential for individual farm workers to actually  
3 expose animals to resistant bacteria.

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

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

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

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

25 You have valid arguments here. You are asking a

1 drug-specific sponsor to buy in, if you will, to a program  
2 that is beneficial to a lot of -- yes, I agree, we have been  
3 struggling with this for a long time. We don't have an  
4 answer.

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

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

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

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

1 DR. SUNDLOF: Let me just answer the last question  
2 that you raised, Richard. It is on page 7 of the framework  
3 document, in the footnote, it says, "FDA anticipates that  
4 the framework, if finalized and implemented, will be part of  
5 the approval of new animal drug applications and as  
6 resources permit will also be used for reviews of uses of  
7 antimicrobial for food producing animals. "

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

15 DR. STERNER: Dr. Flamm.

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

21 DR. STERNER: Joy .

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

24 DR. STERNER: The extra-label use essentially is  
25 what happens when an imminent hazard is determined, and the

1 most recent antibiotic one that I can think of -- well, I  
2 guess there were a number of them that kind of fell all in  
3 at the same time -- but chloramphenicol comes immediately to  
4 mind in use in food animals.

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

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

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

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

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

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

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

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

13 DR. TOLEFFSON: Most of the current antimicrobial  
14 would fall into category II.

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

21 If default assumptions are going to be reasonably  
22 protective of public health and meet the reasonable  
23 certainty of no harm, you are going to have to make a  
24 decision with lack of data. Doesn't the whole process just  
25 bog down when you get to that to continue the statement of

1 lack of data supporting action?

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

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

19 I guess what I was suggesting in my talk would be  
20 a possible way of using a formal risk assessment would be to  
21 have a tiered approach, that initially a qualitative  
22 approach would be used because decisions have to be made  
23 about public safety now. But provision would be made in the  
24 future for incorporating more sophisticated techniques,  
25 incorporating more data as they became available, as

1 confidence grew, as expertise became more widespread.

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

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

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

20           How would that be composed, say, for the  
21 proapproval or the postapproval, and is there going to be a  
22 industry representative? Is there going to be a AVMA  
23 representative? Is there going to be a public-health  
24 representative? Is there going to be at least the group  
25 effort to get all the connections that I think would be

1 .mportant in that?

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

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

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

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

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

1 or as a checkpoint for this problem of at least  
2 antimicrobial resistance?

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

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

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

22 DR. GERKEN: I have a question. It is not obvious  
23 to me who is going to triage the drugs into the different  
24 categories. If company Y has drug X that they are thinking  
25 about developing, is it your intent that they should come to

1 you and justify what category it should be in and then you  
2 should approve that? Or you should make the recommendation  
3 with the--I'm nor sure whether the chicken or the egg comes  
4 first here.

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

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

13 So largely that decision would be based on  
14 information in consultation with the Center for Drug  
15 Evaluation and Research. The exposure estimate would be  
16 determined by CVM in collaboration with the sponsor so that  
17 we would hold meetings with the sponsor, try and determine  
18 exactly how the drug was going to be used, try to get an  
19 assessment of what the incidence of the disease is that the  
20 drug is going to be used to treat so we have an idea of how  
21 many animals may be exposed to the drug and, through that  
22 process, determine the ranking of high, medium or low.

23 DR. GERKEN: I have a subsequent question to that,  
24 then. As you well know, as the drug goes chugging through  
25 the system, it is kind of a long period of time. Once that

1 classification would be decided, would it be held in that  
2 classification during the time that that is chugging through  
3 the system or is this a moving target and can change during  
4 the time that it is chugging through the system, thereby  
5 increasing the burden or, in the rare case that we just  
6 realized that it might decrease the burden--I doubt that  
7 that is going to happen very often--but increasing the  
8 burden to industry while it is chugging through?

9 DR. SUNDLOF: We would do our very best to try and  
10 give the best guidance we could at the time but recognizing  
11 that things do change. We had a recommendation for the  
12 approval of the drug Synercid. If that would have occurred  
13 during the time that we reviewing virginiamycin, that may  
14 have changed things.

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

23 DR. GOLDBERGER: If I could just also comment on  
24 that. I think that, as far as thinking about the  
25 categorization of human drugs, as a practical matter,

1 hopefully some of this can be dealt with on a class basis;  
2 that is to say, that, once the agency, for instance, has  
3 considered a fluoroquinolone, a penicillin, a macrolide, as  
4 examples, one would normally expect, taking into account  
5 issues of cross resistance, et cetera, that subsequent  
6 products that came in in those same classes would normally  
7 get the same ranking.

8 I think that the consistency is an important  
9 issue. There may be circumstances where, for instance, a  
10 company may claim, on the basis of data they have collected  
11 or had experts look at, that cross-resistance may be less of  
12 an issue or there may be certain other properties of the  
13 drug which would warrant some sort of different  
14 classification.

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

21 I think it is legitimate that, obviously, that  
22 receive more attention. I think everybody would agree with  
23 that. The exact process of how we would do that, I think,  
24 remains to be worked out. As you noticed in the  
25 classification system, I think both during my presentation

1 and in a little more detail in the actual document, drugs  
2 with a unique mechanism of action at the moment have a  
3 default into category I.

4 But , obviously, that is an area where at least  
5 there ought to be some discussion. I think those two types  
6 of issues, a genuinely new class which only will occur for  
7 the first product, normally, of that class and a drug from  
8 an existing class that, for whatever reason, for instance,  
9 industry might believe has unusual properties, might be the  
10 exceptions to what we hope would be a relatively consistent  
11 way to classify drugs.

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

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

23 DR. SUNDLOF: That is a good question, Oscar. It  
24 would be my hope that we could do something like that, that  
25 there could be a national program that addressed the issue

1 f having a very robust system for monitoring resistance as  
2 t occurs out there and that that could be supported by  
3 hoever has the money.

4 If it is a government-funded program, I think it  
5 ould be certainly in the interest of the public health to  
6 o that because it is a public-health issue. With the Food  
7 afety Initiative, there is an effort in the U.S. to look at  
8 ood safety from farm to table I think that there are a  
9 umber of opportunities within the Food Safety Initiative to  
10 out together some comprehensive programs that could be used  
11 o monitor resistance and other foodborne issues that occur  
12 on the farm.

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

20 We are beginning to test for Campylobacter this  
21 month. So we are going to also send those organisms into  
22 the system. In envisioning some of the discussions about  
23 on-farm and monitoring of clinical isolates, I see this as a  
24 sort of nice doable place in the food chain to detect  
25 something prehuman, a problem, that could focus on farm

1 studies, if we can do it in real enough time, and I think,  
2 possibly, we could do that.

3 I also haven't spoken up to date, but I do want to  
4 express our support for this framework document and the hard  
5 work that CDC and FDA are doing to try to harmonize some of  
6 the different issues.

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

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

13 [Break.]

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

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

1           so, with that in mind, I think we have enough  
2 people assembled here. If there are questions from the  
3 floor, the floor is open for questions to invited speakers  
4 to this deliberation.

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

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

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

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

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

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

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

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

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

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

23           DR. STERNER: Did you wish to have anybody respond  
24 to your comment?

25           DR. LEIN: I think this was a statement, but if

1 they want to respond, that's fine.

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

10 Dr. Thornsberry?

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

18 But assuming that you did that and that somewhere  
19 down the line in your postmarked approval, you found out  
20 that an organism such as Salmonella was resistant to the  
21 newest fluoroquinolone, if, at that point in time, you  
22 decide to remove the drug, you have got to remember--let's  
23 say it is Salmonella DT104.

24 You are not just removing a fluoroquinolone. You  
25 are removing every fluoroquinolone. And you will have to

at

1 remove every aminoglycoside, likely at least streptomycin.  
 2 You will have to remove chloramphenicol. You will have to  
 3 remove sulfa. You will have to remove trimethaprim. And  
 4 you have to remove chloramphenicol. I think I got them all  
 5 in.

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

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

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

18 DR. STERNER: Thank you, Dr. Thornsberry.

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

24 Yet if you look forward, now, fifty years and you  
 25 look at the problems with penicillin in the animal world

1 versus the human world, we don't have a problem with  
2 penicillin resistance in the animal population. Our  
3 staphylococci are less than 70 percent penicillinase  
4 producers. MRSA is not a problem.

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

8 DR. STERNER: Thank you.

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

13 Interestingly, the point about penicillin, if you  
14 look at Pfizer and its current renown for Viagra, as we move  
15 into our sort of 150th year of existence, the involvement in  
16 penicillin and the discovery and development of penicillin,  
17 is probably one of the issues about which Pfizer is most  
18 proud.

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

25 To invest in a discovery and development program

1 means that you have got to have a first-in-class product  
2 coming out at the other end. As soon as you have a first-  
3 in-class product, the chances are two things are going to  
4 happen.

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

9 To respond to the points made by Dr. Bell  
10 yesterday, I think there would be great benefit to the  
11 industry, to CVM and to CDC to try and get some of the  
12 scientists from all the stakeholders involved here together  
13 to look at that process and look at, as we predict to the  
14 future, how this is going to roll out so that the sort of  
15 please made by Dr. Apley, Dr. Wages and the other  
16 veterinarians yesterday that what we don't do is move this  
17 in the direction where we won't have new pharmaceuticals.

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

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

23 DR. BARKER: This is a question for Dr. Bell. In  
24 terms of foodborne pathogen disease in humans, what risks  
25 are posed by imports and how many foodborne pathogen

1     iseases have occurred and have been documented as having  
2     ccurred from those imports and in how many of those cases  
3     as it due to bacteria that were antibiotic-resistant?

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

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

11            We are in the process of trying to understand that  
12    more fully. We do not know precisely what proportion of  
13    foodborne illness in the United States is caused from  
14    imported food. We do recognize, though, a significant  
15    proportion of foodborne illness in the United States is due  
16    to domestically grown food.

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

24            One of the key questions that we are asking them  
25    is if they had traveled before they became ill because we

1 want to be very sure that we try to eliminate the effect of  
2 increasing resistance due to international travelers.

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

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

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

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

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

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

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

7 DR. TOLEFFSON: What I meant by that comment was  
8 to try to differentiate between a known hazard where an  
9 owner is giving a pet animal an antimicrobial versus the I  
10 will call it risk through food where the consumer of the  
11 food is expecting that food to be free of resistant  
12 pathogens.

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

18 DR. STERNER: Further questions?

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

23 DR. BARKER: I would like to return again to  
24 imports for just a moment because I don't think my question  
25 was answered and that, in itself, may provide the answer

1 that I was looking for. We are asking to consider a  
2 framework document that addresses CFR 52 170.6, reasonable  
3 certainly of no harm.

4 As part of the calculation of determination that  
5 there is harm, we are basing this on statistics from  
6 foodborne pathogen disease in humans. I would like for the  
7 CDC to tell us, if possible, and perhaps this is not  
8 possible, what percentage of these numbers that are part of  
9 the statistics are derived from non-meat production, that do  
10 involve, perhaps, other forms and perhaps do come from  
11 imports.

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

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

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

25 I do not have all the expertise, myself, in any of

1 the numerous areas that CDC is confronting this issue. Dr.  
2 Angulo is CDC's subject-matter expert on the issue of  
3 foodborne zoonotic pathogens and the resistance that is  
4 associated with them.

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

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

13           DR. ANGULO: Could you restate it?

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

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

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

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

1 DR. BARKER: I am sorry to interrupt, sir, but I  
2 am really just trying to get a very simple answer. Perhaps  
3 this has already been answered. I believe that some others  
4 have stated that there are not any deaths on record that  
5 have occurred from antibiotic-resistant bacteria in  
6 foodborne illness; is that correct?

7 DR. ANGULO: That is not correct.

8 DR. BARKER: Could you identify--

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

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

19 That is one instance. I could cite--

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

22 DR. ANGULO: It was an instance in which the  
23 clinical consequence of antibiotic resistance resulted in  
24 the death of the patient. It was a foodborne pathogen. In  
25 this instance, as far as our epidemiological evidence is

1 able to show, it was an instance where the infection was  
2 acquired in a foreign country. The initial case was in a  
3 foreign country.

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

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

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

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

23 Using the example of our School Lunch Program, the  
24 School Lunch Problem is required, by mandate, to purchase  
25 disproportionately from small meat plants. While we are

1 hoping that we get the same performance in pathogen  
2 reduction from them that we have from the large plants, we  
3 don't know yet the performance of that sector of meat and  
4 poultry processing industry.

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

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

20           So I would suggest that, as we look at the  
21 performance of HACCP, we also need always to keep our **eye** on  
22 FoodNet and PulseNet and listen to what it is telling us  
23 about who becomes ill, who truly is becoming ill and, to the  
24 extent that it can, why they are becoming ill.

25           Thanks .

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

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

13 Whether it is in category III or category II, it  
14 could possibly pass along by some as yet unknown mechanism  
15 or even known mechanism resistance to category I, that the  
16 categorization of antibiotics into three different  
17 categories and then subdivision into nine categories is a  
18 somewhat artificial categorization, that the reasonable  
19 certainty of no harm criteria should apply equally to all  
20 antibiotics given the possibility of transference of  
21 resistance.

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

24 DR. SUNDLOF: That would be counter to our premise  
25 that there is a risk associated with certain antibiotics for

1 which the risk is not as great as for others. It is true  
2 that resistance will increase over time. The idea of  
3 setting resistance thresholds on a compound-by-compound  
4 basis was intended to be commensurate with the risk of the  
5 loss of that antimicrobial to human medicine.

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

10 The passage that you referred to, 570.6, also says  
11 that, "It is impossible in the preSent State Of Scientific  
12 knowledge to establish with complete certainty the absolute  
13 harmlessess of the use of any substance. Safety must be  
14 determined by scientific procedures or by general  
15 recognition of safety."

16 What that says is that the standard is not based  
17 on no possibility of anything bad ever happening. It is by  
18 reasonable scientists who can get together and agree upon  
19 what they think, in their best scientific opinion,  
20 represents a reasonable certainty of no harm.

21 DR. BARKER: Does that data current exist?

22 DR. SUNDLOF: I would say it does not. In fact,  
23 part of this process--if it is agreed to that the framework  
24 should move forward, then we would have to go to the next  
25 step which is defining, on a drug-by-drug basis, what is the

1 reasonable certainty of no harm of resistance for that  
2 particular drug.

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

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

14           DR. GOODMAN: Just one other minor clarification.  
15 The way the framework is written, in response to your  
16 question; a drug is called class III or class II if it is  
17 not known to induce resistance to a class I or a class II  
18 drug. So it wouldn't be in that category if it was felt  
19 that it was going to induce resistance to a higher-class  
20 drug.

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

1 no alternative in those other drugs.

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

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

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

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

24 Because the fluorinated quinolones are totally  
25 synthetic, chemical modifications can be made to those drugs

1 that bypass these resistant mechanisms. There are studies  
2 going on today where they are specifically looking at these  
3 mechanisms of resistance, making modifications to counter  
4 those mechanisms of resistance.

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

9 The third and last thing is directed to Dr.  
10 Miller. In the drug approval process, it seems like we have  
11 two diabolically opposed factors that we have to deal with.  
12 One is the residues issue. In order to minimize residues,  
13 we want to use the minimal amount of drug.

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

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

24 DR. MILLER: I have heard that a lot, that the  
25 problem is that food safety is prohibitive. But I just

1 don't think it is true because we have a very valuable tool  
2 which is called the withdrawal time. Provided an ADI is  
3 anything reasonable, the product, if we just wait, the  
4 animal metabolizes the drug and it is excreted into the  
5 environment .

6 so I don't see that there is this problem here.  
7 Whatever the tox study says is the ADI is the ADI. Whether  
8 you have to wait three days or fourteen days--and that is  
9 the time period we are talking about--really doesn't make  
10 much difference.

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

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

25 I am sure--I am not sure, but I would imagine that

1 the FDA would make that distinction.

2 MR. GEYER: The answer was "probably?"

3 DR. MILLER: We think we can.

4 DR. GOODMAN: The distinction is made in the  
5 framework in terms of generations of cephalosporins, for  
6 instance, and their importance to human medicines, I think,  
7 where they are distinct classes. Of course, it is nice to  
8 remind people also that when quinolones came along and were  
9 first marketed, there was going to be no resistance to  
10 quinolones because they were a new class of agents with a  
11 unique chromosomal mechanism of resistance that had a very  
12 low frequency. Of course, that turned out rapidly not to be  
13 true.

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

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

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

1 My question is why do we need to subdivide the  
2 three categories by three subcategories and what do we gain  
3 by doing that at this particular stage. If we look at the  
4 research needed to justify this, if you were in either  
5 category, then what will you get from the sophistication of  
6 dividing it into three subcategories?

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

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

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

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

22 DR. MILLER: I think we have that in the framework  
23 document although there have been so many refs, it is hard  
24 to remember what is in what. But we talked about it, and I  
25 mentioned it yesterday, that if you have a high-exposure

1 scenario, so you do your worst-case scenario, and that ends  
2 up to be not a problem, then anything that is a lesser-case  
3 scenario can be covered by establishing the safety of your  
4 worst-case scenario.

