

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR VETERINARY MEDICINE

VETERINARY MEDICINE ADVISORY COMMITTEE

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

VETERINARY MEDICINE ADVISORY COMMITTEE

Monday, January 25, 1999

8:30 a.m.

Holiday Inn Gaithersburg
Ballroom
Two Montgomery Village
Gaithersburg, Maryland

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Lyle Vogel, D.V.M., M.P.H.

C O N T E N T S

Introductory Remarks: Keith Sterner, D.V.M.	5
Introductory Remarks: Michael Friedman, M.D. Nicole Lurie, M.D., M.S.P.H.	9 12
A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals: Stephen F. Sundlof, D.V.M., Ph.D.	17
The Importance of Antimicrobial Drugs for Human Medicine: Mark Goldberger, M.D., M.P.H.	36
The Animal Drug Approval Process for Antimicrobial Agents: Margaret A. Miller, Ph.D.	50
Post-Approval Surveillance Issues: Linda Tollefson, D.V.M., M.P.H.	66
GUEST SPEAKERS	
Need for Addressing Issue and Benefits of Establishing Threshold Levels: David Bell, M.D., CDC	79
Risk Assessment: Scott McEwen, D.V.M., D.V. Sc., University of Guelph	94
Overview of CSPI Report Recommendations Relevant to Use of Antimicrobials in Food Animals: Patricia Lieberman, Ph.D., CSPI	109
Need for Safe and Effective Antimicrobials for Food Animals and AVMA Efforts on Prudent Use: Lyle Vogel, D.V.M., M.P.H., AVMA	122
The Authorization of Antimicrobial Products in the European Union: J.M. Rutter, D.V.M., Veterinary Medicine Directorate, U.K.	145
Importance of Commensals in the Transfer of Resistance from Animals to Humans: Abigail Salyers, Ph.D., University of Illinois	159

C O N T E N T S (Continued)

Importance of In Vitro Resistance Compromising Therapy for Diarrheal Disease: Sherwood Gorbach, M.D., Tufts University	175
Testimony of Animal Health Institute: Dr. Brendan Fox	191
Dr. Richard Carnevale	210
Alex Mathews	225
PUBLIC SPEAKERS	
Margaret Mellon, Union of Concerned Scientists	252
Dr. Rebecca Goldberg, Environmental Defense Fund	258
Dr. Tom Burkgren, American Association of Swine Practitioners	264
Dr. Diane J. Fagerberg, Colorado Animal Research Enterprises	273
Thomas Shryock, Ph.D., National Committee for Clinical Laboratory Standards and Elanco Animal Health	282
Barb Determan, National Pork Producers Council	291
Dr. Lester Crawford, Georgetown University	305
Joel Brandenberger, Coalition for Animal Health	310
Dr. Clyde Thornsberry, MRL Pharmaceutical Services	319
Harless A. McDaniel, AVID	329
Dr. Dennis Wages, American Association of Avian Pathologists	332
Dr. Mike Apley, Academy of Veterinary Consultants	339
Dr. Robert Walker, Michigan State University	354
Dr. Larry Glickman, Purdue University	362
James S. Cullor, U.C. Davis	371
Dr. Barbara Glenn, Federation of Animal Science Societies	381

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
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P R O C E E D I N G S

Introductions

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

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

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

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

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

DR. GALBRAITH: Peter Galbraith. I am the State Epidemiologist for the Vermont Health Department, and I have done environmental risk assessment and infectious disease

1 epidemiology.

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

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

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

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

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

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

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

23 DR. O'BRIEN: I am Tom O'Brien from Brigham and
24 Women's Hospital and Harvard Medical School in Boston, and a
25 consultant to the committee.

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

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

7 I have just two brief announcements before we move
8 into our scheduled program. First, you will notice on the
9 agenda that we are going to begin with the public speakers
10 at five o'clock today. That is a change from the
11 announcement in the Federal Register. We wanted to make
12 sure that everyone knows this up front. We plan to have
13 most of the speakers in the public session speak this
14 afternoon or this evening. There will be a few who will be
15 speaking in the morning.

16 If any of you who are public speakers have a
17 difficulty with the time that you are scheduled for, please
18 see me sometime today.

19 There is just one other thing. I would like to
20 ask that everyone who speaks today be sure to speak into the
21 microphone and, if you have not been introduced or if your
22 name has not been mentioned, as you start to talk please
23 state your name so that our reporter will be able to get
24 your name correctly. Keith?

25 DR. STERNER: I think that the turnout at this

1 meeting says it all with regard to the issue of
2 antimicrobial resistance.

3 Just to set the tenor a bit, Veterinary Medicine
4 Advisory Committee is just that, an advisory committee to
5 the Food and Drug Administration's Center of Veterinary
6 Medicine. And, they have prepared a framework document that
7 deals with the issue of antimicrobial resistance as it
8 involves approval and usage of antimicrobial agents in
9 veterinary medicine. To that end, this document deals with
10 an increasing level of both public and professional concern
11 over the issue of emerging antibiotic resistance.

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

19 I also would point out to you that people coming
20 to this discussion all hold very strong views, many times
21 from polar opposites on a very contentious issue. I think
22 that the great thinking that you are going to hear in the
23 presentations today will point out just how dramatically
24 opposed some of those views happen to be.

25 But with that in mind, we will introduce our first

1 speaker, Dr. Michael Friedman, who is the Deputy
2 Commissioner for our Operations from the Food and Drug
3 Administration.