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

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

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

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

23 But I think that we would be consistent in our  
24 categorization and I would propose that a sponsor run  
25 through a points-to-consider document. I think we left in

1 there points that you would consider to categorize your  
2 drug, then come in and discuss it with the agency as to why  
3 you came up the way you did.

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

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

18 This is an effort, I think, to produce a  
19 differential set of requirements depending on the given  
20 product. Whether it is entirely successful or not, I think  
21 that is an open question and I think, obviously, without  
22 knowing what these implications are, it is hard for people  
23 to have a real feeling for it.

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

1 products coming in.

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

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

15 so, in a way, it affords sponsors an opportunity  
16 to use these drugs in ways that are safe without having to  
17 necessarily go through all the hoops that they would have to  
18 go through for higher risk uses. So it is, in essence, an  
19 attempt. FDA is really looking for input into what is, in  
20 essence, a qualitative risk assessment embodied in those  
21 categories .

22 DR. FLAMM: To amplify what already has been said.  
23 On the exposure estimate, the main difference in terms of  
24 proapproval studies would be in the pathogen load  
25 requirements. So low exposure wouldn't have the pathogen

1 load requirements proapproval studies as high and medium  
2 exposures would.

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

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

15 Rulemaking, obviously, is a notice and comment  
16 procedure that gets input and provides for input from all  
17 interested parties. Assuming we were to go this route,  
18 there would be a regulation that establishes the criteria by  
19 which a drug is judged as to high, medium or low. And then,  
20 perhaps, one might have guidance documents that would be  
21 referred to in the regulation that would actually list drugs  
22 or drug classes and where they are.

23 The reason we would contemplate doing that aspect  
24 in guidance as opposed to regulation is because of the issue  
25 that circumstances change and then a drug might move into a

1 higher or lower category. And it is much more difficult to  
2 change regulation than to change guidance.

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

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

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

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

23 DR. O'BRIEN: Okay. This implies some kind of  
24 ongoing measure of what that exposure is, and that is  
25 mentioned in the document. That appears not to have been

1 controversial . At least, we didn't hear much. It was  
2 scarcely mentioned in the discussions of the last day and a  
3 half .

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

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

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

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

1 correct?

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

8 In determining the benefit effects of the drug in  
9 the animal, there is a separate determination in which the  
10 drug has to be safe and effective for the animal for which  
11 it is intended. But this document that we are talking about  
12 here today is strictly concerned with the food safety  
13 issues .

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

22 DR. STERNER: Generally, given certain cultural  
23 considerations.

24 DR. LEIN: I have two. One is the mitigation. Of  
25 course, it is not clear how that is going to be set. As we

1 look at that, are we looking at increased resistance in at  
2 least the monitoring of the human side or do we look at it  
3 on the veterinary side. If it is increasing in the human  
4 but staying low on the veterinary side, what happens with  
5 that, versus maybe higher on the veterinary side and not  
6 quite yet at the human side.

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

9 DR. TOLEFFSON: I will try to answer that. You  
10 are really talking about resistance thresholds.

11 DR. LEIN: Right .

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

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

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

24 And then, maybe, possibly another level, again on  
25 the animal side. That struggle we have really been going

1 through--we could design all kinds of scenarios that would  
2 be most beneficial for the animal side of the equation. The  
3 ultimate threshold, if you are speaking of one that we would  
4 request withdrawal from the market or restricted  
5 distribution, that sort of thing, would probably need to be  
6 linked to the animal data.

7 Here, I am speaking as an epidemiologist because I  
8 believe that the human data are much more robust and we can  
9 control for that. Dr. Angulo mentioned the case-control  
10 studies that are already ongoing. I have more confidence  
11 that the human data are more valid. So there would be  
12 several thresholds.

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

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

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

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

1 DR. TOLEFFSON: Correct.

2 DR. LEIN: My other question is to Dr. Vogel.  
3 Being a veterinarian, I am very interested how he sees AVMA,  
4 if we go forward with this framework, being involved in at  
5 least helping FDA come to, hopefully, the conclusions that  
6 are going to make this successful for veterinary medicine  
7 and for human medicine.

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

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

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

1 this issue.

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

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

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

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

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

22 DR. MILLER: Yes. I think one of the things is  
23 should we be doing thresholds, which is the question for  
24 this group. But , certainly, if you look back in history  
25 about how people have established thresholds, and we had

1 this conversation, the first way we do it is what is out  
2 there now. We say, okay, that's the threshold and then we  
3 go ahead and do some further investigation to establish  
4 whether that is too high or too low and make adjustments  
5 there following that.

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

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

17 Then the assumption that we are going to make is  
18 that resistant organisms travel down this pipeline or through  
19 this slope at the same rate as susceptible organisms. Then  
20 we will model. We will say, let's say resistance is  
21 1 percent in the humans; how does this translate back into a  
22 resistance load at the slaughter plant.

23 Once we have that level, then we will go back and  
24 make some prediction about how much you could have on a farm  
25 to reach that threshold in the slaughter plant. That is

1 where we are at with the process right now.

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

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

14 That can all be done because that is just  
15 assumptions.

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

21 DR. MILLER: I don't think we have come to a final  
22 decision yet of how we would set the thresholds, whether we  
23 would go out and monitor for what is the existing level of  
24 resistance now and we would work from that, whether we would  
25 work off of our pipeline model. I think those are open for

1 discussion.

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

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

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

16           DR. ANGULO: The short answer is no. The  
17 explanation is that we participate in the National  
18 Antimicrobial Resistance Monitoring System and the USDA has  
19 data on antimicrobial resistance in slaughterhouses. We do  
20 not collect samples from healthy people in terms of the  
21 current NARMS. We do not collect samples from people  
22 working in processing plants .

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

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

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

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

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

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

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

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

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

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

23 DR. HOLLAND: I have no further questions.

24 DR. HASCHEK-HOCK: I have two questions. One  
25 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 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

1 Distinguish between therapeutic and subtherapeutic uses  
2 although, because of the exposure assessment,  
3 subtherapeutics pay a penalty. Their use would not be  
4 limited to that segment of the population that is ill from a  
5 specific bacterial disease. All animals in the population  
6 potentially would benefit.

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

12           We do not make value judgments on specific uses.  
13 The criteria that we have is that the drug be safe for the  
14 animal and the environment, the user and the public, that it  
15 be effective, that it does what it claims to do and that it  
16 meets certain quality standards.

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

23           Yet, that is not the type of decision that I think.  
24 you want a bunch of regulatory scientists making, making  
25 those kinds of value judgments about what should be approved

1 and what should not be approved. If there are issues that  
2 deal with values, those are better dealt with outside of the  
3 FDA scientific regulatory process .

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

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

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

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

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

8           DR. STERNER: Any further questions?

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

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

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

1 With the framework document, the establishment of  
2 proapproval thresholds will allow us to make a determination  
3 up front whether or not these products have exceeded what  
4 has been agreed upon prior to the approval as the point at  
5 which it no longer meets the criteria of reasonable  
6 certainty of no harm which should greatly expedite the  
7 removal of the drug from the market with much less debate  
8 than we usually consider.

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

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

16 DR. SUNDLOF: Yes .

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

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

1 I think both sides agree that the cup is half  
2 empty of adequate science, details, specificity. Industry  
3 may also see it half full of unknowns and regulatory  
4 horrors, but I think the FDA sees it half full of promise,  
5 of also addressing, perhaps not finally but at least to some  
6 degree, this issue of antimicrobial resistance and their  
7 requirement to provide safe, effective and reasonable  
8 products to the market.

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

13 Thank you.

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

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

25 I think that Dr. Salyers' comments and

1 presentation yesterday, and other data, would give pause to  
2 that. I would be happy for the FDA to respond. But my  
3 concern, and I think the concern of those of us who are  
4 taking care of patients, particularly in nosocomial  
5 settings, is not so much with foodborne pathogens, although  
6 I would hate to see multi-drug-resistant Salmonella  
7 epidemics, obviously.

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

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

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

21 If you take an organism and repeatedly expose it  
22 to a low contamination of antibiotic, you induce resistance.  
23 I would see that that may well be happening in animals and,  
24 therefore, since antimicrobial resistance is the subject of  
25 this meeting and what we are all trying to deal with and

1 reduce, I would suggest that subtherapeutic use may be an  
2 important issue.

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

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

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

18           DR. ANGULO: Thank you. I have three short  
19 questions which follow up very nicely, I believe, with Dr.  
20 Norden's points. The first question is I have serious  
21 concerns about what is written on page 14 about the  
22 possibility of recategorization. CDER has explained an  
23 elaborate procedure for establishing the categories. But  
24 then there appears to be an option to recategorize a  
25 category I drug to a category III drug based upon a

1 subjective opinion.

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

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

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

19 DR. ANGULO: I think we have very clear parameters  
20 on how to categorize based from CDER. But this paragraph  
21 implies that there is some other unknown parameter that  
22 could be worrisome.

23 DR. FLAMM: Just to clarify there. That was one  
24 of our considerations of how we might categorize drugs.  
25 Based on comments, we will review whether that concept

1 should remain. Again, it was intended to be used in  
2 specific circumstances where we thought a specific drug/bug  
3 combination was such that it might not cause a drug that  
4 otherwise would be category I to be category I.

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

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

12 DR. TOLEFFSON: Yes; it would remain confidential.

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

15 DR. TOLEFFSON: That's correct.

16 DR. ANGULO: I would disagree with that process.  
17 The last point is the categorization--I actually have  
18 greatest concerns on how we categorize category III drugs  
19 because I just foresee a controversy in the future and that  
20 is if category II drugs are categorized such that they are  
21 those little used in humans or not used in humans, we will  
22 forever debate what little used means, or also other  
23 questions about little importance.

24 I would strongly encourage, and I would like to  
25 ask if you have considered this, strongly encourage that

1 either we have a fourth category that is drugs not used in  
2 humans which we could all agree to put ionophores in and we  
3 could set ionophores aside and eliminate them from the  
4 debate, or to take category II and have two parts to  
5 category III, those of little use and those of no use.

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

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

14 A subcategorization of category III is a way that  
15 we could handle this and we will take that comment into  
16 consideration like all other comments. But our idea that  
17 this could in no way be a static document I think is worth  
18 considering.

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

25 I think that we could try to adopt what they are

1 doing in that categorization. So I would strongly encourage  
2 having such a categorization because ionophores just  
3 shouldn't be included in the same debate as Bacitracin or  
4 some of the other drugs which are used in humans.

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

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

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

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

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

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

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

25 MR. GEYER: The drug was approved for use in small

1 animals and it was being misused extralabely in calves.  
2 There was the aplastic anemia problem that Keith mentioned.  
3 But we did have to offer the sponsor an opportunity for a  
4 hearing. They did not elect to pursue that opportunity so  
5 we were able to remove the product from the market fairly  
6 expeditiously perhaps in a year or so from the time we first  
7 started the process.

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

10 DR. ANGULO: I know things have changed  
11 dramatically in terms of food safety in the last several  
12 decades, but there was a chloramphenicol-resistant  
13 Salmonella outbreak following the ban or use of  
14 chloramphenicol and it was traced to dairy farms in  
15 California that were using chloramphenicol.

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

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

25 DR. STERNER: I will editorialize for just a

at

1 moment and say that that very well exemplifies one of the  
2 potential negative consequences of regulations that limit  
3 the approval of new products.

4 With that, we stand adjourned until 1:00.

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

## 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.]

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

1 Veterinary Medicine Advisory Committee.

2 DR. COOPER : Thank you . [Applause.]

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

6 DR. LEIN: Thank you.

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

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

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

18 DR. STERNER: How about a standing ovation.

19 DR. SUNDLOF: I think that is even better.

20 [Standing ovation.]

21 MR. GEYER: I am surprised. Thank you very much,  
22 Steve, and thanks to all of you. It has been a great time  
23 and I have really enjoyed it. My best to all of you in the  
24 future. Three more hours and I am really retired.

25 DR. SUNDLOF: Dick was my mentor when I was on the

1 Veterinary Advisory Committee. So it is sad to see you go,  
2 Dick. We really do appreciate all the efforts you have gone  
3 to.

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

6 Committee Deliberations

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

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

18 I think that when we look at the interpretation of  
19 scientific data it is very clear that people from different  
20 perspectives in industry and regulatory and practice see  
21 these issues vastly differently. I didn't mean to ignore  
22 consumer-interest groups as well. We all bring different  
23 baggage to the table here. To quote Dr. Bell a bit from  
24 yesterday, it is time to move on.

25 With that as a preamble, Dr. Sundlof stated when

1 he first came to chair the Center for Veterinary Medicine as  
2 Director that it was CVM's goal to have more new animal drug  
3 approvals rather than less so that veterinarians and the  
4 issue industry had safe and effective products to use and  
5 that the public health was provided for and protected by  
6 products that had gone through the approval process.

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

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

16 I see a head shaking, but that is a done deal.  
17 That is correct, Steve? So the issue rather deals with the  
18 framework document, I think, as an initial starting point  
19 and to give advice on where the agency or whether the agency  
20 should proceed.

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

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

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

12           The anticipated economic costs of the current  
13 framework-document proposal and uncertainties associated  
14 with the future approvability of an NADA cast serious doubt  
15 on future veterinary antimicrobial compounds ever being  
16 submitted for an NADA with a food-animal indication.

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

22           Underlying the whole issue of antibiotic  
23 resistance is the issue of subtherapeutic and growth-  
24 promotion issues which, while viewed as intrinsically bad by  
25 many, serve to obscure the more critical issue of most

1 stakeholders with regard to therapeutic uses. We must  
2 weight carefully our deliberations so that our  
3 recommendations, no matter how well intended, do not result  
4 in unintended diminishing of the public health status of our  
5 human and food-animal populations.

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

13 We have a document before us and all that remains  
14 are the details and the devil is in the details. With that,  
15 Dr. Sundlof, I turn the floor to you to ask the committee  
16 the questions.

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

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

1 animals. "

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

8           DR. STERNER: The floor is open for comments from  
9 the Veterinary Medicine Advisory Committee. I would like to  
10 canvas the members. How many of you have a comment to make  
11 with regard to Question No. 1? Just a show of hands. In  
12 that case, I am not going to canvas every member and I will  
13 just start to my left since I happen to be looking in that  
14 direction.

15           Richard, I think that you were first.

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

22           But, in a way, that is a good step because that  
23 means it is a transparent process and that we have been  
24 brought in at an early point in that process to provide  
25 input and direction. So we also applaud that step not only

1 of establishing the framework but allowing us all to be a  
2 part of the early formulation of that framework document as  
3 well .

4 We would hope that that kind of transparent  
5 process would continue through the ensuing steps that follow  
6 today's meeting. The scientific focus of placing the  
7 framework around human health implications from a lay  
8 perspective looks to us as sound. But from a consumer  
9 perspective, I think I need to say that we, as consumers,  
10 read the newspapers and then we sit down and we feed our  
11 children or, in my case, my grandchildren from time to time-  
12 -as of Saturday, one more.

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

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

25 Regarding risk assessment from the experiences

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

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

14 Thank you.

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

23 so, in putting this together, I think working with  
24 the industries, working with, again, other government  
25 agencies, universities, down through where the expertise is,

1 along with your expertise, should be utilized in putting  
2 this together.

3 DR. LANGSTON: I would just like to say this has  
4 been a complex problem. As was said earlier, I don't think  
5 anyone on one side is either trying to penalize the animal  
6 health industry or agriculture nor, on the flip side, would  
7 any veterinarian honestly put the public at risk in their  
8 own mind.

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

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

23 So I am torn between wanting to protect those  
24 drugs vital to human public health while not willing to  
25 endorse a system that relies somewhat on thresholds that

1 tend to be, at best, guesses.

2           To me, I think the scientific basis of it is what  
3 causes me some concern. I would probably, since I have to  
4 make a decision for some form of very strict definition of  
5 category I such that diseases that are life-threatening or  
6 have serious residual injury associated with them and there  
7 are no other legitimate choices in their treatment would be  
8 so designated and those would be relatively few.

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

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

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

1 I guess I view the document as kind of a straw man  
2 to put out there for discussion. What was brought out this  
3 morning was that it was actually a composition of many  
4 organizations within the government getting together and  
5 deciding what to put in this. I think that is really good.

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

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

20 There were probably things that could have been  
21 discussed in the last two days that weren't such as where  
22 the European community is with this and how we compare. My  
23 concern right now is that we will not have any new drug  
24 applications for food-animal use and that if we go back and  
25 review the ones that are currently being used, we may not

1 have any of those.

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

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

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

23 I think that, certainly, this committee--it has  
24 been a difficult task for this committee. We come from all  
25 different backgrounds and, certainly, I think experts, which

1 you have already approached for information but, as you move  
2 forward, you need to make use of the expert information  
3 available in the specific areas that need to be addressed  
4 for this to be a sound scientific basis.

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

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

16 The other response to that question I would make  
17 is it obviously depends on where you sit and where your view  
18 is as to whether or not it provides a sound scientific basis  
19 or not. The trick is to try to bring together enough of a  
20 consensus to be able to move forward in this whole arena and  
21 address the critical issue and that is what can be done to  
22 minimize the risk to a level that allows the agency to meet  
23 its statutory requirements.

24 I would have to say, Steve, I didn't fully  
25 appreciate that until you made the comments this morning

1 about what the statutory requirements are which put a little  
2 bit of a different context that I think we have to wrestle  
3 with.

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

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

17 I'm sure that those who wrote it realize this,  
18 that there are other peer-reviewed references that can be  
19 cited that go counter to some of those approaches. So I  
20 don't know that that necessarily helps make any progress but  
21 there needs to be at least an acknowledgment that there is  
22 that difference of opinion supported by whatever one would  
23 choose to be able to find in the literature to support that  
24 point of view.

25 But the sensitivity to the availability of

1 appropriate antimicrobial for veterinarians to use in  
2 protecting the health of food animals is critically  
3 important because that does have, in a broad sense, an  
4 impact on public health as well.

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

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

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

23 Don Lein's need for good science which I back up,  
24 that is not a good omen when you have ten states going in  
25 ten different directions. This is not an issue that is on

1 the horizon, on the radar screen of public-health officials  
2 right now and the public, but I think it could become one  
3 very easily.

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

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

13 DR. BARKER: Does the framework document provide a  
14 sound scientific basis? It depends on what kind of  
15 framework is being perceived as being created, in part. Is  
16 this a framework for a Gothic cathedral or a framework to  
17 build a parking lot?

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

24 The frame may be missing lintels and lallies. It  
25 may be missing a major support wall. It is missing some

1 scientific support. It is missing industry support. It is  
2 missing some decisions that need to be made. But, clearly,  
3 the frame in which this is going to be placed is a solid  
4 foundation.

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

12 An awful lot of the details are left to be filled  
13 in and, to a large extent, I think that has created the  
14 controversy. No one is clear exactly what we are building  
15 here. Hopefully, in the process of our discussions and  
16 deliberations in which we take up each of the individual  
17 questions, we will be able to do that.

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

22 DR. ANGULO: I am very encouraged. But as I think  
23 back on the discussion yesterday, and trying to think of  
24 what the main comments people said against the framework,  
25 there were some what I kind of view as peripheral statements

1 such as that there would be no new drug approvals or that  
2 there would be antimicrobial available for food-animal  
3 practice, even, although not stated but perhaps even  
4 implied, that there would be no FDA/CVM if that would be the  
5 case.

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

9 One of the things, though, that I did understand  
10 and a critique well taken was the statement that some  
11 thought that the background information provided in the  
12 framework document did not adequately defend the need for  
13 the framework document. There have been many statements  
14 made about the lack of data or the uncertainty of the data.

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

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

24 So, in closing, I think that I am very excited and  
25 encouraged by this document. I do believe it is the way

1 forward. I think it is a visionary document by the FDA and,  
2 as a member of the U.S. Public Health Service, I am very  
3 proud to be a sister agency of the FDA for them to have put  
4 forward such a thoughtful and visionary document.

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

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

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

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

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

1 wording?

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

5 DR. LEIN: What would you like to add?

6 DR. GALBRAITH: I think the consultation is  
7 absolutely essential but I think that there needs to be some  
8 affirmation that this is a reasonable framework to build on  
9 and move ahead with adequate consultation as you have  
10 pointed out.

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

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

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

25 Do you think that is fair? Do you think that is

1 :he way business should be done? What if this does take a  
2 great deal of time and veterinary medicine is withheld from  
3 possibly getting an new antimicrobial that we all feel is  
4 important?

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

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

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

23 I think it is relevant to the question how this  
24 should affect current applications when it has not been  
25 clearly demonstrated that there is, indeed, a problem. I

1 would endorse this statement as presented.

2 DR. STERNER: If I may, let me editorialize here  
3 or suggest that what you are talking about is grandfathering  
4 and that for those applications, there may be plenty or  
5 there may be none in the pipeline, that they be  
6 grandfathered under the previous rules and that new  
7 applications, before you would consider them, would have to  
8 undergo the scrutiny of the new framework document as it  
9 comes to bear on new animal drug-applications.

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

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

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

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

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

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

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

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

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

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

22 What I mean by that is that if there are specific  
23 questions that we have regarding the safety that have not  
24 been satisfactorily addressed, we always reserve the right  
25 to ask the companies for additional information or

1 additional studies.

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

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

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

22 DR. BARKER: My consideration of that logic may be  
23 faulty, but if we extend it a little bit, we are saying that  
24 new drugs in the pipeline are more of a threat than existing  
25 drugs that are already approved. Is there something wrong

1 with that logic somewhere? If we are considering applying a  
2 very flexible, ethereal rather moving target for drug  
3 approval for new antibiotics when we already have a fairly  
4 large number of antibiotics that are in the market and are  
5 already assumed to be in category I or category II and a  
6 possible threat, then how is it that this will only be very  
7 specifically applied to drugs that are in the pipeline.

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

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

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

21           Further comments?

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

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

6 Dr. Lein, have you done any wordsmithing?

7 DR. LEIN: Could you repeat what you said?

8 DR. STERNER: Dr. Angulo?

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

15 The question is do you support the framework in  
16 concept. Your point, I think, is a question of  
17 implementation, not of--it doesn't make sense to me why you  
18 would pick this one thing. If you are going to pick on this  
19 one point of implementation, why don't you talk about some  
20 of the other very worrisome parts of implementation. We  
21 could cite many examples of people worried about how this  
22 would be implemented.

23 Why do you pick this one point?

24 DR. LEIN: I think those will come up. I think  
25 what we were worried about is there is no time frame that we

1 have seen for this to be accomplished. If it does take a  
2 year or two years, I think I, as a veterinarian, and  
3 thinking about at least animal health, we would like to see  
4 at least any applications that are in there for new drugs  
5 proceed, not be stalled waiting for a new system and proceed  
6 under the old system.

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

14 So I am sure that will take place. It is just  
15 that you don't want to see something sit and sit. I am  
16 thinking of industry now. I am thinking that, really, we  
17 want to promote industry to work with us but we also don't  
18 want to hinder our situation of discouraging them from their  
19 applications that they put into the pipeline because I think  
20 they have invested money into this.

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

24 DR. ANGULO: So a compromise for consideration  
25 because your point, your clause that you want to add, is out

1 of deference to the industry. I think we could balance that  
2 clause out of deference to public health by having another  
3 clause that is something along the line that of a strong  
4 desire to have finalized the framework document as rapidly  
5 as--some urgency of timeliness.

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

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

12 DR. STERNER: Dr. Flamm? I am going to stop this  
13 because we have four more questions to go through and we are  
14 at a point where we have bogged down. You had a comment to  
15 make and then I am going to ask for the committee to vote on  
16 the statement as Dr. Lein has it and you are free to  
17 disagree, and we will note that.

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

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

1 divide this into two sections.

2 Dr. Flamm, you had a comment to make ?

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

9 Whether we have this framework or not, we are  
10 going to be reviewing new applications. And the standard  
11 that the drugs will have to meet is a reasonable certainty  
12 of no harm. This framework is a way for us to--we are  
13 contemplating that this would be a way for us to establish  
14 that reasonable certainty of no harm.

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

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

24 [Chorus of ayes.]

25 DR. LEIN: I did put in something with haste.

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

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

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

19 So I will finish that off.

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

23 DR. ANGULO: While we are wordsmithing that,  
24 because we are answering a question that wasn't asked, could  
25 just ask CVM's impression of answering questions that they

1 didn't ask us to answer?

2 DR. STERNER: Sure. Dr. Sundlof?

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

7 DR. STERNER: There is an intrinsic sense of  
8 fairness about the rules as they apply, and the suggestion  
9 about a date or a time in which people could focus on seems  
10 the right thing to do in terms of not changing the rules  
11 capriciously or arbitrarily.

12 Dr. Lein?

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

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

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

1 maintains some accountability.

2           The first statement he made is that this was in  
3 response to a legal dilemma that they had with a animal-drug  
4 industry in approving new antimicrobial. The second, he  
5 said that it proposed a regulatory framework that is  
6 consistent in the drug-approval process. And he said, and I  
7 might just say parenthetically, without disrupting the  
8 current process.

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

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

22           Then if we have any approval action from this  
23 point, then it has a referent from which we set the stage.  
24 It is not to disrupt the current process. But the comment  
25 that Dr. Flamm made is that we are assuring that whatever

1 happens in this regulatory process is that there is a  
2 reasonable certainty of no harm.

3 I think that forms the basis of everything that we  
4 do. Having that preface statement, I think, will be  
5 somewhat useful in explaining the actions that we take here  
6 today.

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

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

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

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

1 committee to divide it into two.

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

4 Those in favor of seeing it divided?

5 [Show of hands.]

6 DR. STERNER: And those opposed?

7 [Show of hands.]

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

10 I am rushing you, Dr. Cooper.

11 DR. HASCHEK-HOCK: Could I make an alternative  
12 suggestion?

13 DR. STERNER: Yes .

14 DR. HASCHEK-HOCK: Perhaps what we should ask is  
15 that the CVM make a specific determination of how it handles  
16 current and new applications so that everybody knows how it  
17 going to be handled but that this committee not make the  
18 specific recommendation?

19 DR. COOPER: I would agree. I am not making a  
20 specific recommendation for setting a referent. I would  
21 agree with your statement.

22 DR. STERNER: All those in favor of that raise  
23 their hand.

24 DR. HASCHEK-HOCK: Does that mean it is place of?  
25 am not sure whether I am phrasing this quite right but

1 what I would like to do is that the committee recommend that  
2 the CVM state how it will handle current and future  
3 applications until this process is completed.

4 MR. WOOD: And that is a substitute to the second  
5 section?

6 DR. HASCHEK-HOCK: Correct.

7 DR. STERNER: All those in favor raise your hand.

8 [Show of hands.]

9 DR. STERNER: You will go ahead, then, Dr. Cooper  
10 and give that to Don who will, in turn, give it to Richard

11 Any further comments on Question 1?

12 MR. GEYER: Just to make sure on where we are on  
13 this, is the committee adopting the first part of what Dr.  
14 Lein wrote?

15 DR. STERNER: The answer is yes.

16 MR. GEYER: And then they are substituting for the  
17 second part what Dr. Haschek-Hock stated.

18 DR. STERNER: That's correct.

19 MR. GEYER: Then I am not clear as to where Dr.  
20 Cooper's statement will fit into that. Is that a preface?

21 DR. COOPER: I was proposing it as a preface.

22 MR. GEYER: And there is consensus on that?

23 DR. STERNER: yes. Dr. Sundlof, we are ready for  
24 question No. 2.

25 DR. LEIN: Before we go forward, are we going to

1 hear their statement to the question, of how they are going  
2 to handle the applications in the pipeline?

3 DR. STERNER: Dr. Sundlof says, "Trust me."

4 DR. SUNDLOF: I thought that the idea was that a  
5 recommendation came from the committee that the Center  
6 should make public that information; is that correct?

7 DR. LEIN: Right .

8 DR. STERNER: The committee is recommending to the  
9 Center that they make that information public. That is just  
10 a recommendation.

11 Dr. Sundlof?

12 DR. SUNDLOF: Question 1. "Categorization of  
13 Antimicrobial Drugs;" and that says "for Human Medicine. " I  
14 think what that probably would be better stated as, and  
15 please correct me, CVM people, if I am wrong, that it should  
16 be "Categorization of Antimicrobial Drugs Based on their  
17 Importance to Human Medicine. " Okay. So if you could make  
18 note of that because it isn't clear. It' sounds like we are  
19 trying to regulate the approval of human medicines.

20 "The agency is proposing that the categorization  
21 of antimicrobial drugs based on the importance to human  
22 medicine take into account the usefulness of drugs in both  
23 foodborne disease and non-foodborne infectious disease when  
24 evidence exists that the use of the drug may result in the  
25 induction of resistant pathogens or the transfer of

1 resistance elements to human pathogens.

2 "This approach recognizes not only the well-known  
3 risk of resistance transfer through classical foodborne  
4 pathogens but also the threat of transfer of resistant  
5 bacteria or resistance genes from other intestinal bacteria  
6 of food-producing animals resulting in resistant infections  
7 of humans with other types of pathogens; for instance,  
8 resistant E. coli or Enterococcus.

9 "Does the committee agree with this approach?"

10 DR. STERNER: How many members of the committee  
11 wish to make comments to Question No. 2? Quite a few.

12 I will start with Dr. Angulo this time.

13 DR. ANGULO: The short answer is yes. Concerns  
14 are, again, on page 14, the way of once categories are being  
15 established, then recategorizing. And the example they give  
16 is the respiratory patient in humans. It doesn't match with  
17 this paragraph as stated. So I agree with this paragraph  
18 but not what was written on page 14, the recategorization.

19 The last part is I think the category III drugs--  
20 or we should have a fourth category--but there should be a  
21 category of drugs which are not used in human medicine  
22 because we can all, I think, agree on more lenient policies  
23 on those that are not used in human medicine rather than  
24 being clouded by those that are "little used in human  
25 medicine. "

1 DR. GALBRAITH: The short answer is yes. I agree  
2 with the characterization.

3 DR. BARKER: I believe the characterization is  
4 overly complex. It would seem to be a little bit simpler  
5 matter based on the statements that are made here to take a  
6 slightly different approach. Clearly, different drugs fall  
7 into categories that are of similar structure and mode of  
8 action as those used in human medicine could be considered  
9 to be most of interest.

10 Others, certainly, that have no use in human  
11 medicine may be of less interest. It is reasonable to have  
12 categories I, II and III. However, the statement, itself,  
13 says that when evidence exists that use of a drug may  
14 result. Until that evidence is actually present in the form  
15 of the monitoring program where resistance is starting to be  
16 noticed, should it then be determined whether it is of high  
17 risk, low risk, moderate risk and maybe move something from  
18 one category to the other.

19 I would like for the CVM and the people who put  
20 this together to try to find some method of combining both  
21 the simplification of the categories based on speculation  
22 and expectation but then underscore that with actual  
23 evidence collected from field studies, either from the NARMS  
24 program or as part of the original approval application  
25 where a company will examine, for labeling purposes, the

1 effect of their antibiotic on a range of different pathogens  
2 into any further consideration about its category or any  
3 real risk.

4 DR. HOLLAND: This is the one item that I had some  
5 anxious moments over. I just didn't feel that data were  
6 presented to support some of the categories. I would like  
7 to see more information or more data presented to support  
8 the categories that have been proposed.

9 I also have some questions relative to  
10 considerations given to categorizing drugs for use in  
11 animals. We have major animals and then we have minor  
12 animals. Where would all the minor animals fit into this  
13 equation?

14 DR. STERNER: Could somebody from the agency  
15 address the issue of minor animals since it has not  
16 previously come up in discussion? Dr. Sundlof?

17 DR. SUNDLOF: I have three people beside me that  
18 want to answer it. That minor use would fit into the  
19 exposure category such that minor species--they are  
20 considered minor because they are not eaten very often or  
21 they comprise a small, very relatively small, proportion of  
22 the diet compared to beef, pork, chicken and turkey.

23 So, from the exposure assessment side, they would  
24 benefit, minor species would benefit from this approach as  
25 opposed to other species. The benefits would be greater for

1 minor species just because the exposure would be less.

2 DR. STERNER: Does that answer your question, Dr.  
3 Holland?

4 DR. HOLLAND: Yes .

5 DR. STERNER: Further comments? Dr. Lein?

6 DR. LEIN: I was just trying to formulate what I  
7 have been hearing here. I think I agree with Dr. Holland  
8 and wanted to bring that up. How do we consider this. I  
9 think if we looked at fluoroquinolones and their use today  
10 and knowing what we know in the human and what is needed  
11 because of the class of organisms that are resistant and  
12 could cause death, you can see where it fits into category I  
13 before we know much about what it is going to do in animals.

14 But if you look at the rest of this, and I don't  
15 know how this categorization would work, then, are you  
16 looking at the concern of a drug as it starts to increase in  
17 resistance and whatever is going to be the warning point--I  
18 don't know if we know that at this point--and this is  
19 beginning to be seen in at least the human part as well,  
20 does that move it into the category, then, of I, basically,  
21 even though it might have been a II, something of that  
22 nature ?

23 Does that change the category? I think that is  
24 where Dr. Holland was coming from, too.

25 DR. STERNER: Any comments from agency personnel?

1 DR. TOLEFFSON: We are not sure what you are  
2 asking.

3 DR. LEIN: Let's say penicillin started to show a  
4 lot of resistance in the food-animal industry. I don't know  
5 where penicillin would be today is your categorization? II?  
6 Medium? High?