4 **Introductory Remarks**

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

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

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

19 Today's issues represent, I think, a competition
20 between a variety of different areas where there are
21 competing needs and competing expectations. There are very
22 legitimate, important veterinarian and animal owner needs.
23 Antimicrobials are important drugs for veterinary use as
24 well as for human use, obviously.

25 FDA recognizes the critical need for

1 antimicrobials in veterinary medicine to treat animal
2 diseases; to improve the health of animals and prevent
3 suffering; to help ensure that animals raised for food
4 production are health.

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

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

16 The framework document that you have for your
17 consideration and which will be discussed today represents a
18 proposal for a conceptual regulatory framework, an approach
19 toward balancing the needs for safe and effective animal
20 health products against the potential impact on human health
21 that would result if pathogens acquire resistance to
22 important antimicrobials.

23 This is a document for your discussion and
24 consideration. This is a framework document. It represents
25 FDA's current thinking. It represents a synthesis of

1 different opinions from within the agency, but please let me
2 reinforce the idea that none of this document is etched in
3 stone. The discussion here is no mere empty exercise but a
4 serious, thoughtful debate that will be considered very
5 carefully by the agency. We honestly desire input from
6 stakeholders as we move forward to implement the concepts
7 embodied in the document. We will take very seriously this
8 input. We will use it to help guide us in developing a
9 rational science-based process for regulating antimicrobial
10 drugs intended for use in food producing animals.

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

16 Our goal is to articulate a public policy based on
17 the best science that positions us well for today and
18 positions us well for the future. And, as we search for a
19 formulation that is both practical and one supported by the
20 optimal public health position, we deeply appreciate all of
21 your contributions and help. Thank you.

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

25 Our next speaker this morning is Dr. Nicole Lurie,

1 who is the Principal Deputy Assistant Secretary for Health
2 at the U.S. Department of Health and Human Services. Her
3 background includes her degree from the Minnesota School of
4 Medicine where she held the post of Director of Primary Care
5 Research and Education, Director of the Division of General
6 Internal Medicine. She has taught within the University of
7 Minnesota system since 1985, and serves currently in her
8 capacity as Deputy Assistant Secretary since September of
9 1998. Dr. Lurie?

10 **Introductory Remarks**

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

13 [Laughter]

14 I am pleased to be here today on behalf of the
15 Surgeon General and Assistant Secretary for Health to
16 welcome you here, and pleased -- very pleased that you are
17 meeting together to address this very important and timely
18 public health concern about antibiotic resistance, treating
19 sick animals and its relationship to veterinary use.

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

24 As you may know, not only has antibiotic
25 resistance been designated by the CDC as a high priority in

1 its emerging health concern, but the World Health
2 Organization has also designated it as a very high priority,
3 and in its focus on emerging and re-emerging infections it
4 is right up there with our concerns about multi-drug
5 resistant tuberculosis.

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

12 Everywhere I go I hear now about this issue. I
13 hear about it from health plans and insurers, including
14 people in the healthcare financing organizations and managed
15 care organizations, who are concerned not only about
16 antibiotic costs and provider prescribing behavior but about
17 the morbidity and mortality of antibiotic resistance. Among
18 doctors the concerns span the range from pediatricians to
19 geriatricians.

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

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

9 The questions I get asked are the questions you
10 are going to help address today: What is the government
11 going to do about this problem? What is the right mix of
12 regulation and voluntary effort? What kinds of
13 partnerships, both between government entities and between
14 government and private sector organizations and businesses,
15 can produce the best public health outcome?

16 I want to stress, as Mike did, the term "public
17 health outcome" because our job here is to protect the
18 health of the public. One of our overriding principles is
19 that prevention is the best alternative. Another is that,
20 to the extent possible, we use the best possible science to
21 do so. Often the emotion surrounding an issue and the
22 scientific evidence leads us to alternative conclusions, and
23 I am sure there will be a long period today where that will
24 appear to be the case. But we also understand that science
25 does not yet have all the answers. So, we need to consider

1 in this equation not only the potential risks and benefits
2 but also public confidence in our public health decision-
3 making.

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

8 We also recognize that for uncommon events
9 surveillance systems alert us to problems often later than
10 we wish they would. We must strive to improve those too.
11 In both cases we hold ourselves to a commitment that when
12 the science improves, or when the evidence changes, we may
13 need to make different public health decisions than we might
14 today. But we certainly don't want to wake up five or ten
15 years from now with a massive problem of resistance and ask
16 where were we; where was the FDA; where was the CDC where
17 was agribusiness; where was the pharmaceutical industry;
18 where was the Public Health Service to allow this to happen?
19 This is why prevention is so absolutely critical.

20 We recognize, as you have been reminded twice
21 already this morning, that we are dealing with a difficult
22 issue. The science will get us a good part of the way there
23 but not all the way. There are competing views of risk and
24 sometimes competing goals for government, business and the
25 public. Yet, I believe that it is not only possible but

1 that we must find a common ground here, and I think it will
2 be easier to find a common ground if we remember our common
3 overriding goal -- protecting the public's health.

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

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

12 [Laughter]

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

16 [Laughter]

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

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

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

4 **A Proposal Framework for Evaluating and Assuring the Human**
5 **Safety of the Microbial Effects of Antimicrobial New Animal**
6 **Drugs Intended for Use in Food-Producing Animals**

7 DR. SUNDLOF: Well, thank you very much, Mr.
8 Chairman. I always said that you stay in this job until you
9 make a critical mass of enemies and then it is goodbye. So,
10 I am not sure that those remarks last night were too
11 comforting.