7 DR. TOLEFFSON: It would depend on the use. An  
8 injectable form of penicillin would probably be low.

9 DR. LEIN: But if that got high in the low, would  
10 it move to a different category?

11 DR. TOLEFFSON: No. The resistance, as it occurs,  
12 doesn't have anything to do--the categorization is based  
13 only on importance for human therapy.

14 DR. LEIN: Would this bother you, Fred, if it  
15 moved? Say we had 80 percent resistance--

16 DR. ANGULO: I think a point that is not clear to  
17 many people is the categorization is going to be heavily  
18 weighted towards category II drugs. There are going to be  
19 very few category I drugs and very few category III drugs  
20 which I think would alleviate a lot of people's concern.  
21 Most things are going to be wrapped up in category II and  
22 there are not that many that are going to be category I.

23 DR. LEIN: If we look at that--I have been driven  
24 back to Dr. Thornsberry's statement that we look at these  
25 multiple resistance situations and, in his mind, it puts all

1 of them into category I. At least that is what I heard when  
2 I listened to him.

3 DR. TOLEFFSON: But he is not correct. Jesse, do  
4 you want to say something?

5 DR. GOODMAN: I think the intent here was to make  
6 category I drugs, as stated, those that are essential for  
7 treatment of serious or life-threatening diseases in humans  
8 where, in general, there is not an equally safe and  
9 effective alternative therapy available. That is the main  
10 category of drugs trying to be captured here.

11 It is also recognized that if a drug is a unique  
12 member of a new class or there is very little resistance to  
13 that drug that it would probably be captured in this  
14 category.

15 The issue you are raising about increasing  
16 resistance, actually that would tend to make the drug lower  
17 in category because it would tend to make it become less  
18 useful in human medicine.

19 DR. LEIN: As long as there is an alternative.

20 DR. GOODMAN: As long as there is an alternative  
21 therapy.

22 DR. LEIN: I think Clyde wants to defend his--

23 DR. TOLEFFSON: But it would have been a  
24 category I drug anyway.

25 DR. GOODMAN: Right . If there is not an

1 alternative, it is not going to move up. Now it could  
2 become that, let's say, X drug, previously there were  
3 multiple alternatives to it but resistance develops to all  
4 those alternatives, a drug could move up in category.

5 DR. LEIN: Because that is all you have left.

6 DR. STERNER: The chair recognizes Dr.  
7 Thornsberry.

8 DR. THORNSBERRY: Thank you for letting me defend  
9 myself. If you look on page 9, if I read this right, it  
10 says any antimicrobial that can induce or select for cross-  
11 resistance for a category I drug would be considered a  
12 category I drug.

13 What I said was if you select fluoroquinolone as a  
14 category I drug because of resistance to DT104, then you  
15 also, based on that statement, have to make--Linda is  
16 shaking her head, but what does that sentence mean, Linda,  
17 if it doesn't mean that?

18 DR. TOLEFFSON: That is not what it means. What  
19 you are talking about is the multi-drug-resistant cassette.  
20 That would actually come into play for the threshold, for  
21 reaching the threshold, probably more quickly but it  
22 wouldn't when you first characterize that drug.

23 For example, if you are saying that automatically  
24 puts ampicillin into category I--correct?

25 DR. THORNSBERRY: Yes.

1 DR. TOLEFFSON: Because of DT104. That is not  
2 what we meant.

3 DR. THORNSBERRY : Yes; but that is what it says.

4 DR. MILLER : Let me tell you what I think we  
5 meant. We were thinking about something like if there is  
6 chloramphenicol resistance and, let's say, chloramphenicol  
7 was very important in human medicine and we had something  
8 that was a structural analogue of that and it didn't cross-  
9 react with chloramphenicol, then it wouldn't be a type I.

10 But if it did cross-react with chloramphenicol and  
11 selected for chloramphenicol resistance, then it would be a  
12 category I. That is what we meant by that.

13 DR. THORNSBERRY: That is what I just said, I  
14 think.

15 DR. O'BRIEN: I think maybe a distinction that  
16 will help you, the distinction between selection for a  
17 resistance gene by its product, by its gene product in self-  
18 selection, as opposed to coselection which is selection of  
19 that agent for other genes that happen to be linked to it.

20 Both are important but I think, for the purposes  
21 here, you are talking about selection only, not coselection.

22 DR. THORNSBERRY: But how do you separate the two  
23 because it doesn't make any difference. Fluoroquinolones,  
24 Tom, would be no more of a selective agent than would  
25 chloramphenicol or ampicillin.

1 DR. O'BRIEN: The circumstance, I would think--  
2 DT104 would be a good example. If you now have DT104 which  
3 is reasonably prevalent in the United States and other parts  
4 of the world with its four or five drug resistance, whatever  
5 it is, if you now had a subclone emerge, which is what you  
6 are describing, a subclone that is also quinolone-resistant,  
7 then it is true that all of the agents still select for the  
8 DT104 but only quinolones will favor that subclone over its  
9 cousins.

10 DR. THORNSBERRY: No, no, no. Not true. The  
11 subclone would be selection by fluoroquinolone and  
12 ampicillin and sulfa and streptomycin and every one of  
13 those.

14 DR. O'BRIEN: Again, it depends what you select  
15 them against. If you have got a neutral population; yes.  
16 If you are comparing it to other DT104s, then only quinolone  
17 will make that subclone--

18 DR. THORNSBERRY: There is no case in what you are  
19 saying, Tom, where fluoroquinolone would be the only  
20 selective agent. When you add fluoroquinolone, you are  
21 adding one more to the five that are already there.

22 DR. O'BRIEN: Again, selection is always in terms  
23 of what the competing population is. If you put one of  
24 those DT104 organisms that has the quinolone resistance in a  
25 chemostat with other DT104s that don't have it, only

1 quinolone would favor it.

2           If you put it in a chemostat with another  
3 *Salmonella typhimurium* that doesn't have any of these  
4 resistances, then any one of them would favor it. So I  
5 think that there is a difference depending on what the  
6 competing populations are.

7           DR. STERNER: We are proving, at this point, what  
8 Dr. Thornsberry predicted last night that this portion of  
9 the debate is the subject of microbiologists. Few of us  
10 here are microbiologists.

11           DR. THORNSBERRY: I expected the microbiologists  
12 to agree with me. That's all.

13           DR. STERNER: That points out the need, as we move  
14 down--in the future, as this document gets fleshed out, the  
15 need for those very arguments to go ahead and be self-  
16 satisfied. I think Dr. Thornsberry brings up a very valid  
17 point. The language says one thing, and he certainly  
18 interpreted it one way, and CVM says no, that is not what it  
19 means.

20           That is why Dr. Lein said, in our opening answer  
21 or caveat to question No. 1, that these groups do need to  
22 get together down the road and come to some reconciliation  
23 of these issues. It detracts from us as a committee  
24 answering these questions. Yet they are very, very  
25 important questions.

1           If the folks at the agency ignore this kind of  
2 debate, then a lot of what we spend our time on here is  
3 wasted. So take note of this. I trust that you will. It  
4 looks to me like the language needs some revision so that  
5 the microbiologists, at least, don't say that this document  
6 is B.S. End of discussion there.

7           I have further panel-member opportunities to  
8 comment on this question.

9           DR. COOPER: As I read the document, this was the  
10 one question I had this morning. I still think that,  
11 perhaps, this three-by-three concept is overly complex. But  
12 I accept the guidance that I was given this morning from the  
13 staff .

14           The encouragement that I make as you look at an  
15 implementation strategy, sometimes, I would encourage you to  
16 be on the side of the public, the people who have to use the  
17 regulation. Sometimes, you have to be simple in conveying  
18 the meaning of this complexity that you have here.

19           So, as you move ahead, I would encourage you to  
20 find ways to simplify this so that the public will have a  
21 better understanding of how this categorization is used for  
22 I, II and III and what you perceive as subcategorization.

23           I am convinced that, because you have already  
24 moved it down to a three-by-three from a larger factor, that  
25 you will consider that as you move forward. I would just

1 give that as guidance. It is one thing to have regulatory  
2 responsibilities . It is another thing to convince the  
3 public that you know what you are doing in a way that they  
4 understand what you are doing.

5 DR. STERNER: Thank you. I heard comments  
6 starting with Dr. Angulo and I would ask the committee to  
7 look at page 14 and the language in the middle of the third  
8 paragraph that says, "Given our current understanding of the  
9 mechanisms of resistance, FDA believes that generally it  
10 would not appear biologically plausible for resistance to be  
11 transferred from animal enteric pathogens to the human  
12 respiratory pathogen."

13 I believe your move was to strike that sentence?

14 DR. ANGULO: Yes .

15 DR. STERNER: How many would agree with what Dr.  
16 Angulo had to say? Show of hands in favor of agreeing that  
17 we strike that sentence from the document.

18 [Show of hands.]

19 DR. STERNER: It looks like the "ayes" have it.  
20 So that sentence is recommended to be stricken from the  
21 framework document.

22 DR. BARKER: To follow up on Dr. Cooper's  
23 statement, I think it would also be quite beneficial, and it  
24 would appear that at least some of this information is  
25 already in the minds of the framers of this framework

1 document, to provide examples of existing drugs that are  
2 already approved as to which would be in category I, which  
3 would be in category II, which would be in category III,  
4 which ones are already considered to be high-risk, low-risk,  
5 medium-risk.

6 It would have been very helpful for our  
7 deliberations had that been provided earlier on. But I  
8 think, at this point, certainly for the guidance of private  
9 industry to understand where their new drugs may be going,  
10 certainly where the approved drugs may already stand in the  
11 mind of the FDA, would be quite useful.

12 DR. STERNER: Dr. Angulo indicated that he also  
13 would prefer a fourth category, a "no human use" veterinary  
14 category.

15 DR. ANGULO: Either a subcategory III or a fourth  
16 category.

17 DR. STERNER: I will, just for purposes of  
18 complexity, suggest that a fourth category of no human use  
19 be proposed in this framework document. Those in favor of a  
20 fourth category signify by saying aye.

21 [Chorus of ayes.]

22 DR. STERNER: Those opposed, the same.

23 [No response.]

24 DR. STERNER: Then we would recommend a fourth  
25 category or whatever you wish to incorporate into the

1 document. Don, you are recording this?

2 DR. LEIN: Yes.

3 DR. STERNER: We heard several comments from many  
4 members regarding simplification of categorization. I am  
5 not sure that I heard any clear-cut examples as to a  
6 proposal, but our charge to you would be that, if possible,  
7 in working out the details in future seminars, you, to the  
8 extent that it is possible, attempt to simplify.

9 I emphasize the word "attempt" because that may  
10 simply not be possible.

11 DR. BARKER: As part of the simplification, I  
12 think what makes this complicated is that right now people  
13 don't understand what the criteria really will be to put  
14 them in the categories that do exist. One of the reasons  
15 that it seems extremely complex is because we don't know  
16 what we are dealing with just yet.

17 The guidelines, the criteria, for putting  
18 different drugs in these different categories, are not  
19 there. I would suggest that once that is clear, once those  
20 criteria are well defined and spelled out, that it is not  
21 really that complex.

22 DR. STERNER: Point well made.

23 Further comments? Is it the consensus of this  
24 committee that question No. 2, as it reads--does the  
25 committee agree with this approach with the provisions that

1 we had with regard to striking the sentence on page 14 and  
2 recommendation of a fourth category, no human use, and  
3 simplification, where possible, be our recommendations to  
4 you .

5 All those in favor of question No. 2, or in  
6 agreement with, signify by saying aye.

7 [Chorus of ayes.]

8 DR. STERNER: Those opposed, the same.

9 [No response.]

10 DR. STERNER: Dr. Sundlof, the floor is open for  
11 question No. 3.

12 DR. LEIN: Do you want a statement on this?

13 DR. STERNER: At the end of No. 3, I will assume  
14 you will be able to read No. 2.

15 DR. LEIN: I made it very short.

16 DR. STERNER: I will go back, then; Dr. Lein, if  
17 you just read it.

18 DR. LEIN: "categorization of antimicrobial drugs  
19 for food animals, considering the importance of this  
20 antimicrobial drug for human medicine, is accepted by the  
21 committee as a workable category for the importance of  
22 antimicrobial resistance. A fourth category of only food-  
23 animal drugs be considered by FDA," or I could make it "not  
24 human drugs."

25 DR. ANGULO: Just in the first sentence, I would

1 request that you also say--because it says importance of  
2 that drug. But actually there are concerns about cross-  
3 resistance of drugs of the same class. The framework  
4 document captured that kind of language, but if we want to  
5 be specific, I think we would include that language in your  
6 statement.

7 DR. LEIN: I was trying to leave out the working  
8 parts of it. But you think that is important to put it in,  
9 to leave it to the committee, just that categorization was  
10 going to depend on how important it was to human medicine,  
11 basically. Whether it crosses over or not--

12 DR. ANGULO: The way that statement reads, the  
13 categorization for virginiamycin would be zero. It would be  
14 the lowest possible because it is of absolutely no  
15 importance to humans. But Synercid is of extreme  
16 importance. So it is not virginiamycin that causes it to be  
17 important, it is an analogue.

18 DR. LEIN: Okay. So I will add that other part  
19 in.

20 Why don't you go on with 3.

21 DR. STERNER: We will revisit question 2.

22 DR. SUNDLOF: Question 3; "Monitoring Threshold  
23 Levels, " which was contained on pages 15, 16, 18 and 20 of  
24 the framework document and has two parts.

25 "Should multiple monitoring threshold levels be

1 established and should they be based on animal data, human  
2 data or both? Should the levels be tied to specific  
3 actions--for instance, need for further investigation, need  
4 for mitigation strategies, need for withdrawal of product  
5 from the market?"

6           The second part of that question is, "What  
7 organism or organisms should be the basis for the monitoring  
8 thresholds? In the interest of cost-containment, would a  
9 sentinel organism be designated or should foodborne  
10 pathogens be used?"

11           DR. STERNER: I guess I repeated twice to the  
12 left. Dr. Angulo, you are up again first.

13           DR. ANGULO: The answers to this question, in all  
14 honesty, CDC has not fully considered. I don't know what is  
15 best, whether to use animal data or human data. CDC will be  
16 looking at human data and we would hope there would be  
17 actions based upon what we find in human data.

18           But the first question really goes way down the  
19 road in kind of implementation. I agree there should be  
20 monitoring thresholds which do result in corrective actions,  
21 but what those monitoring thresholds are based on, whether  
22 it be animal data, human data or both, I would just hope to  
23 defer to another opportunity for us to more fully evaluate  
24 and have people talk about the surveillance systems and how  
25 robust one part is versus another part, et cetera, which we

1 have not had much discussion about the intricacies of the  
2 surveillance systems.

3           Personally, quite frankly, we haven't answered  
4 this question yet.

5           DR. BARKER: Should multiple monitoring thresholds  
6 be established? Should they be based on animal data or  
7 human data or both? Clearly, I think that you will have to  
8 establish multiple monitoring threshold levels for different  
9 actions. So the first part of that question and the second  
10 part of that question, should the levels be tied to specific  
11 actions, need for further investigation, mitigation  
12 strategies, et cetera, would be incorporated into the need  
13 to do multiple monitoring thresholds.

14           Should that be based on animal data and human  
15 data? Absolutely. If we are mainly talking about the  
16 effect on human microbe antibiotic resistance or human  
17 pathogen antibiotic resistance, we would want to observe  
18 that as well as seeing it occur in animals.

19           So I would think that you would want to monitor  
20 both, that you would want to have multiple thresholds and  
21 that those thresholds would be tied to specific actions.  
22 What organisms should be the basis for monitoring? I am not  
23 of the opinion that it should be simply a sentinel organism.  
24 I think the development of antibiotic resistance and the  
25 transfer of this resistance between pathogens clearly

1 requires that other, more important, foodborne pathogens  
2 also be monitored.

3 To simply do a sentinel and to miss the actions  
4 that would be occurring on the biochemical levels of other  
5 types of pathogens would be remiss on the part of the  
6 agency.

7 DR. FLETCHER: I think this is an area where there  
8 is a tremendous opportunity to partnership with several  
9 different approaches to monitoring. I would urge the agency  
10 to take advantage of that opportunity.

11 We heard yesterday from a lot of groups that are  
12 talking about the kinds of things that they are doing. I  
13 think it ought to be incorporated in this approach. I think  
14 it needs animal data and human data and there needs to be  
15 some comparison and some correlation.

16 This is also an area where there needs to be a lot  
17 of additional work in the next few months to answer some of  
18 these questions. We have been talking about Salmonella and  
19 Campylobacter. It was suggested yesterday that Proteus  
20 might be a sentinel.

21 I think there needs to be additional work done on  
22 what organisms should be the targets. But I see a  
23 tremendous opportunity to use multiple sources of  
24 information and tie it together in some kind of national  
25 database or national network. I would urge the agency to

1 take into consideration the comments that various groups  
2 made yesterday and try to put that package together.

3           It goes, maybe, beyond what simple regulatory  
4 requirement would be and I don't really know who would play  
5 the lead role in that, but I see an opportunity here. I do  
6 not think that it should be the burden of the drug industry  
7 alone to do the monitoring.

8           So I think there needs to be sensitivity to that.  
9 There are the issues of who is going to do it and who is  
10 going to pay for it.

11           We have mentioned in our questions I think a  
12 number of different possibilities, the diagnostic lab  
13 network that already exists, the FSIS HACCP program within  
14 plants, the quality-assurance programs that the various  
15 associations are implementing need to be tied together in  
16 some way, in my opinion.

17           DR. HASCHEK-HOCK: I think the simple answer to A)  
18 is yes, both animal and human data should be used and the  
19 levels should be tied to specific actions. But, obviously,  
20 we don't have data here to make any more recommendations.  
21 And I don't think we have enough data, really, to make any  
22 statements about what organisms should be the basis for  
23 monitoring thresholds.

24           DR. HOLLAND: Again, I think the simple answer is  
25 yes, as well. But I have trouble in seeing how a lot of the

1 mechanics of this will be worked out. We can only trust  
2 that the mechanics will be worked out.

3 I think that we should look at the animal data,  
4 the human data, the pet data, as well as the vegetable data  
5 because feces from most farms, as an example, just don't  
6 stop with the animal. It goes out into the environment at  
7 some place. So we have got vegetables and fruits that you  
8 may want to consider there as well. But that is not a part  
9 of this.

10 I think we need to be cognizant of the financial  
11 constraints that some of these studies may put on the  
12 pharmaceutical industries and look to government support or  
13 other supports to help finance these.

14 Regarding to organisms? Who knows? I think that  
15 is one that you really have got to get down and get dirty.  
16 When I say "get dirty," get out on farms and really look at  
17 what is going on. At Michigan State, we laugh about the  
18 epidemiologists. We tell the ones that work and the ones  
19 that work at their computers because they have dirty  
20 coveralls on. And they are the ones that you trust their  
21 data, by the way.

22 DR. GERKEN: I think this is one of the areas  
23 where a lot of us have a problem because of what we perceive  
24 to be animal data-gap, or the data being missing, and the  
25 missing link of making these things fit together in the

1 underpinnings of this document.

2           At any rate, I believe, wholeheartedly, that the  
3 animal data need to be collected along with the human data  
4 in order to see whether this grand experiment really is  
5 going to be the way people think it will turn out.

6           I would like to see, at the end--or, not at the  
7 end but during this middle time, that this be revisited a  
8 little bit about whether there is actually the animal data  
9 to support the human outcome or whether there is no change  
10 in animal resistance patterns but there is change in human  
11 resistance patterns, that this may be made public so that we  
12 all could understand a little bit more about what actually  
13 is going on.

14           I just don't think the data is there. As far as  
15 the organisms, I think this is definitely a microbiologist  
16 field and I defer to those people.

17           DR. LANGSTON: Should multiple monitoring  
18 thresholds be established? Again, the short answer is yes.  
19 Again, the short answer, we don't know how to do it quite  
20 yet. Hopefully, it can be done expeditiously.

21           Animal data, human data; I think you have to look  
22 at human data, obviously. But, because of the potential for  
23 magnification where undercooked hamburger in one pot of  
24 spaghetti may cause 100 cases, you absolutely have to have a  
25 animal data to correlate it with.

1           From what I know, I would argue more for pathogens  
2 rather than sentinels. But I think that would be a better  
3 question, again, for a microbiologist panel.

4           DR. LEIN: Yes . Again, both animal and drug data.  
5 Certainly, and I have said quite a bit about this already,  
6 but increasing the power of the national antibiotic group at  
7 this point in their antimicrobial resistance survey. Also,  
8 I think, utilizing the diagnostic lab data would be  
9 important if that can be standardized and put together.

10           I think a third component, and Clyde Thornsberry  
11 made reference to this, too, would be to have an independent,  
12 group with a centralized lab that would at least be  
13 responsible also for some of the on-farm data that could be  
14 collected from normalized animals basically or normal  
15 groups .

16           The diagnostic lab data is, at this point, pretty  
17 biased toward sick animals so it would be good to have some  
18 monitoring of a sentinel-type system throughout the United  
19 States. Again, I feel that this should not all be left up  
20 to industry to support but needs a wide basis of support,  
21 both industry and, hopefully, government support for these  
22 initiatives .

23           MR. WOOD: Just briefly, as a lay person, I don't  
24 really feel equipped to deal with particulars of this  
25 question, but do support the establishment of thresholds. I

1 most particularly want to say that as thresholds are created  
2 and determined and established that consumer groups have the  
3 opportunity to be a part of those discussions and  
4 particularly to review the decisions that are made because  
5 we also are stakeholders in this whole process and that kind  
6 of participation is important.

7 DR. O'BRIEN: I think yes, you do need some kind  
8 of thresholds to give it structure although I think exactly  
9 how those will be arrived at will have to be on a case-by-  
10 case basis because we can't anticipate--again, we can't  
11 anticipate what the bacteria will do.

12 The same is true for sentinel organisms. I don't  
13 think you can pick sentinel organisms in advance and, as  
14 much as you can afford, you have to look broadly. I think  
15 who would have guessed *Enterobacter faecium* would be the  
16 sentinel organism for avoparcin or who would have guessed  
17 *Campylobacter* for fluoroquinolones.

18 These things pop up at some time and they are very  
19 unpredictable. So I think you would have to look broadly  
20 rather than at a few sentinel organisms.

21 DR. COOPER: I have one question before I answer  
22 it. If you turn to page 15, third paragraph, where it says  
23 monitoring threshold, I believe the statement, "If a  
24 resistance threshold can be established, " should not be  
25 there.

1           To me, if you read it for a category I drug, "The  
2 agency would establish monitoring thresholds for resistance  
3 development in animals to guide the postapproval monitoring  
4 program for these products. " Is that so? Or should that  
5 statement be in?

6           DR. LEIN: Is that No. 4?

7           DR. COOPER: Yes; where it says monitoring  
8 threshold, on page 15.

9           DR. LEIN: Aren't we going to answer that in No.  
10 4?

11           DR. TOLEFFSON: Dr. Cooper, it should be there.  
12 That would be established proapproval if we could establish  
13 a resistance threshold.

14           DR. COOPER: Okay. My assumption was that you  
15 would always establish a resistance threshold. That is not  
16 so?

17           DR. TOLEFFSON: We would. But if we couldn't--

18           DR. COOPER: But the reason I raise the question  
19 is when you look at the way this statement is written and  
20 you look at the same paragraph for category II and  
21 category III, it is not written that way.

22           DR. TOLEFFSON: Correct.

23           DR. COOPER: So if that is the correct way, then I  
24 don't--

25           DR. TOLEFFSON: For category II and category III,

1 it is not required at all. But for category 11, we could  
2 define--we are assuming we could define a level, a  
3 resistance threshold proapproval that would be protective of  
4 public health.

5 For category I, we might be able to for some  
6 drugs . We may not be able to for other drugs. In other  
7 words, it would be zero for the ones we couldn't establish a  
8 threshold. That is the transfer of resistance from the  
9 animal to the human, that threshold.

10 DR. COOPER: That answers my question.

11 DR. STERNER: When in doubt, the answer is zero.

12 DR. COOPER: Okay. I would say yes.

13 DR. LEIN: Could I come back to one more statement  
14 on this and that is I also agree that we shouldn't select an  
15 indicator organism or think of one organism. I think that  
16 came out again from our microbiologists that you need to  
17 look across a group of organisms for resistant changes.

18 DR. ANGULO: I agree. One of the weaknesses of  
19 our current system, of NARMS, right now is that it is all  
20 Gram-negative -spectrum organisms and there is not a Gram-  
21 positive. I would encourage that we move towards having  
22 some Gram-positive-spectrum organisms.

23 But I think, as I have heard comments, there is  
24 some confusion about what the monitoring thresholds are  
25 because there have been increasing statements that industry

1 should not sponsor this alone. But my understanding of who  
2 is sponsoring the monitoring threshold part is that this is  
3 largely going to be the sponsorship of FDA through the  
4 existing National Antimicrobial Monitoring System and it  
5 would not be a major burden for industry.

6 Is that the vision of the--

7 DR. TOLEFFSON: Yes .

8 DR. ANGULO: My impression is that these  
9 monitoring and resistance thresholds, in my understanding,  
10 have no industry sponsorship. Industry sponsorship is  
11 called into question in question No. 5, the on-the-farm  
12 survey. My understanding is the on-the-farm studies are not  
13 part of the thresholds; is that right?

14 DR. TOLEFFSON: They could, actually, give us more  
15 information about approaching the threshold. But, no; YOU  
16 are right, Fred. Your concept is right that since we know  
17 we have the NARMS, we would use that to monitor, for the  
18 monitoring thresholds.

19 DR. STERNER: Implicit in that, however, is the  
20 ability to devote resources to a greatly expanded program as  
21 described here. We may or may not have those available  
22 through the Food Safety Initiative.

23 DR. ANGULO: The last clarification, with such a  
24 strong statement for the animal data, which I wholly  
25 endorse, I think there is agreement that the best quality

1 animal data are the ones at slaughter because those are the  
2 closest towards to consumer. So we are very encouraged that  
3 FSIS is so supportive of this and has offered to make those  
4 HACCP or slaughterhouse samples more readily available.

5 DR. STERNER: Dr. Barker, you indicated a  
6 question?

7 DR. BARKER: Just to follow up on Dr. Angulo's  
8 statement. I think in any statement that we make about this  
9 question that it should be made clear that the monitoring  
10 will a part of existing programs and would not be expected  
11 to be part of the approval process for private industry.

12 DR. STERNER: So be it.

13 DR. LANGSTON: I simply wanted to echo what Dr.  
14 Lein said in that I think we are wasting a valuable resource  
15 in our diagnostic labs not only in terms of ability to track,  
16 potential trends for public-health purposes but realizing  
17 when we are talking about judicious use, you are talking  
18 about empirical use.

19 It is imperative that you know the probable  
20 pathogen that is going to be isolated in a disease and its  
21 probable antibiotic, in a biogram. So I would strongly  
22 encourage AAVLD and NCCLS to get together and certainly USP  
23 has had an interest in this in our Vet Med Panel to come up  
24 with some way of implementing such a scheme.

25 DR. STERNER: The question to the committee is, in

1 question No. 3, monitoring threshold levels. I will read  
2 this off in segments. I think everybody has had an adequate  
3 opportunity to comment at this point.

4 DR. LEIN: Could I comment? I just wanted to come  
5 back again to a couple of things. One is that I think we  
6 mentioned existing programs. There may be one beyond this.  
7 I had brought out that I almost think you need an  
8 independent center, basically, for the on-farm. I think the  
9 diagnostic lab data would be good. It is biased toward sick  
10 animals.

11 Some of the data in labs, because they will be  
12 doing some sentinel work, too, if we get into herd-health  
13 quality-assurance programs, could be important from the  
14 standpoint of random, normal animals.

15 But, to get that type of data, an independent  
16 group, if we had a centralized lab, could be helpful in  
17 support of that. We had talked about the concept some when  
18 we talked with the microbiologists here. I don't see a  
19 reason why that wouldn't increase our capabilities of  
20 understanding on-farm data.

21 The idea there is support by government--I'm  
22 seeing government as a very broad sense here--and industry.  
23 So it could be state governments. It could be federal, if  
24 we can talk USDA or someone else into some money. And  
25 industry could be the drug industry or it could be the

1 animal industries, basically, that we are talking of in  
2 this.

3 So I am making that sort of broad by just saying  
4 government and industry if people agree with this.

5 DR. GERKEN: Don't you think, Don, though, that  
6 the diagnostic labs are uniquely positioned to try to  
7 identify whether there is antimicrobial resistance in the  
8 animal population? In other words, if an antibiotic has  
9 failed on the farm, you are more likely, as a diagnostic  
10 lab, to receive that sample because there are deaths or  
11 there is some kind of continuing disease and, therefore, you  
12 could be able to determine whether there is resistance  
13 because that is where the failures are going to be, or some  
14 of the failures that we are going to come to.

15 So that data is really important. I agree we have  
16 to have the normal data but, for therapeutic failures, that  
17 would be good data to have.

18 DR. LEIN: I agree 100 percent. I am just going a  
19 step beyond that and say that there are a lot of organisms  
20 out there that don't kill animals that run around with  
21 antimicrobial resistance in them. I think Fred would agree  
22 with that. Could you pick that up by sentinel-type farm  
23 situations?

24 DR. STERNER: We have two more questions to deal  
25 with, but first we have to vote on No. 3. I will read

1 through the two parts in segments. "Should multiple  
2 monitoring threshold levels be established and should they  
3 be based on animal data, human data or both?" I heard a  
4 consensus that it was both animal and human data. So let's  
5 go ahead and vote on that first.

6 All those in favor, raise your right hand.

7 [Show of hands.]

8 DR. STERNER: Those opposed, the same.

9 [No response.]

10 DR. STERNER: "Should the levels be tied to  
11 specific actions; for example, the need for further  
12 investigation, need for mitigation strategies, need for  
13 withdrawal of product from the market?" Any disagreement  
14 with that?

15 [No response.]

16 DR. STERNER: By consensus, then, we agree.

17 Under part B) , "What organisms should be the basis  
18 for the monitoring thresholds?" I heard pretty unanimous  
19 consent that we need to look at a broad range of organisms  
20 and we weren't going to look at sentinel organisms, that was  
21 inappropriate.

22 Any disagreement with that? All those in favor  
23 of no sentinel organisms but looking at as broad a range as  
24 is practical within the resources of the monitoring program  
25 signify by saying aye.

1 [Chorus of ayes.]

2 DR. STERNER: Those opposed, the same.

3 [No response.]

4 DR. STERNER: Mr. Director, we are open to  
5 question No. 4. Oh; one more time. I will retract. Are  
6 you ready with question No. 2 and the statement?

7 DR. LEIN: I have 2 and 3.

8 DR. STERNER: Okay.

9 DR. LEIN: 2; "Categorization of antimicrobial  
10 drugs for food animals considering the importance of this  
11 antimicrobial drug for human medicine is accepted by the  
12 committee as a workable category for the importance of  
13 antimicrobial resistance and transfer of resistant genes  
14 from other bacteria of food animals. A fourth category of  
15 only food-animal drugs should be considered by FDA."

16 DR. STERNER: We are in agreement with that?

17 DR. ANGULO: Just to wordsmith it. The fourth  
18 category shouldn't be only food-animal drugs, because you  
19 could have a companion-animal food-animal drug. It should  
20 be non-human drugs.

21 DR. LEIN: Thank you. That was the European--

22 DR. STERNER: No human use.

23 DR. ANGULO: Drugs not used in humans.

24 DR. BARKER: Wasn't there something in our  
25 discussions about requesting simplification if feasible,

1 possible?

2 DR. STERNER: That was duly noted by the agency.  
3 don't know that it has to be a formal statement. You  
4 card us loud and clear, didn't you, Dr. Toleffson? She is  
5 nodding her head, but not at me.

6 MR. GEYER: It is in record. It is in the  
7 transcript . It will be highlighted in the summary minutes.  
8 So I think it is covered.

9 DR. STERNER: Did you want to do a reading of  
10 question No. 3?

11 DR. LEIN: "Monitoring threshold level is the  
12 important tool for the proposed framework and assures the  
13 human safety of the microbial effects of new animal drugs.  
14 We encourage the use of both human, animal and other  
15 environmental data to be obtained for making these  
16 decisions. The committee feels the national program using  
17 JARMS , diagnostic laboratory data and an independent central  
18 lab for on-farm data using sentinel farms be supported.  
19 These should be supported by government and industry. A  
20 broad range of organisms should be used for monitoring  
21 antimicrobial resistance. "

22 DR. STERNER: Any disagreement the statement as  
23 read?

24 [No response.]

25 DR. STERNER: Seeing none, Mr. Director,

1 Question 4.

2 DR. SUNDLOF: Thank you, Mr. Chairman. Question 4  
3 is in regard to Resistance Threshold Levels. The issues are  
4 addressed on pages 14 through 16, 18 and 20 of the framework  
5 document.

6 "The agency has proposed the creation of different  
7 levels of resistance transfer to humans that would be  
8 acceptable based on the importance of the drug or drug class  
9 in human medicine. Category I antimicrobial drugs would  
10 require that the use in food-producing animals results in  
11 little or no resistance transfer to humans.

12 "Category II antimicrobial drugs would require  
13 that a predefined level of maximum resistance transfer be  
14 established prior to approval that would depend on several  
15 factors such as the existence of alternatives to the drug,  
16 the human pathogens of concern, " et cetera.

17 "The level of resistance transfer must be low  
18 enough that there is a reasonable certainty of no harm to  
19 humans associated with the use of drug or the product in  
20 food animals. What criteria should the agency use to safely  
21 define the acceptable level of resistance transfer, if any,  
22 for antimicrobial drugs that fall into categories I and II?"