12 This is, as most of you are aware, a very, very
13 important meeting for CVM. It lays out a plan for a
14 regulatory framework dealing with some of the very complex
15 issues of antimicrobials. A number of people inside the
16 agency worked very, very hard, through long, arduous,
17 contentious meetings but it never got personal. It was
18 always very much a collegial effort although people held
19 very different views. The resulting framework document, as
20 Dr. Friedman indicated, is more or less the synthesis of
21 many diverse views.

22 I would also like to reiterate what Dr. Friedman
23 said in that this document represents the best thinking to
24 date out of FDA. It is not a document that is etched in
25 stone. It is out there for broad discussion and broad

1 consideration. It is our first attempt to try and lay out a
2 total package, a framework for dealing with these issues.

3 The development of resistance of zoonotic enteric
4 organisms, pathogens, is the main subject of concern. We
5 all know that the science clearly supports that exposure of
6 microbes to antimicrobials will select from those
7 populations organisms that have genetically encoded
8 resistance. So, the use of antimicrobials does promote the
9 emergence of resistant organisms. In many of the organisms
10 that we are concerned about from a foodborne pathogen
11 standpoint are normal commensal organisms in food animals.
12 So Salmonella and Campylobacter are normal gut flora of food
13 animals. They don't produce clinical disease most often in
14 those animals but those diseases do occur in humans as
15 foodborne problems.

16 [Slide]

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

23 The second is indirect. That is, the transfer of
24 genetic material from one organism to another organism,
25 which is even a more complex issue. I will say that the

1 issues that we are going to be dealing with are very
2 complex, and we have tried simple answers; simple answers
3 just don't seem to get us very far. So, that is why the
4 framework document looks as complex as it does.

5 [Slide]

6 Let's talk about our current regulatory approach.
7 We have fairly stringent pre-approval standards. As
8 everybody I think in this room understands, there is strict
9 evaluation of the toxicologic data. We don't want residues
10 in food which are harmful to the public. But until
11 recently, we have only required microbial safety studies for
12 subtherapeutic antimicrobials used in food for more than 14
13 days. In those cases we did require some safety studies to
14 look at the issues of resistance and pathogen load.

15 [Slide]

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

24 So, there are approvals now for cattle and
25 poultry. We made sure that those products were available

1 only through veterinary prescription; that it would be
2 illegal to use them in any way that was extra-label or off-
3 label. We asked the firms to engage in post-approval
4 monitoring programs, and we initiated a national
5 antimicrobial resistance monitoring system.

6 [Slide]

7 So, FDA's goal then is to protect the public
8 health by preserving long-term effectiveness of human
9 antimicrobial drugs while, at the same time, providing for
10 the safe use of antimicrobials in food-producing animals.

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

18 [Slide]

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

1 system for dealing with that.

2 Earlier this year or late last year, we published
3 a notification of a draft guidance, number 78, and it is in
4 the book that participants have. Basically, it establishes
5 the regulatory authority for FDA to deal with the issue of
6 antimicrobial resistance. That was the first step in going
7 forward with the program, total program, to deal with the
8 antimicrobial resistance issue. From there, the framework
9 document was published last month, in December, and you have
10 that in your package. That is the second part.

11 Furthermore, we plan to hold workshops to look
12 specifically in detail at what kind of studies would best
13 give us the kind of information that will be necessary to
14 allow decisions of whether or not to approve these products.
15 Throughout this process, we have asked for a lot of input
16 from the public, and we will continue to do so.

17 [Slide]

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

23 The two issues that have to be addressed are
24 resistance -- what is the potential for the products to
25 cause resistance, and in what organisms? And, what effect

1 does the drug have on the pathogen load that the animal may
2 be carrying at the time it is used for human food?

3 [Slide]

4 So, those are the two issues. Now, the draft
5 guidance has been out there since November 18, and the
6 comment period ended on December 18. We only received a
7 few comments on the guidance, and the comments that we did
8 receive did not materially affect the guidance as it stands.
9 So, we will continue to accept comments, and anybody can
10 comment anytime on the guidance. Pretty much, we think we
11 have put the guidance out there; we have listened and
12 received comments, and the comments have not caused us to
13 revise that document.

14 [Slide]

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

24 [Slide]

25 The framework document was issued in December, and

1 we will be accepting comments on it until April 6. We are
2 now in the comment period, and we will take all of the
3 information that comes out of this meeting -- all the
4 transcripts, go through those, try and sort out the
5 comments, but in addition, if there are additional comments,
6 they can be accepted up until April 6, and we encourage a
7 lot of comments.

8 The VMAC meeting was called to provide input and
9 to address the specific questions related to the framework
10 document, and the focus of this meeting is the framework
11 document, as was mentioned, and the questions provided to
12 the committee. There are a lot of peripheral issues
13 associated with antimicrobial resistance but we want to keep
14 the focus of this meeting squarely on the framework
15 document.

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

20 [Slide]

21 Now, the framework document lays out a conceptual
22 regulatory construct for addressing the microbiological
23 safety of antimicrobial drugs intended for use in food-
24 producing animals. The elements of the document include
25 adequate and well-controlled studies in the pre-approval

1 phase to provide predictive value on the likelihood and
2 extent to which antimicrobial resistance may develop when
3 the drug is marketed for its intended use.

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

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

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

15 [Slide]

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

23 Secondly, it will assess the safety of the
24 proposed animal uses of drugs according to their importance
25 in human medicine. That is, if you are talking in terms of

1 a risk analysis, this is the hazard analysis. The hazard
2 that we are referring to is the impact on public health that
3 would result if the antimicrobial in question was no longer
4 effective in the treatment of diseases transmitted directly
5 or indirectly through animal-derived foods. That is the
6 hazard.