23 DR. STERNER: I am going to split and go this way  
24 and this way, so, Diane, be prepared after Dr. Cooper.

25 Dr. Langston?

1 DR. LANGSTON: I have significant concerns about  
2 the ability to do this. Presently, I don't believe that we  
3 can. I would say either that we delay this in terms of  
4 setting any sort of criteria until that can be established.  
5 If not, then those should be established for category I and  
6 anything in category II or III would simply be monitored and  
7 reviewed.

8 MR. WOOD: As the criteria are created, and I  
9 don't hear us ready to list them out now, I am continually  
10 concerned, as others have also expressed, about the  
11 existence of subtherapeutic use of antibiotics that may  
12 impact human therapies.

13 That use has been narrowed and defined a little  
14 further by our creation of a fourth category. Apparently,  
15 subtherapeutic drugs will be dealt with in the same light as  
16 therapeutic. I do appreciate the assurances that we  
17 received this morning that, regarding exposure questions,  
18 subtherapeutic use will receive the attention that it  
19 deserves.

20 I also want to again reiterate our concern about  
21 prior approvals. As we talked about grandfathering and  
22 making certain that we were only talking about new animal  
23 drugs, I still wanted to raise that question and to lift up  
24 how important the footnote is on page 7 that would allow for  
25 a risk assessment of prior approvals if funds are there.

1 DR. O'BRIEN: I think the questions about  
2 transfer--it is kind of a second-level question. You are  
3 monitoring levels of resistance. Now, a second level of  
4 examination is how much of that is due to transfer or can  
5 you measure transfer rates in between.

6 It is possible, and it is possible, probably,  
7 within the framework of a good surveillance system to find  
8 suspicious anti-biotypes and, now, increasingly easy, to do  
9 genetic markers to show that they are the same and to begin-  
10 CDC's work, of course, traces some of these lines.

11 So I think that it is good to have this in because  
12 it will be increasingly possible to do at least some studies  
13 like this. I think it would add another dimension. But I  
14 think, at the moment, you can't really say the extent to  
15 which you will be able to do this very easily right now.

16 DR. COOPER: I don't have any comments. I will  
17 yield to my expert colleagues.

18 DR. GERKEN: You talked about it in the context of  
19 a monitoring program but the way I read this, this is  
20 something that would be established prior to the approval  
21 and speaks to the drug-approval process. I am not very  
22 comfortable with it. I agree with Dr. Langston. I am not  
23 sure that it can be done.

24 I don't understand it well enough to understand  
25 how it can be done as a proapproval. Those are all my

1       :omments.

2                   DR. HOLLAND: I think this is the one that the  
3 microbiologists really need to work with from my  
4 perspective.

5                   DR. HASCHEK-HOCK: Ditto .

6                   DR. GALBRAITH: I am certainly not qualified to  
7 say how it should be done, but I think if the public health  
8 is going to be adequately protected, there has to be some  
9 reasonable level effect.

10                   DR. STERNER: Dr. Barker, surely you have an  
11 opinion.

12                   DR. BARKER: I am even less qualified than  
13 everybody else but I have never let that stop me. There is  
14 a small problem that I have with it. I would underscore  
15 what has already been said. It seems right at this point  
16 very difficult to understand exactly how this is going to be  
17 done.

18                   But , clearly, even if you have a category III drug  
19 that demonstrates significant resistance, that that is also  
20 of concern, not just for the human medicine part but for the  
21 veterinary use, continued veterinary use, of that drug under  
22 your mandate to provide products that are both safe and  
23 effective.

24                   If you prove that the drug is no really no longer  
25 effective, then you have to take some action, I would think,

1 based on the information that you generate here. But, as  
2 far as being able to actually make resistant threshold  
3 levels at this point, I don't think it is possible. You  
4 simply have to start to generate the data for one, all the  
5 existing drugs that are on the market and start to look at  
6 how those impact the position of the different drugs in the  
7 categories.

8 One is how we speculate that they will today and  
9 how they actually come out. I would be very interested to  
10 see the result of that.

11 DR. ANGULO: I recognize this is a critical  
12 question and very difficult to answer but I hope it will be  
13 one of many and there will be much continued discussion to  
14 find a rational approach. But, clearly, my impression is  
15 that we do not want antimicrobial resistance to emerge in  
16 humans to such an extent that it causes a clinical  
17 consequence.

18 So, at the very least, we can put a conservative  
19 threshold in human data and we could even make sure that it  
20 was focused because we could--besides monitoring resistance  
21 levels in humans, we could also interview those humans that  
22 had a resistant infection and make sure, like I have said  
23 before, that they didn't travel and didn't take  
24 antimicrobial and, if necessary, we could follow that up  
25 with more analytical studies which would include

1 interviewing people who were not ill and doing an  
2 epidemiological study to try to pinpoint what the most  
3 likely source of their infection is.

4           Nonetheless, I think the point is that we can make  
5 a threshold based on human data because we do know there  
6 would be a clinical consequence if a certain level of  
7 resistance should emerge in humans. So there is sufficient  
8 data, we believe, to understand what the clinical  
9 consequence to humans would be, for instance, if we were to  
10 have emergency of 1 percent fluoroquinolone-resistant  
11 salmonella in the United States.

12           To the extent that we use animal data at all for  
13 this or the other questions I agree fully much additional  
14 discussion needs to be held but, at the very least, human  
15 data could be used to set a resistant threshold.

16           DR. O'BRIEN: One other point might be, if I  
17 understand it properly, that the information on transfer, if  
18 it were to become available, might be modulating in the  
19 thresholds. In other words, if you found that the level in  
20 humans of resistance to a certain agent had reached what  
21 appeared to be a threshold, but if transfer studies tended  
22 to exonerate an animal source or pinpoint an alternative  
23 source, it might be a way of keeping that threshold from  
24 provoking a remedy in the animal-food industry.

25           DR. ANGULO: To follow up on that, I think we do

1 have a good example in the United States that, in 1991, we  
2 did surveillance on *Campylobacter* and we had zero  
3 fluoroquinolone-resistant *Campylobacter* in the United  
4 States . Now we are at 13 percent fluoroquinolone-resistant  
5 *Campylobacter*.

6           There was an analytical study done in Minnesota  
7 which demonstrated two important things; one, over half, I  
8 think almost 60 percent, of their infections were in  
9 international travelers mostly to Mexico which demonstrates  
10 the concern about international travel.

11           But the other 40 percent were domestically  
12 acquired which they followed up with retail studies and  
13 found the same isolates in poultry at retail, et cetera. So  
14 we can exonerate animal sources by doing further analytical  
15 studies if necessary. So I agree with the point that you  
16 made, Dr. O'Brien.

17           DR. STERNER: I think the committee has pretty  
18 universally said that we don't have enough information here  
19 so that is job security for some researchers. My own  
20 comments to this, and I feel this is a very critical  
21 question as well, were that the background materials and the  
22 invited speakers did not provide enough data or information  
23 on which to base a recommendation at this time.

24           DR. LEIN: I wrote something down as I was  
25 listening here. "Resistant levels for category I

1 antimicrobial drugs would require that use in food animals  
2 result in little or no resistant transfer to humans. If  
3 resistant transfer is detected, a review by FDA with an  
4 expert group would review the data and discuss mitigation  
5 for the future use of this drug in food animals. "

6 DR. ANGULO: But it sounds post hoc instead of a  
7 priori. Before a drug is approved, we can convene an expert  
8 committee and decide what we are going to do if resistance--  
9 [ mean, I don't think you need to wait to see it emerge and  
10 decide what to do.

11 If the decision as a category I drug should result  
12 in little or no resistance, then we should decide a priori  
13 before we approve that drug--

14 DR. LEIN: What I worry about in that is, again,  
15 this idea that we are going to consider only the human data,  
16 we are not going to look at on-farm data if we can get that  
17 to a point that may be meaningful.

18 If we are seeing now an increase in resistance in  
19 reman data, we really don't see that in background on-farm  
20 data. It is a question I asked before; what are you going  
21 to do with this? Does this mean that it is definitely  
22 coming from the farm or is it someplace in that process  
23 chain?

24 I think that Dr. Toleffson mentioned this pipe  
25 situation where we look at both ends and we are looking at

1 some of the materials in between from plants, from other  
2 places, talking about where this may be entering the system.  
3 What I am trying to do here is trying to spare the fact that  
4 we are going to pull a drug from the food-animal industry  
5 when it may not be required at that level but needs to be  
6 required at HACCP or some other level or treatment of  
7 humans .

8 DR. LANGSTON: Would you agree that largely we are  
9 concerned about category I drugs, Dr. Angulo? Really, it is  
10 not too much of an issue on class II. Given that, if they  
11 are going to be monitoring all along anyway, the question  
12 becomes, do you set a threshold proapproval that, when it  
13 reaches, you automatically do something.

14 My argument would be that yes, you can set a  
15 threshold but you really but you realize it is somewhat  
16 arbitrary on human data and instead of automatically  
17 triggering a mitigation or a withdrawal, the trigger would  
18 then be to a review panel.

19 DR. BARKER: Sometimes things are a little slow to  
20 dawn on me but it would seem that the driving force here  
21 really isn't where we place blame. It is not whether it  
22 occurred on the farm, whether it occurred from contamination  
23 in the environment, or whatever, that if we see in the human  
24 data a large increase in resistance to a particular  
25 antibiotic to treat a particular pathogen, that that takes

1 precedence over everything else and that simple continued  
2 use of the antibiotic in animals would raise the risk that  
3 other further additional resistance would be passed on.

4 Am I wrong about that?

5 DR. ANGULO: I think you are missing just  
6 slightly. Just because on the human data, we detect an  
7 increase in resistance, we would not assume, necessarily,  
8 that it is a food-animal source without first interviewing  
9 the people and making sure they didn't travel  
10 internationally and make sure that they didn't take  
11 antibiotics before they became cultured for this organism.

12 Then we would look at the animal data. If the  
13 animal data shows that there is no change in resistance,  
14 then I think we would have to do a more in-depth analytical  
15 study to find--I don't think would have found the answer  
16 yet .

17 But that **raises** two points. The first point is it  
18 answers question No. 5 which is if you don't do an on-farm  
19 study, then when we see changes in human data, you don't  
20 have the data to refute--refute is too strong a word, but it  
21 is the truth--you don't have the data to refute the change.  
22 So you obviously need on-the-farm studies.

23 DR. LEIN: I agree with you 100 percent,

24 DR. ANGULO: The second point, though, is the  
25 point about arbitrary setting of human thresholds. True, it

1 is arbitrary, but we can put in on the clinical threshold.  
2 It is arbitrary, but it is arbitrary to the extent that you  
3 are uncomfortable with having 25 people a year with an  
4 invasive Salmonella infection with fluoroquinolone-resistant  
5 Salmonella and in the first 48 hours while they await  
6 culture results, they will be being treated with  
7 fluoroquinolones, whether that makes you uncomfortable, or  
8 whether it is 2 percent or whether it is a half of  
9 1 percent, and we will have a spectrum of uncomfortableness  
10 from different groups.

11 We can set it arbitrarily but we can put it  
12 somewhere. There should be some place where we could say  
13 25 people at risk is too high or 50 people is too high or  
14 100 people is too high.

15 DR. GERKEN: Dr. Lein, the comment that you read,  
16 was that in summary of what I just heard us say around the  
17 table or was I in another world? I kind of thought Keith  
18 summarized it and then, out of your mouth, came something  
19 that I didn't--

20 DR. LEIN: Oh; I changed what he said. Yes.

21 DR. GERKEN: Okay. Now I understand what I didn't  
22 recognize it. Are you making a motion to change what the  
23 rest of us all said?

24 DR. LEIN: What I am stating is that we all feel  
25 like category I is a very important group if we are going to

1 look at it as single-type agents that are available for  
2 human medicine and that this should create a warning,  
3 basically, if we see an increase in antimicrobial resistance  
4 and that, then, should provide for FDA and this expert  
5 panel, whoever that is going to be, to review that and, if  
6 we could, in the ultimate, have good farm data and human  
7 data, some decisions made as to where the problem is.

8 I think Fred explained it very well, if we had all  
9 the datapoints that we could look at, what would make a  
10 decision--at least, that is much more important to source of  
11 problem, whether it is at a human level or whether it is at  
12 the farm level or whether it is at an environment level.

13 DR. GERKEN: I guess I am not quite understanding.  
14 I thought that the rest of us said that this was a very  
15 complex--

16 DR. LEIN: It is. I didn't mention a threshold.  
17 I didn't mention anything.

18 DR. STERNER: If I may. We all are in agreement  
19 that category I antibiotics, that the threshold is zero or  
20 very, very low. The problem comes in category II in  
21 establishing resistance threshold levels and we simply  
22 didn't have enough data.

23 My statement was background materials and invited  
24 speakers did not provide enough data or information on which  
25 to base a recommendation. Therefore, it should be deferred

1 to a later time at which point, hopefully, we will have  
2 better information to base a recommendation to the Center.

3 DR. BARKER: I would move to substitute that for  
4 the comments from Dr. Lein.

5 DR. STERNER: But, with regard to category I  
6 drugs, make no mistake that the resistance threshold levels  
7 would be effectively zero.

8 DR. LANGSTON: It sounds like we really have two  
9 parts to this. It is really saying that we don't have the  
10 information to set a threshold. The other part is that we  
11 may need a working threshold for a category I in the  
12 meantime. Am I misinterpreting that?

13 DR. STERNER: I am going defer to the agency here  
14 since you folks came up with this document and we are  
15 charged with answering it. I am not sure I have the  
16 insights to answer this. This is a tough one.

17 DR. SUNDLOF: I think we are asking you to think  
18 in the conceptual terms that we agree that it may be  
19 difficult to set one, set it based strictly on scientific  
20 evidence. But assuming that we had all of the information  
21 that we needed to establish these thresholds, conceptually,  
22 would these be a good idea?

23 DR. STERNER: For all three categories?

24 DR. SUNDLOF: There is none for category III.

25 DR. STERNER: Excuse me; categories I and II. I

1 guess I will just speak for the committee, not seeing any  
2 heads nodding in the opposite. We agree with category I and  
3 more research is needed for category II at this point, more  
4 data.

5 Is there disagreement around the VMAC, in the  
6 interest of moving on? One of our members has an airplane  
7 before too long that he has to pay attention to.

8 Donald, would you wordsmith that. We will make it  
9 into two parts. Is there agreement? Okay.

10 DR. ANGULO: On category II, I am not sure we need  
11 more data. We just need more discussion. I am not sure we  
12 need to do a new study--I am not sure we are going to get  
13 any more new data to answer--I think we just need to come  
14 together and try to decide what the levels would be.

15 DR. STERNER: It was envisioned that there will be  
16 workshops and other meetings to more specifically address  
17 this, hopefully, with more expertise in the area, that can  
18 come to some agreement. You, the agency, are charged with,  
19 in fact, coming up with that if you would like us to make a  
20 recommendation there.

21 Nobody felt a comfort level at knowing at this  
22 point the right thing to recommend to you.

23 Mr. Director, question No. 5.

24 DR. SUNDLOF: Thank you, again, Mr. Chairman. The  
25 last question, question No. 5. refers to on-farm

1 postapproval monitoring programs. The question is, "On-farm  
2 postapproval monitoring programs will be necessary for  
3 certain antimicrobial in category I and category II, high,  
4 and some category II medium products." That is referred to  
5 on pages 17, 19 and 20 of the framework document.

6 The question to the committee is, "Should on-farm  
7 monitoring be instituted immediately postapproval or should  
8 it be triggered by a change in the data generated from other  
9 sources such as NARMS?"

10 DR. STERNER: Dr. Sundlof, just for clarification  
11 purposes, the responsibility for the monitoring program on-  
12 farm will be on a case-by-case basis for the NADA applicant,  
13 or will responsibility for administration of this program  
14 like with the agency?

15 DR. SUNDLOF: That has not been determined. I  
16 think everybody is in agreement that we would not like to  
17 see a drug-by-drug system put into place, that we should  
18 have a more global, comprehensive system. Where the funding  
19 comes from for that has not been determined. In terms of  
20 this discussion, we can deal with the funding issue  
21 separately. We are just interested in your thoughts on  
22 whether or not having such a program out there makes sense  
23 in light of the rest of the framework.

24 DR. STERNER: This on-farm monitoring, however, is  
25 so integral to this whole issue that who is going to pay for

1 it becomes almost an overriding issue here. We can wish for  
2 a lot of things. We have all got a great wish list. But  
3 that resource pie, again, becomes a very critical factor.

4 Maybe I am speaking out of turn here. I will  
5 stop .

6 DR. FLETCHER: This is, in part, where I was  
7 making my plea earlier for some kind of coordinated effort.  
8 I would actually like to see on-farm monitoring even before  
9 any approval, as some kind of benchmark. I have a lot of  
10 problems with knowing how this is going to actually work. I  
11 understand what the agency is asking for and I support that  
12 in concept, but I am having difficulty knowing how a company  
13 is going to do this.