7 Then, the second part of a risk assessment is the
8 exposure assessment. How likely is it that people will be
9 exposed, that the public will be exposed to resistant
10 organisms that are produced as a result of drug use in
11 animals? So, those are the two components to how we intend
12 to evaluate these.

13 We also intend to assess pre-approval data showing
14 that the level of resistance transfer from proposed uses
15 will be safe. We want some pre-approval studies that will
16 give us a predictive value that once the drug is approved
17 the likelihood of resistance development will be manageable.

18 Then, we also will be talking about establishing
19 resistance and monitoring thresholds. That gives us a
20 target against which to regulate. Without those kinds of
21 targets out there it becomes a very difficult regulatory
22 process to say at some point in time, "well, I think now is
23 the time when it is not safe anymore." So, we want to have
24 a target out there from a regulatory standpoint where we can
25 all declare that actions need to be taken, and those actions

1 may not necessarily mean removal of the product from the
2 market, but to take intervention steps that will mitigate
3 the continued emergence of resistance. Then, establishing
4 pre-approval studies and post-approval monitoring will be
5 necessary.

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

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

24 [Slide]

25 The pre-approval and post-approval requirements

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

4 [Slide]

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

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

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

21 [Slide]

22 So, depending upon the category, pre-approval
23 studies may be needed. Post-approval studies and
24 monitoring, and possibly on-farm monitoring studies may be
25 required. We will rely increasingly on the national

1 antimicrobial resistance monitoring system to give us the
2 kind of surveillance information that will be necessary for
3 us to make the right regulatory decisions.

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

10 [Slide]

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

18 But we are seeking comments on whether the
19 framework will, indeed, accomplish the goals. Is this
20 conceptual framework that we have laid out going to
21 accomplish the goals of protecting public health, while
22 giving us an avenue for allowing the approval of drugs when
23 they meet the standards that we have set out, and whether it
24 will provide for the safety of these drugs in food animals.
25 So, we are seeking comments.

1 [Slide]

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

10 [Slide]

11 Question two, categorization of antimicrobials --
12 the agency is proposing that the categorization of
13 antimicrobial drugs for human medicine take into account the
14 usefulness of the drugs in treating both foodborne diseases
15 and non foodborne infectious diseases. What evidence exists
16 that the use of the drug may result in induction of
17 resistant pathogens or the transfer of resistance elements
18 to human pathogens? This approach recognizes not only the
19 well-known risk of resistance transfer through classical
20 foodborne pathogens, but also the threat of transfer of
21 resistant bacteria or resistance genes from other intestinal
22 bacteria of food animals resulting in resistant infections
23 of humans with other types of pathogens, for instance, E.
24 coli or Enterococcus. The question to the committee is do
25 you agree with this concept?

1 [Slide]

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

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

14 [Slide]

15 The fourth question deals with resistance
16 threshold levels. The agency has proposed the creation of
17 different levels of resistance transfer to humans that would
18 be acceptable based on the importance of the drug or drug
19 class in human medicine. Category I antimicrobial drugs
20 would require that the use in food-producing animals results
21 in none or little resistance transfer to humans. Category
22 II antimicrobial drugs would require that a predefined level
23 of maximum resistance transfer be established prior to the
24 approval that would depend on several factors, such as the
25 existence of alternatives to the drug, the human pathogens

1 of concern, etc. The level of resistance transfer must be
2 low enough that there is a reasonable certainty of no harm
3 to humans associated with the use of the product in food
4 animals. What criteria should the agency use to safely
5 define the acceptable level of resistance transfer, if any,
6 for antimicrobial drugs that fall into Categories I and II?

7 [Slide]

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

15 So, those are the five questions that we hope to
16 have answered by the end of tomorrow, and we will have to
17 have answers by the end of tomorrow because most people have
18 flights that are leaving tomorrow afternoon.

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

24 DR. STERNER: Thank you, Dr. Sundlof. Do any
25 members of the VMAC have any questions of Dr. Sundlof at

1 this time?

2 [No response]

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

12 Setting the ground rules with regard to questions
13 of invited speakers, VMAC members and agency personnel will
14 be extended the opportunity to ask questions. During the
15 public comment period the same applies. If at the end of
16 the public comment period we progress as we have so far,
17 questions from the audience will be entertained of any
18 public speakers that remain.

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

1 Dick, do you have some additional housekeeping
2 details?

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

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

16 MR. GEYER: No time outs. Then to red. We will
17 set that according to the time that we have agree with all
18 of the speakers that they will actually use for speaking.
19 There will be time beyond that set aside for questions as
20 well, except I think, Keith, as we get into the public
21 speakers this evening we are just going to go right on with
22 one presentation after another and, as Keith said, hold
23 questions until the end.

24 One of things that I need to do as Executive
25 Secretary is to read a conflict of interest statement.

1 Please bear with me as I do that.

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

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

14 In accordance with 18 USC 208(b)(3), waivers have
15 been granted to Dr. Steven Barker, Dr. Wanda Haschek-Hock,
16 Dr. Robert Holland, Dr. Carl Norden and Dr. Keith Sterner.
17 Under the terms of the waiver Drs. Barker, Haschek-Hock,
18 Holland, Norden and Sterner will be permitted to participate
19 fully in discussions and deliberations which will involve
20 human and veterinary medical issues related to antimicrobial
21 resistance associated with drug use in animals.

22 In regard to FDA's invited guest speakers, Dr.
23 David Bell, Dr. Sherwood Gorbach, Dr. Patricia Lieberman,
24 Dr. Scott McEwen, Dr. J. Michael Rutter, Dr. Abigail Salyers
25 and Dr. Lyle Vogel, the issues to be addressed at the

1 advisory committee meeting will not constitute a conflict of
2 interest for the above-names guest speakers.

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

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

11 I would like to introduce a couple of staff
12 members for VMAC who are here helping today and who will be
13 able to help out with questions that you all might have:
14 Jackie Pace -- if you would stand up, Jackie; John Sheid --
15 John, are you in the back of the room somewhere? I think he
16 is coming in. Michelle Talley. Michelle is back there.
17 Hold your hand up, Michelle. And, is Susan Simmons in the
18 room? She may be outside. Those are the staff members and
19 they and I can answer questions that any of you might have.

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

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

25 [Brief recess]

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

6 **The Importance of Antimicrobial Drugs for Human Medicine**

7 DR. GOLDBERGER: Thank you.

8 [Slide]

9 Just by way of introduction, I am Director of the
10 Division of Special Pathogens within the Center for Drug
11 Evaluation and Research, and we have the responsibility for
12 a substantial number of anti-infective products, including
13 the fluoroquinolones, drugs for anti-parasitic disease,
14 drugs for systemic antifungal disease, drugs for
15 microbacterial disease, and some assorted other products.
16 It is a pleasure, obviously, to be here today.

17 [Slide]

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

25 [Slide]

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

9 For those individuals who are interested in a more
10 detailed discussion of issues related, for instance, to
11 definitions of serious and life-threatening diseases, one
12 useful resource is the Federal Register, and the citation is
13 52:19466-19477, May 22, 1987. This was a section that dealt
14 with the IND regulations, and there is a substantial
15 discussion of the topic of serious and life-threatening
16 disease.

17 [Slide]

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

23 After discussion with the Center for Veterinary
24 Medicine, we did include specific language regarding
25 treatment of foodborne infections. However, I did want to

1 say that we do not regard the issue of importance of the
2 antimicrobial drugs by any means to be limited to that type
3 of infection.

4 [Slide]

5 We put together our approach by utilizing some of
6 the resources within the Center. A number of medical
7 officers from my Division and the Division of Anti-Infective
8 Drug Products as well as microbiologists from those two
9 divisions met weekly for a period of several months. After
10 we put together an approach we had it reviewed internally, a
11 little bit within our Center at the level of the Office of
12 the Commissioner, including the new coordinator of
13 antimicrobial resistance activities for the agency, Dr.
14 Jesse Goodman. Then externally, we shared our approach with
15 our colleagues at the Center for Disease Control.

16 [Slide]

17 I did want to make, however, some caveats and a
18 comment about this. First of all, and I think that this
19 will come as no surprise, the importance of a product in
20 human medicine will sometimes change over time and whatever
21 approach is going to be used will need to recognize that.

22 Our system is currently qualitative rather than
23 quantitative. I think that this is an issue that may need
24 to be revisited over time, depending on the construction of
25 the ultimate approach to these issues.

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

6 Finally, we expect and invite comments. We do not
7 regard this as a completed work. I mean, this is now being
8 presented publicly as part of the larger framework document
9 and we would expect that there will be some modifications
10 over time that will need to be made, as well as discussion
11 at different points on how the actual implementation of this
12 approach will need to be done.

13 [Slide]

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

17 [Slide]

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

1 threatening disease, 21 CFR 314.500, as well as in the
2 recent FDA Modernization Act.

3 As I indicated earlier, we also included some
4 specific language about foodborne disease. I think this is
5 important given some of the data that exists about transfer
6 of pathogens from animals to human beings. Nonetheless, I
7 do want to emphasize as we think about the importance of
8 drugs in human medicine we are not certainly, from our
9 approach, limiting this to importance in foodborne disease.

10 [Slide]

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

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

20 Finally, certainly we looked at issues related to
21 mechanisms of resistance and cross-resistance. In terms of
22 issues like that, let me just say a couple of things. One
23 is that there is certainly a recognition that a product in a
24 class may often, when it produces resistance, produce
25 resistance to all the drugs in the class. That is by no

1 means invariable but it tends to be more common than not,
2 and I think that this is an important issue as we think
3 about a product, for instance, that might have veterinary
4 use, might not be the identical product that is used in
5 humans, but we must recognize that if resistance develops to
6 one product it is likely to develop to many others.

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

16 [Slide]

17 I think, therefore, a crucial issue that came up,
18 not surprisingly again, reflecting the way physicians
19 approach the management of patients with serious illness is
20 the availability of alternatives in treatment. And, I think
21 one way we thought about this was that there are essential
22 agents, that is, these are drugs for which really currently
23 there are no adequate substitutes or replacements. There
24 are also drugs of choice for infections or important therapy
25 by alternatives exist. Finally, there are drugs that

1 realistically appear to be of lesser importance, that may no
2 longer have major use in human medicine. There may be
3 really little therapy of serious infections with them, or
4 they may have basically essentially been replaced for almost
5 all infections. We think that these categories are
6 extremely important in looking at the overall issue.

7 [Slide]

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

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

21 The drawback, however, is that there is a
22 difficulty in determining what the appropriate points and
23 weights for different categories ought to be. So, this is
24 an issue that we may very well need to revisit, but we must
25 keep in mind that although on the surface it would seem as

1 though using a point system would provide greater
2 discrimination, and it may, we must recognize that it also
3 carries the potential for a lot of subjectivity and we would
4 have to be careful how we did this.