14 I think it does get back to a drug-by-drug basis.  
15 I think this coupled with--I did not appreciate that the  
16 monitoring thresholds levels was not going to be also a  
17 responsibility of the industry. It wasn't clear to me from  
18 the framework document who was going to have responsibility  
19 for that.

20 But I think here is an opportunity for the  
21 quality-assurance programs, perhaps, to provide some kind of  
22 information in a database that could be drawn upon as  
23 benchmark kinds of information and then you don't  
24 necessarily have to worry about immediately postapproval or  
25 triggered by a change. You have it ongoing.

1           How to work that into a framework regulatory mode,  
2 I don't know. But my plea is to find a way to do that  
3 because if the breed association groups are saying, "Look;  
4 we have got quality-assurance programs, " and if the  
5 integrators say, "On-farm quality-assurance is important, "  
6 then that ought to be able to be coupled with data that is  
7 coming from the slaughterhouse and from product and from  
8 what is happening in the human population.

9           That, to me, is the one compelling argument that I  
10 see for looking at this framework in a very positive way to  
11 say that could take us down the road as opposed to endless  
12 debate. But there needs to be some coordination about it.

13           DR. HASCHEK-HOCK: I guess when I see this--in  
14 response to one of my questions earlier, I was told that on-  
15 farm monitoring would be non-drug-specific and non-sponsor-  
16 specific. So where does postapproval come in? I think I  
17 would support what Dr. Fletcher says that we need continual  
18 monitoring, however that is going to be established, and  
19 that it would not be triggered postapproval for any specific  
20 drug.

21           DR. ANGULO: Obviously, resources are going to be  
22 restrictive . So if we were to prioritize the animal data, I  
23 think it is very clear, but worth reiterating, that the  
24 slaughter samples are paramount. And the more slaughter  
25 samples we can do, the better. And if we have limited

1 resources, that is what we should do most.

2 So then should there be an on-the-farm component.

3 That is a good question worthy of discussion. I realize  
4 that that could be very expensive for the industry. It  
5 obviously would be to industry's advantage to have on-the-  
6 farm studies so that they could help, if we noted a trend in  
7 human data, explain that.

8 But how extensive it should be on the farm, those  
9 types questions, I think the resources are going to direct--  
10 the more the better, but I don't think it is essential, not  
11 like the slaughterhouse samples are essential.

12 DR. GERKEN: I don't quite understand how this  
13 could be a burden of industry since, on the farm, they are  
14 going to be using probably more than one antibiotic regime.  
15 So you are going to get really a mixed message. If they  
16 were going to be using just one antibiotic for a whole year,  
17 you might say, well, that could be borne by the company.

18 But I don't think that is realistic. So you may  
19 have a whole variety of antibiotics used during a given  
20 period of time. I don't know how you can ask a sponsor of  
21 one antibiotic to be looking for drug resistance in other--I  
22 don't know. Maybe I am missing something but I have a  
23 concern about that.

24 MR. WOOD: I also support the on-farm studies  
25 either initiated postapproval or, as was suggested earlier,

1 beginning as soon as possible. It was indicated earlier, as  
2 well, in terms of identifying where resistance might take  
3 place that if resistance monitoring began there and no  
4 resistance was found but it was found as it went into the  
5 plant, it would certainly help to clarify some issues at  
6 that point, too.

7 I think any kind of monitoring that would take  
8 place, though, needs to be coupled with other kinds of  
9 review of on-farm management practices and steps that are  
10 taken that would have to do with creation of pathogen load  
11 or creation of resistance levels dealing with stress or  
12 biosecurity or density of animal populations that would have  
13 an impact in both those areas.

14 Related to the on-farm studies, although they are  
15 one piece of the pie and even though it is not a question, I  
16 think it needs to be supported again that the drug-sale data  
17 needs to be another part of that pie as well as what we have  
18 talked about many times, the resistance monitoring, overall  
19 resistance monitoring such as through NARMS, that all those  
20 are part of the whole and they all need to be a part of an  
21 effective framework system.

22 DR. LEIN: I think there are two things that are  
23 present here, one already existing and I will come back to  
24 diagnostic lab data, as soon as new drug is seeking approval  
25 and it is available, even before, possibly, licensed, the

1 diagnostic labs have the disc. They start to incorporate  
2 that in for that animal group.

3 They will start to look at background because a  
4 lot of the companies need background data before that is  
5 ever licensed. From there on in, we will be looking at that  
6 drug, basically, in whatever melee of animals come through  
7 as far as the diagnostic labs. So I think diagnostic-lab  
8 data is important again.

9 Second, I talked about an independent laboratory,  
10 a centralized laboratory, that has good QA, good QC, that is  
11 certified and basically it could even be CLIA certified. It  
12 could go that far to say it is into the human health part of  
13 it. And it would be looking at sentinel farm data again.

14 I think if you could develop that, that would work  
15 very well. I agree very wholeheartedly with Dr. Fletcher  
16 that our herd-health programs or animal-health program,  
17 quality-assurance programs, are going to be calling for this  
18 basically as we go forward.

19 Today, we do work with independently--not  
20 available to government agencies because it is done  
21 privately with industry--we monitor a lot of industries for  
22 bacterial background. That is done in the poultry industry.  
23 It is done in the semen industry. It is done in the embryo  
24 industry. It is done in some of the production units.

25 So that already has started, basically, in helping

1 them determine what their bacterial load is and what their  
2 antibiotic use is and their problems within that industry.  
3 So I think our step towards quality assurance is going to be  
4 a monitoring program.

5 As we put together these programs, basically, and  
6 we are developing one in the Northeast, it is certainly  
7 going to be developed that way for the dairy industry or  
8 other industries as we go forward.

9 Now , who will pay for this? Basically, industry,  
10 I think, will be involved with paying for a share of this.  
11 Again, I would throw out government and I am using a broad  
12 statement when I say government, be it state or be it  
13 federal or other agencies, to look at this. So I think this  
14 will be important data for us to glean.

15 We are going to need it for world trade. I think  
16 that day is here. And for the production units, we are  
17 certainly going to need it. So I think we should say, yes,  
18 we are going to look at on-farm data, make a statement and  
19 go forward.

20 DR. BARKER: Is part of the approval process for a  
21 new antibiotic drug that the manufacturer, the sponsor, must  
22 generate a baseline set of data about the effectiveness of  
23 their drug so there are acceptance of isolates from a range  
24 of different diagnostic laboratories and other sources? As  
25 part of the efficacy trials, in many cases, isolates are

1 taken from the animals involved in the study to verify that  
2 it is a particular type of pathogen and the MICs on those  
3 are examined.

4           So as far as implementing anything immediately, it  
5 would seem that the data are made available to the FDA in a  
6 reasonable form already as to what the MICs of these  
7 antibiotics are.

8           Is it reasonable to expect that one, a question of  
9 legal ability of the FDA to do this and, certainly, others  
10 know more about this than I do, but to have them go on-farm,  
11 first get permission to go onto a farm, and to monitor for  
12 general resistance on a farm that, perhaps, is not even  
13 using their drug.

14           Of course, it would not be reasonable for them to  
15 go ask to monitor on a farm that didn't have their drug, but  
16 it is so complex, the variables there are so difficult to  
17 get a handle on, that the data that comes through from that  
18 is part of their approval process, may be quite difficult to  
19 interpret.

20           I would suggest that there might be another way to  
21 approach this problem that might be more acceptable.  
22 Certainly, the baseline data must be generated. Private  
23 industry will do that anyway. We will know what the  
24 resistance patterns are in a very large number of animals  
25 prior to approval of the drug.

1           Part of the second question here is after a  
2 trigger--I certainly, after the product is on the market, if  
3 we start to see antibiotic resistance from the NARMS data,  
4 that suspicion will be raised as to what the cause of that  
5 is .

6           Slaughterhouse data is far more important to  
7 prevention of transfer of pathogens to the human than on-  
8 farm data, would be my position, that we would be far better  
9 served to recognize, one, that there is a problem, that  
10 resistance is occurring and then make the attempt to  
11 identify that through epidemiological approaches where a  
12 company may be invited to do another on-farm study that is  
13 controlled, where they would be asked to administer drug now  
14 to this herd of animals and examine the resistant patterns  
15 to see if they have changed rather than to mandate a  
16 continuous monitoring on-farm where the variables are  
17 extremely high and, for quite some period of time, what you  
18 will observe is no change.

19           DR. ANGULO: In terms of a public-health  
20 safeguard, the on-the-farm testing is not essential to  
21 establish adequate public-health safeguards. The adequate  
22 public-health safeguards would be in place, I believe, by  
23 monitoring slaughter samples and monitoring human samples.

24           But we do have the disadvantages of we have  
25 noticed different changes in those two surveillance systems.

1 If we don't have on-the-farm data, then we will just have to  
2 assume that it came through on-the-farm if we are going to  
3 have an adequate public-health safeguard, which may be an  
4 unfair assumption.

5 From a public-health perspective, I don't have an  
6 opinion whether there is an on-the-farm study or not. I do  
7 see a huge advantage of having some on-the-farm data because  
8 if there is on-the-farm data, you could fine-tune the  
9 current prudent use guidelines that are being developed by  
10 the data that is being generated.

11 I just believe that getting the on-the-farm data  
12 is in the best interest of the animal-health community. But  
13 it needs probably to be done by a group basis rather than  
14 individual companies so I would strongly encourage the  
15 Animal Health Institute to take the leadership in developing  
16 on-the-farm studies, maybe through an independent center or  
17 lot, but it seems prudent that the whole industry should  
18 support it rather than an individual company.

19 DR. STERNER: Dr. Lein, for everybody's  
20 information, would you have any idea about what a problem,  
21 an on-farm monitoring program nationally might cost?

22 DR. LEIN: No. I haven't thought about it.

23 DR. STERNER: It is one thing simply to go ahead  
24 and say to the pharmaceutical manufacturers, "We ought to go  
25 ahead and do this, " and we may no idea about the price tag

1 attributable to it. I say that, if somebody were going to  
2 say, "It is a small problem for me, " but they may not know  
3 what my circumstances are either.

4 DR. LEIN: I think when we say industry, though ,  
5 we shouldn't be just thinking about Animal Health Institute.  
6 I think we are talking about animal industries, also,  
7 kicking in on this. That is what happens today in some of  
8 the bigger industries. The poultry industry is a good  
9 example of that.

10 DR. BARKER: I believe there is already a wealth  
11 of information out there that just simply is not being taken  
12 advantage of. A lot of the cases, and you mentioned this  
13 earlier, that are seen on-farm where there are treatment  
14 failures or where there is actually a development of  
15 resistance are seen by a lot of diagnostic labs.

16 That data is very important, that good  
17 documentation of those cases is made by diagnostic  
18 laboratories and that there are more standard methods  
19 applied there, that there is already existing a very  
20 valuable resource for examining certain aspects of this.

21 To add one more layer of this as proposed here,  
22 individual companies would be responsible for establishing  
23 monitoring programs which the FDA has cited they would  
24 really have no control over, so it is not clear exactly what  
25 they would be monitoring and how, just doesn't seem either

1 practical or reasonable and, in the end, fair, particularly  
2 if you are not going to make it drug specific, you are just  
3 going to make it species specific.

4 DR. HASCHEK-HOCK: I think we would all like to  
5 see on-farm monitoring. I think the question is how much is  
6 it going to cost and how would it be implemented to make the  
7 data useful across multiple farms and multiple sources of  
8 information.

9 So I think maybe we should just say that  
10 slaughterhouse data is essential. Diagnostic lab data  
11 should be used because that is a wealth of information and  
12 there should be at least a mechanism to do on-farm  
13 monitoring once a problem is detected so that there would be  
14 ability to investigate.

15 The other things, I think, would be nice to do but  
16 may not be absolutely essential at this point.

17 DR. ANGULO: I think, in terms of this independent  
18 center, one possibility, of course, is the Center for  
19 Epidemiology Animal Health at Fort Collins, part of APHIS,  
20 which is an independent science-based agency and does to on-  
21 the-farm surveys, and they could head such a survey as this.

22 Those types of surveys that Fort Collins does,  
23 although expensive, are not resource-prohibitive, I don't  
24 believe. A similar type scale of study could be done by  
25 Fort Collins.

1 MR. WOOD: I would hope, though, that as we deal  
2 with this question, we deal with it in the same framework or  
3 the same understanding as the other questions in that we are  
4 not, at the same time as we answer this question, trying to  
5 work on budget questions.

6 We certainly have to live within the realities of  
7 what might be feasible but, to me, I think we are being  
8 asked conceptually whether or not on-farm monitoring, either  
9 postapproval or triggered, makes sense to us.

10 What I have heard us say earlier is that, yes, on-  
11 farm monitoring does make sense to us although there may be  
12 some financial implications that would make it difficult.

13 DR. STERNER: I think you have also heard that the  
14 validity of the on-farm monitoring presents some logistical  
15 nightmares, particularly for an individual manufacturer when  
16 we look at category I or II-H in terms of being able to  
17 mandate that for a sponsor.

18 DR. BARKER: Just one quick question, legal. Do  
19 you think that it is legal for the FDA to require a sponsor  
20 to monitor resistance on a farm where it does not directly  
21 and specifically involve their drug as part of proof of  
22 safety and efficacy?

23 MS. DAWSON: I haven't discussed that issue with  
24 the Center. I certainly would have the same concern. I  
25 think, under the statute, the types of reports and

1 information that we are allowed to get are to serve the  
2 purpose of determining whether the drug continues to be safe  
3 and effective.

4 In my view, there would have to be some connection  
5 between the sponsor's drug and the information that we  
6 require the sponsor to collect. But that is just my  
7 preliminary view.

8 DR. STERNER: Is there further discussion from the  
9 committee? Dr. Lein?

10 DR. LEIN: Looking further at the herd-health  
11 quality-assurance programs, we are developing one in New  
12 York State. Similar programs will be developed in Ohio and  
13 Pennsylvania. We are looking at a regional concept for this  
14 at this point really for the Northeast.

15 That would look at modules that would be involved  
16 with monitoring. Some of this is disease-oriented. If we  
17 had a Salmonella outbreak, obviously, it is quite easy to  
18 diagnosis Salmonella. It only takes, usually, the one  
19 animal that is sick or has a problem for those that have  
20 illness connected with it.

21 But there might be environmental monitoring that  
22 we would be doing as well because of Salmonella. We do that  
23 today in the egg industry for Salmonella enteritidis. It is  
24 a routine procedure that goes on within our states and  
25 several states in the Northeast and further, all the way out

1 to the California Coast.

2 But in this situation, basically, what we are  
3 looking at in the new type of herd-health quality-assurance  
4 programs is that once we have an outbreak of Salmonella on a  
5 farm, usually it is typhimurium or it may be DT104, or it  
6 may be something less than that, the difficult thing for the  
7 farmer and the practitioner is to manage that.

8 In managing that, frequently what we want to do is  
9 give help to the farmer and the practitioner in providing at  
10 least a post-diagnostic test to show that his management  
11 strategy is clearing up this condition.

12 That means that you are going to be doing  
13 environment testing as well as animal testing because you  
14 are looking for source of that infection and where it is  
15 harboring. It includes also rodents and birds and other  
16 wild animals that may be involved or other species on the  
17 farm because the cat becomes a big problem in this, dogs at  
18 times, and could include people.

19 In our situation, we are also pulling in the New  
20 York Agricultural Medicine and Health Group which is really  
21 an arm, a research arm, that comes through a regional  
22 concept throughout the United States and has the ability to  
23 work on-farm with farm families.

24 In that situation, they can look at the farm  
25 family as well through a questionnaire but also through

1 testing and provide help or local health departments. Peter  
2 has been involved in a few of these before, too, where they  
3 become the arm that is necessary to be working with the farm  
4 family as the veterinary group works with, basically, the  
5 animals and environment.

6 So I think putting those two things together gives  
7 us a unit, really, to go forward to start to look at some of  
8 these problems.

9 DR. STERNER: To the committee, the question says,  
10 "Should on-farm monitoring be instituted immediately  
11 postapproval or triggered by a change in data generated from  
12 other sources such as NARMS?" Implement immediately or  
13 after trigger? You have heard enough discussion and, I  
14 assume, have been taking notes that you have a consensus.

15 DR. LEIN: Just see how this fits. "On-farm  
16 postapproval monitoring programs, " and I didn't specify what  
17 category, "would be encouraged by the committee- " This sort  
18 of doesn't say it has to be there for category I or II. It  
19 is just encouraged by the committee.

20 DR. STERNER: Would you specify ownership?

21 DR. LEIN: Yes. "Slaughterhouse data should be  
22 increased. Diagnostic laboratory data and an independent  
23 accredited central laboratory should be developed utilizing  
24 government and industry moneys to monitor sentinel farms."

25 DR. STERNER: What is the committee's comfort

1 level with the statement as read? Comments?

2 DR. ANGULO: I like it, but the possibility of  
3 getting enough resources--I know we are not supposed to talk  
4 resources, but getting enough resources to develop an  
5 independent laboratory kind of weakens the statement. So I  
6 think it might be a good idea to have an independent center  
7 participate but it is not essential to the statement.