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

13 [Slide]

14 Category I -- and I have titled it "essential
15 agents" because I think that is one of the most important
16 aspects of it, although not the only one -- are drugs really
17 for serious and life-threatening disease, essential agents
18 where there are no substitutes, or important for treatment
19 of foodborne infections where, due to resistance or other
20 reasons, there are really limited alternatives, and finally,
21 the mechanism of action or the nature of resistance
22 induction is unique. Keep in mind that these by no means
23 are necessarily mutually exclusive. The fluoroquinolones,
24 for instance, which are one of the examples I have for
25 multi-drug resistant Salmonella, although they are very

1 important in serious Gram-negative infections and
2 increasingly important for Gram-positive infections both are
3 useful in serious or life-threatening disease, important for
4 the treatment of foodborne infections and, ultimately have a
5 mechanism of action and nature of resistance induction that
6 are somewhat unique.

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

13 [Slide]

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

22 We recognize here that, again, there will be a
23 number of diseases, a number of drugs in this category, some
24 which are stronger choices than others; some for which there
25 will be multiple diseases, others there may be only one.

1 So, it may be necessary over time to revisit Category II a
2 little bit to get a little better definition.

3 [Slide]

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

10 [Slide]

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

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

20 Finally, obviously, and this goes beyond simply
21 the CDER component, is addressing the implications of what
22 we have here. Obviously, this is an important aspect for
23 human medicine. It now needs to be fit into a more complete
24 document and, in fact, we now need to understand how we are
25 going to successfully utilize this. Thank you.

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

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

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

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

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

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

15 DR. GOLDBERGER: Well, if you recall, that was
16 under my caveats, that the importance of antimicrobial
17 therapy will change over time and we can think about
18 examples of that, I mean, if you think about the role of
19 vancomycin today and the role of vancomycin twenty years
20 ago, as an example; if you think about the potential role of
21 erythromycin not only in terms of Campylobacter which was
22 the example that we used but also in terms of the role that
23 it has had for many years, perhaps being supplanted recently
24 in terms of the management of a typical pneumonia which
25 became more and more of an issue starting in the later

1 1970's.

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

13 DR. STERNER: Dr. Angulo?

14 DR. ANGULO: Mark, of the parameters that you
15 list, the one that you did not list is the likelihood of
16 genetic transfer. On page 14 of the framework document it
17 discusses the possibility of taking the categories that you
18 have placed and treating a Category I or II drug as a
19 Category III drug if the likelihood of genetic transfer is
20 deemed to be low. For instance, it points out that if a
21 drug is an essential drug for the treatment of respiratory
22 disease in humans and the likelihood of transfer of genetic
23 resistance from an enteric organism in animals to the
24 respiratory pathogen in human is thought to be low there
25 would be this treatment of Category I or II into Category

1 III.

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

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

14 Subsequently, as this approach is integrated into
15 the entire framework document, alterations in
16 categorization, etc., may be made based upon other data.
17 But our first goal was simply to get some sort of approach
18 to how we thought of the drugs themselves. Whether drugs
19 get moved up or down by other factors is an issue that I
20 think needs to be addressed in the totality of the document
21 rather than just in our approach.

22 But, certainly, this is an important issue and I
23 think it is an important issue in terms of the concept, and
24 it is an important issue in terms of how we would actually
25 go about demonstrating that aspect about the level of

1 transmission, and I think that is going to be one of the
2 more challenging aspects to this whole exercise.

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

7 **The Animal Drug Approval Process for Antimicrobial Agents**

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

12 [Slide]

13 What I want to do today is talk a little bit about
14 the studies that we require in the approval of a new animal
15 drug, new antimicrobial drug; how we evaluate these studies;
16 and how we use these studies to make a prediction of whether
17 or not the product is safe; and then talk a little bit about
18 how we could apply these techniques or similar techniques to
19 making a determination about the safety in the
20 microbiological area.

21 [Slide]

22 Before any new animal drug is approved for use in
23 the United States, the drug sponsor must have an approved
24 new animal drug application. In the new animal drug
25 application the drug sponsor provides data to show that the

1 drug is efficacious, that it is safe for the target animal,
2 that it is safe for the environment, and that it can be
3 manufactured to uniform standards of purity, strength and
4 identity. If the drug is going to be used in a food-
5 producing animal, the drug sponsor must also provide data to
6 show that the drug is safe for humans.

7 [Slide]

8 In the area of environmental safety the agency
9 uses an exposure threshold approach to determine when
10 environmental fate and effect testing are needed.
11 Environmental studies are not needed for compounds that have
12 limited environmental introductions. When an environmental
13 assessment is needed the drug sponsor conducts laboratory
14 toxicity studies and in vertebrates, plants and microbes
15 representative of the environmental compartment of concern.
16 The no observed effect level, or MIC in the case of the
17 microbes, is divided by a safety factor to arrive at a
18 predicted environmental no-effect level.

19 [Slide]

20 The predicted environmental concentration of the
21 drug is then calculated, and we compare the predicted
22 environmental concentration, which is referred to as PEC,
23 with the predicted environmental no-effect level to come up
24 with a PEC/PNEC ratio. If this ratio is less than 1 the
25 agency concludes that the compound is safe for the

1 environment or that there will be no significant
2 environmental effects from the use of the drug.

3 [Slide]

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

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

17 [Slide]

18 The toxicology studies are designed to show a dose
19 that causes a toxic effect and a dose that causes no effect.
20 The no observed effect level is not always a classical tox
21 endpoint. CVM considers the development of diarrhea
22 following treatment with an antibiotic as an adverse effect
23 although clinically this is generally considered a side
24 effect of the drug. The Center views the results of
25 toxicity tests conservatively because we believe that

1 consumers should experience no effects from drug residues in
2 their food.