8 I don't know whether you want to include that.

9 DR. LEIN: I put it in because we put it in once  
10 before, basically, back someplace in the third one or  
11 whatever it was. It could be CAH, or it could be NVSL; a  
12 centralized laboratory. We don't have to make it  
13 independent .

14 DR. FLETCHER: I don't think it adequately  
15 expresses my feeling that there should be some partnership  
16 with quality-assurance programs, for example.

17 DR. LEIN: Good idea.

18 DR. BARKER: I don't think it expresses my  
19 feelings at all, but--no; it does. I think it is desirable,  
20 that the committee would consider it desirable, to have on-  
21 farm data. I think there are still issues about the  
22 legality of requiring it, certainly, in terms of public  
23 health, that there are, in that list of things that you  
24 gave, I would think, different priorities.

25 I think Dr. Haschek's description was actually a

1 little more appropriate, that there are mechanisms to do  
2 these individual things with existing programs and that, at  
3 some point, after a trigger, that we should apply the on-  
4 farm testing under a more controlled manner than is  
5 described in the framework document.

6 DR. STERNER: I am hearing some rumblings of  
7 agreement.

8 DR. LEIN: I have added the on-farm health  
9 quality-assurance programs. I say, "On-farm postapproval  
10 monitoring programs utilizing health quality-assurance  
11 programs should be encouraged by the committee, " or, "would  
12 be encouraged by the committee, " and then go on from there  
13 to say about slaughterhouse data, diagnostic lab and a  
14 central laboratory monitoring sentinel farms."

15 DR. HASCHEK-HOCK: Could you read that again,  
16 because maybe what we need to do is put some priorities in  
17 there, what the priorities for each of those would be.

18 DR. LEIN: "On-farm postapproval monitoring  
19 programs using health quality-assurance programs would be  
20 encouraged by the committee." We are not saying it has to  
21 be done. We are encouraging that they be developed.

22 DR. (//@): It occurs to me--I have a little bit of  
23 a problem with postapproval in on-farm monitoring programs  
24 because I would like to see monitoring programs on-farm  
25 without regard to approval.

1 DR. LEIN: I agree with you. Let's take it out,  
2 if everyone is in agreement with that.

3 DR. STERNER: I will ask for a show of hands at  
4 this time for removal of "postapproval." Those in favor of  
5 removal of "postapproval?"

6 [Show of hands.]

7 DR. STERNER: We have seven. We have a majority.  
8 so, "On-farm monitoring programs, " is how you start out  
9 reading it?

10 DR. LEIN: Let me put in here, "antimicrobial  
11 resistance. " "Monitoring programs utilizing on-farm health  
12 quality-assurance programs would be encouraged by the  
13 committee. "

14 DR. HASCHEK-HOCK: Is that the whole statement?

15 DR. LEIN: Then, "Slaughterhouse data should be  
16 increased. Diagnostic lab data and an accredited central  
17 laboratory should be developed utilizing government and  
18 industry moneys to monitor sentinel farms. "

19 DR. HASCHEK-HOCK: I guess I would like to see  
20 some priority starting off, perhaps, with the slaughterhouse  
21 as being absolutely essential, increasing that first, and  
22 having the ability to do on-farm investigation when  
23 triggered by a change in the slaughterhouse samples and then  
24 say that we would also encourage on-farm monitoring.

25 MR. WOOD: I am a little concerned with setting up

1 a situation where we would immediately turn this over to  
2 quality-assurance programs, as valuable as they are.  
3 Quality-assurance programs do, in some areas, particularly  
4 with the pork producers and others, address--and we have  
5 heard from others today or yesterday--address this question  
6 on how they address resistance.

7 But not all of them do. Not all producers are a  
8 part of the quality-assurance programs. I am not sure that  
9 quality-assurance programs are in all commodity areas. I  
10 don't know about aquiculture, for example. So that would be  
11 an avenue, but I would not want to see it established that  
12 it would automatically be relied upon.

13 DR. LEIN: I think, in answer to your question, we  
14 are really not saying that this is mandatory. What we are  
15 saying is we are encouraging it. I feel that any production  
16 group of food animals today is into a quality-assurance  
17 program including aquiculture. I know they have started  
18 one.

19 I think this is going to become necessary if they  
20 are looking at any foreign trade. It might even be if they  
21 are looking at interstate trade. I will tell you today, if  
22 MacDonald's is buying it, it is probably going to be  
23 mandatory because they are asking for these things today as  
24 we go forward.

25 So I think we are going to see the consumer

1 pushing the quality-assurance program. We may as well add  
2 to the push at this level.

3 DR. O'BRIEN: I don't understand all the  
4 ramifications of implementation but I think, beyond just  
5 encouraging the on-farm monitoring, I think it would be nice  
6 if we could think of somehow getting enough resources to do  
7 some pilot on-farm monitoring, at least to have that as a  
8 firm recommendation to get some samples of data, to see how  
9 it would work, to explore it as a source of information a  
10 little bit more than we can now.

11 The examples that I know of are the studies of  
12 Wolfgang Witte and the ones that Stuart Levy did years ago.  
13 But I think the interrelationships between use and  
14 resistance in different species and in different kind of  
15 farming operations would be extremely valuable to at least  
16 have small samples of, either triggered by just exploratory,  
17 just trying something, to see what kind of information you  
18 could get and how such a program could be fine-tuned, and  
19 then keep it as a possibility for the regulatory process,  
20 as, for example, to be triggered by events at the  
21 slaughterhouse.

22 But I think not to wait for that, but to try to  
23 find the resources to pilot it so you have models as to how  
24 to do it in-hand and then think where it fits into  
25 implementation.

1 DR. LEIN: Some of that has been done already.  
2 'he NAHMS Program, the National Animal Health Monitoring  
3 ervice, and Dr. Angulo mentioned the Center for  
4 epidemiology and Animal Health which is a USDA division for  
5 epidemiology out of Fort Collins, has done this type of  
6 monitoring with several different species, now, over the  
7 .ast seven or eight years.

8 More recently, now, with both beef cattle, some  
9 dairy cattle, where they take a different species each year  
10 and set up a program statistically to test an industry and  
11 would look at several states. New York has been involved  
12 with both the dairy cattle, the Western states more with  
13 beef cattle, but spread across those states of interest and  
14 have looked at Salmonella.

15 Certainly, all those samples have gone through the  
16 NARMS testing because that is some of the data that has been  
17 in there for Salmonella and looking at antimicrobial  
18 resistance . There will be one starting in poultry, I think,  
19 in another year. They are doing the horse right now and  
20 that is looking, again, at a set of that fecal shed,  
21 basically, that could be present.

22 So we are getting background data ready out of  
23 that system. All the testing is done out at the National  
24 Veterinary Services Laboratory out at Ames, Iowa. NARMS is  
25 doing the susceptibility testing. All the Salmonella are

1 typed.

2 DR. STERNER: We are at the end of our agenda,  
3 here. Time flies because we are having so much fun. The  
4 committee needs to come to some recommendation with regard  
5 to question 5. You have some language that I would like you  
6 to read for the committee.

7 Before you do, are there any last burning points  
8 that any individual committee members need to bring to this  
9 discussion? Wanda, yours have been expressed. We will get  
10 an opportunity to hear them in a moment.

11 DR. ANGULO: To second what Wanda said, the  
12 slaughterhouse samples are so essential, I think we could  
13 take that sentence out first and just say that, and then the  
14 rest on the on-the-farm.

15 DR. LEIN: I separated that out and simply said,  
16 "Slaughterhouse data must be increased."

17 DR. ANGULO: You could say even more. You could  
18 say--

19 DR. LEIN: "Slaughterhouse data is paramount to  
20 this--"

21 DR. STERNER: "Is of paramount importance." There  
22 is agreement. I am seeing head nods universally around here  
23 with regard to slaughterhouse data being of paramount  
24 importance. That is statement No. 1.

25 DR. LEIN: And we'll say to the postapproval data

1 or to the framework.

2 DR. STERNER: The framework is here. We have all  
3 pointed out some of the shortcomings, potential  
4 shortcomings, of on-farm monitoring, period, postapproval in  
5 particular.

6 DR. LEIN: We will make that number one,  
7 basically.

8 DR. STERNER: Yes . On-farm monitoring, period, as  
9 being problematic and postapproval, perhaps, even more more  
10 so . The rest of the statement reads--

11 DR. LEIN : "Slaughterhouse data is of paramount  
12 importance to the framework. On-farm antimicrobial  
13 resistance utilizing farm-health quality-assurance programs  
14 would be encouraged by the committee and diagnostic  
15 laboratory data and development of an accredited central  
16 laboratory should be developed utilizing government and  
17 industry moneys. "

18 DR. BARKER: We may not be sufficiently addressing  
19 the question as that is stated. It is specifically about  
20 on-farm monitoring and whether it should be implemented  
21 immediately after approval of a drug or after a trigger.  
22 What we state there is just that it is encouraged, but we  
23 are not saying encouraged when, if ever.

24 DR. HASCHEK-HOCK: I think, in my statement, I  
25 indicated that, in addition to the slaughterhouse sampling

1 :hat there needs to be a mechanism when triggered for on-  
2 :arm monitoring. So could we add that in between those two  
3 statements?

4 DR. ANGULO: Which I am comfortable with. It is  
5 just that it places the drug company at a disadvantage, or  
6 animal health at a disadvantage, because if it is not in  
7 place until a trigger, it may be too late to have a mature  
8 system in place to refute the evidence that is coming  
9 through the food supply.

10 But that is a tradeoff.

11 DR. STERNER: I am going to take a little license.  
12 Dr. Carnevale, you have had an opportunity, or Mr. Mathews,  
13 to listen to this. Would you care to comment about the  
14 Animal Health Institute's view on this, speak for the  
15 industry? This is pretty critical to you folks.

16 Dr. Carnevale, could you come to the microphone  
17 and perhaps just let us know what a semiofficial feeling  
18 would be? I apologize for blind-siding you on this, but I  
19 think it is very germane.

20 DR. CARNEVALE: Thank you, Mr. Chairman. I guess,  
21 listening to the discussion, we clearly support, as we said  
22 yesterday, the focus of the monitoring being at the  
23 slaughter plant. I think we have always stated that. We  
24 felt that that was the best measure of exposure.

25 I think, as Mr. Mathews stated yesterday in his

1 Summary/conclusions, we felt that using that slaughterhouse  
2 data as an indicator of trends in resistance, that there be  
3 follow up, epidemiologic investigations done, to try to  
4 determine, if one can, where that resistance is coming from,  
5 what species and where, maybe geographically, that is coming  
6 from.

7 so, conceptually, I think we completely support  
8 that notion. We understand that there is some concern about  
9 increasing sampling in slaughter plants. We have to be  
10 careful about recommending that. But, to the extent that we  
11 can strengthen and continue to fund the basic component of  
12 slaughter-plant sampling being the real trigger for further  
13 action, I think AHI would support that notion.

14 DR. STERNER: Would you care to comment to Dr.  
15 Angulo's comments about a program that was already in place  
16 versus post-trigger?

17 DR. CARNEVALE: That is a bit troublesome. I  
18 don't think the industry ever had a problem with on-farm  
19 testing in and of itself. I think that the problem that  
20 industry has with on-farm testing was on an individual  
21 product-by-product basis being somehow managed by the  
22 individual drug sponsor.

23 If the federal government and other sources were  
24 able to set up some sort of monitoring system on the farm, I  
25 don't think that industry would have any specific objection

1 to that. I think it was the responsibility being placed on  
2 the drug sponsor to manage this whole thing on their own,  
3 which is really what stimulated the concern we had for this.

4 So, yes; certainly it would be a good idea to have  
5 something already in place. The problem is, as a routine  
6 basis, it is very difficult for a drug sponsor to accomplish.  
7 that on their own.

8 DR. ANGULO: But don't you agree that for the on-  
9 farm system to be most useful, the more robust it is the  
10 better and, therefore, the more sampling done, necessary.  
11 So it would be advantageous to the Animal Health Institute,  
12 or at least the whole animal-health pharmaceutical  
13 companies, to provide also sponsorship of the on-the-farm  
14 study to make sure it is robust.

15 Just the way resources are in the government, if  
16 you rely on the government to only do sponsorship to run the  
17 entire on-the-farm, it may not be robust enough to answer  
18 the questions that all of us would like to have answered.

19 DR. CARNEVALE: That may be the case. This is a  
20 very difficult area. We can talk about on-farm testing, but.  
21 when you actually get down to it, it is a pretty big deal.  
22 I think what you ought to do is ask some of the producer  
23 groups in the audience, too, what their opinion is because,  
24 obviously, if we embark on something like this, it is going  
25 to have to be a cooperative effort.

1 MR. WOOD: That kind of survey probably does need  
2 to be taken. I know that with it being a trigger, that  
3 smells to me like traceback, then. I think that that kind  
4 of perception or phenomenon has not been taken to very  
5 kindly by a number of producers at least as I know as  
6 important as it is.

7 If there were postapproval monitoring, it would  
8 all be in place. All producers would be participating in it  
9 who were administering that antibiotic and so it would  
10 overcome the stigma of a traceback. Also, quite often, a  
11 traceback has some arbitrary qualities to it. So I would  
12 argue, again, for postapproval monitoring.

13 DR. STERNER: Don, are you ready to read the  
14 statement ?

15 DR. LEIN: Yes . "Slaughterhouse data is of  
16 paramount importance to the framework." Now , I can make  
17 that I or II. "On-farm antimicrobial-resistance programs  
18 utilizing on-farm health quality-assurance programs would be  
19 encouraged by the committee to look at postapproval  
20 antimicrobial levels for high-category antibiotics.  
21 Diagnostic laboratory data and development of an accredited  
22 central laboratory should be developed utilizing government  
23 and industry moneys."

24 DR. STERNER: The committee has heard the  
25 statement. Anybody vehemently disagree at this point?

1 Could I see a show of right hands for those in favor as it  
2 reads .

3 [Show of hands.]

4 DR. STERNER: Those opposed, the same.

5 [No response.]

6 DR. STERNER: I see unanimous consent.

7 That brings to a conclusion the five questions.

8 Steve Barker, you have a comment?

9 DR. BARKER: Oh, as usual. I want to commend the  
10 people that worked on the framework document for bringing  
11 forward what they knew people would take potshots at and  
12 that they would have to sit and listen to an awful lot of  
13 both complaints and approval.

14 As Dr. Bell brought out, we did need to get off  
15 the dime. This have to move forward. The FDA does have a  
16 responsibility to address these issues and, hopefully, that  
17 will be done.

18 But , at the same time, I would like to direct just  
19 a comment to Dr. Bell. All of this time that we have spent  
20 here and all of these efforts will be absolutely meaningless  
21 if the CDC and the government do not come down hard on the  
22 misuse of antibiotics in the human medical area.

23 DR. STERNER: Dr. Sundlof, I would invite you to  
24 add any concluding comments that you have from the agency.  
25 I wish to thank those in the audience for their very kind

1 Indulgence for this very long meeting. We have tried very  
2 hard to keep on schedule. We have met that goal but barely.

3 My apologies. I thought we could run a bit  
4 further, but this issue transcends the need for speed.

5 Dr. Sundlof?

6 DR. SUNDLOF: Thank you, Mr. Chairman. I just  
7 want to add my congratulations to the committee for all of  
8 the hard work and for all the long hours that you have spent  
9 here and the long hours you have spent reviewing all this  
10 massive amount of information in preparing for this meeting.  
11 I think we are very happy with the deliberations that took  
12 place in this.

13 I want to thank our consultants, Dr. Galbraith and  
14 Dr. O'Brien, for taking the time out of their busy schedules  
15 to come here today. I want to especially thank our outgoing  
16 members, Dr. Gerken, Dr. Lein and Dr. Cooper, and to Dr.  
17 Lein a special thank you for your years as chairman but for  
18 being such an able rapporteur for this session. That is  
19 truly a gift.

20 I also want to thank all of the special  
21 consultants who attended here today and yesterday for taking  
22 the time to come here and give us their insight and their  
23 expertise, and to the people in CVM who spent a lot of time  
24 staffing this meeting, making sure that it came off as well  
25 as it did and, especially, again a hearty thank you to Dick

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1 eyer for all the years of service he has put in there.

2 [Applause.]

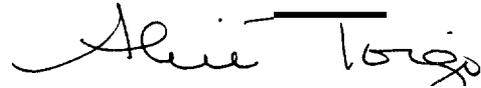
3 DR. STERNER This meeting stands adjourned.

4 [Whereupon, at 4:00 p.m., the meeting was

5 adjourned.]

**C E R T I F I C A T E**

I, **ALICE TOIGO**, the **Official** Court Reporter for Miller Reporting company, Inc., hereby certify that I recorded the foregoing proceedings that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script that reads "Alice Toigo". The signature is written in black ink and is positioned above a horizontal line.

ALICE TOIGO