3 Once we have established the no-effect level for
4 all endpoints, the most sensitive effect in the most
5 predictive species -- and by that we mean predictive of man
6 -- is established. This no-effect level is divided by a
7 safety factor, and the safety factor takes into account
8 uncertainty, that is, the extrapolation between the animal
9 model and the human as well as variability, which is the
10 difference among individuals. After dividing by the safety
11 factor we calculate an acceptable daily intake, and the
12 acceptable daily intake is defined as the level of drug
13 residue that can be safely consumed daily for a lifetime.

14 [Slide]

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

24 The perturbation of barrier effect is of concern
25 because normally the gut flora prevent the overgrowth and

1 invasion of pathogenic bacteria. When the normal flora is
2 disturbed by an antibiotic, for example, overgrowth of
3 pathogens can occur and infections.

4 [Slide]

5 While the adverse effects of therapeutic doses of
6 antimicrobials on the human intestinal microflora have been
7 well documented, in most cases the lowest dose at which
8 these effects occur have not been established. Based on the
9 literature available at the time and the advice of experts
10 in the field, CVM established an exposure threshold for
11 concern of 25 mcg/person/day. For antimicrobial products
12 meeting an acceptable daily intake of greater than 25
13 mcg/person today the food safety evaluation must include an
14 examination of the effect of the drug on the human
15 intestinal microflora in addition to the standard battery of
16 toxicology tests.

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

1 in the target animals following antimicrobial treatment.

2 [Slide]

3 Now, as was mentioned by Dr. Sundlof, we have
4 asked for microbial safety studies in the past for
5 antibiotics that were administered in feed for more than 14
6 days. These studies, which are often referred to as 558.15
7 studies, were performed to look at the level of drug
8 resistant bacteria and the level of pathogenic bacteria.

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

18 [Slide]

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

1 and prevalence.

2 [Slide]

3 The design of the coliform study was similar to
4 that of the Salmonella shedding study, except that the
5 animals were not inoculated with bacteria. Rather, the
6 effect of the drug on the endogenous E. coli was evaluated.

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

13 [Slide]

14 I want to say that we do not have standardized
15 protocols developed for the microbial safety studies
16 mentioned in the framework document. However, the
17 techniques that have been used to measure the effect of
18 antimicrobial drugs and residues on the human intestinal
19 microflora, together with a modification of the traditional
20 558.15 studies, could serve as a basis for developing
21 protocols for these studies, and we are seeking scientific
22 input on both the design and interpretation of these studies
23 and feel that the protocols will be improved if we have
24 significant public input into the process.

25 As discussed in the framework document, we intend

1 to look at pathogen load issues on an exposure based
2 threshold. Then we will determine, based on the amount of
3 the exposure, when a drug sponsor will need to determine if
4 their product alters the level of pathogenic bacteria.

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

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

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

1 [Slide]

2 The framework document discusses that we intend to
3 use human health concern to determine when studies will be
4 needed to determine resistance. The objective of these
5 studies is to characterize the development of resistance so
6 that we can make some prediction about the product's safety.
7 To accomplish this, we will need to make several
8 modifications to the traditional 558.15 studies. For
9 example, the traditional 558.15 studies were designed like a
10 bioequivalence study. They were designed to show no
11 difference between the treated and control groups. In order
12 to characterize the development of resistance it will be
13 necessary to design the studies such that the null
14 hypothesis states that there is no difference, and the
15 alternative hypothesis states that there is a drug effect.
16 This type of design will facilitate statistical analysis and
17 improve our ability to make a prediction from the study.

18 The traditional 558.15 studies were done in the
19 target species, and we suggest that the new pre-approval
20 studies should continue to use the target species. However,
21 we believe that there need to be more numbers in order to
22 improve the power of the test and to actually show the
23 development of resistance, how that is going to occur.

24 In the past we extrapolated data from chickens to
25 pigs to cattle. I think this approach is still acceptable

1 provided that the first study provides a more protective
2 standard than the subsequent species.

3 [Slide]

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

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

17 As far as dosing, in the traditional 558.15
18 studies animals were dosed continuously throughout the
19 eight-week treatment period, and this is because it was
20 assumed that for feed administration the animal would be
21 continuously exposed to the antibiotic. For products that
22 are intended for food-producing animals by therapeutic
23 routes the continuous administration is not appropriate.
24 Perhaps some type of short-term repeat dosing regime, using
25 the dose and route of administration intended in the target

1 animal, would be more appropriate. One could assume that we
2 would do repeat dosing to cover the maximum amount of doses
3 that an animal is likely to encounter under field
4 conditions.

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

10 [Slide]

11 Finally, we come to indicator organisms. In the
12 traditional 558.15 studies we looked at the development of
13 resistance in Salmonella, E. coli and, in some cases,
14 enterococci. It seems to me that having one set of
15 indicator organisms for all antibiotics may not be
16 appropriate. We may need to change what indicator organism
17 we are looking at depending on the antibiotic. We might
18 have to have drug sponsors provide a justification for what
19 indicator organism they are choosing. Alternatively, we
20 could look at a panel of indicator organisms as we are in
21 the gut flora studies. In those studies the indicator
22 organisms cover both anaerobes and aerobic bacteria.

23 [Slide]

24 Bacterial load issues -- in order to look at a
25 susceptibility change in an indicator organism you need to

1 have sufficient quantities of the bacteria there to make an
2 accurate measurement. In the 558.15 studies animals were
3 inoculated with a laboratory strain of Salmonella to ensure
4 that they had sufficient quantities of the pathogen present
5 to measure the drug effect.

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

12 [Slide]

13 As I mentioned before, the 558.15 studies relied
14 on no difference between the treated and control groups to
15 predict that the use of the antimicrobial would not affect
16 antimicrobial resistance or pathogen load. The new studies
17 really should be designed to characterize the differences
18 between the treated and control groups using standard
19 statistical procedures. In this way, we will have
20 information that we can use to make some prediction about
21 the likelihood of resistance development and transfer to
22 humans.

23 I want to reemphasize that there will be numerous
24 opportunities for comment on how these studies should be
25 designed and interpreted but, conceivably, we could develop

1 a safety assessment, a risk assessment process similar to
2 that used to do safety assessments in the area of
3 environmental and residue. For example, we could look at
4 the level of resistance development seen in the pre-approval
5 study and compare that to a threshold level in order to make
6 a prediction of safety. The threshold level then would
7 represent the level of resistance that causes an adverse
8 public health outcome.

9 [Slide]

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

14 The framework document lays out an approach for
15 when we would look at the studies to address these different
16 areas and, as I have just talked about, one way of trying to
17 do predictions in this area would be to apply the safety
18 assessment procedures used in other areas, to make a
19 modification of that to look at the public health and help
20 ensure product safety.

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

23 DR. O'BRIEN: I would just make one comment. One
24 difficulty with this general type of study is that if one
25 looks back at the antimicrobial agents that did cause

1 selective overgrowth of resistant bacteria that came over
2 the years to cause this problem, for almost none of them
3 would it have been detected at the time when the drugs were
4 new.

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

11 So, the general problem -- and I don't know how
12 one could approach it in testing a new agent -- is that in
13 any experimental model when the agent is new the resistance
14 gene is unlikely to exist and, therefore, the new agent will
15 have no selection for resistance strains. There is nothing
16 to select. Again, I think this has to be at least
17 recognized as a general problem for new agents. And, the
18 general issue that runs throughout this is that it is hard
19 for us to know what the bacteria are going to do.

20 DR. MILLER: Yes, I don't think that pre-approval
21 studies can supplant the need for continuing monitoring, and
22 Dr. Tollefson will talk about monitoring in a minute. But I
23 do think that they can provide us some information about
24 what we should be monitoring; what indicator organisms we
25 should be looking at. And, I do think that if resistance

1 develops in a very short or relatively short time frame, I
2 would have some real concerns about recommending approval of
3 that product. So, without this type of information I can't
4 make any predictions that can help even in following this
5 along.

6 DR. STERNER: Other questions? Steve?

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

11 The environmental aspects of the approval for
12 antibiotics, the environmental safety studies that are done
13 for microbes currently address the MIC picture. Given that
14 the soil and environmental bacteria that become a component
15 of normal gut flora are exposed to a range of antibiotics
16 through urine and feces dilution in the environment, what
17 contribution to the development of drug resistance might
18 environmental bacteria be adding to the picture, and is
19 anyone examining that?

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

1 these issues, but we thought that might be the most
2 convenient way.

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

9 DR. BARKER: Just to follow up, that certainly is
10 a component of controlling your studies but I think my
11 question goes a little bit further than that about what
12 contribution this might have just to the general production
13 of resistant bacteria in the environment.

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

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

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

5 **Post-Approval Surveillance Issues**

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

10 [Slide]

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

14 [Slide]

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

23 I will describe this national antimicrobial
24 resistance monitoring system, including its strengths and
25 limitations, and then discuss why the agency is considering

1 on-farm studies to monitor antibiotic resistance for
2 Category I and some Category II drugs.

3 [Slide]

4 The program monitors changes in susceptibilities
5 to a number of antimicrobials of zoonotic enteric pathogens
6 from human and animal clinical specimens, from healthy farm
7 animals and carcasses of food-producing animals at
8 slaughter. We are currently monitoring susceptibilities to
9 17 antimicrobials among Salmonella, E. coli 057 and
10 Campylobacter. The antimicrobials are either broad-spectrum
11 or have a Gram-negative spectrum. We have recently begun a
12 pilot study of human Enterococcus isolates using a group of
13 Gram-positive drugs but have not done this for the animal
14 isolates.

15 [Slide]

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

25 [Slide]

1 The goals and objectives of the monitoring program
2 are to provide descriptive data on the extent and temporal
3 trends of antimicrobial susceptibility and enteric organisms
4 from both human and animal populations; facilitate the
5 identification of resistance in humans and animals as it
6 arises because we are interested in the emergence of
7 resistance rather than looking at the absolute prevalence of
8 resistance; provide timely information to all practitioners;
9 prolong the life span of approved drugs by promoting prudent
10 use; identify areas from our detail investigation; and guide
11 research on antibiotic resistance.

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

16 [Slide]

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

1 data to particular practices of concern.

2 [Slide]

3 Findings from the system then will often require
4 complementary sources of information or more focused
5 analytical studies to be validated. Also, selection biases
6 arise in both the human and animal populations that we are
7 testing and this can severely limit the statistical
8 inferences that can be derived from the data. For example,
9 only a percentage of humans may visit a physician when they
10 do have a foodborne disease. There are questions concerning
11 accurate diagnoses. Samples are not always taken and
12 submitted or reported. Similar problems occur with ill
13 animals.

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

22 [Slide]

23 Post-approval monitoring programs would fill many
24 of these gaps for critical drugs. FDA has proposed that
25 these studies be conducted for all Category I drugs and some

1 Category II drugs. They may be necessary for other drugs if
2 the national program, for example, or another source of
3 information found unexpected or unacceptable resistance.

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

13 We anticipate that these objectives could be
14 accomplished from a broad national on-farm program rather
15 than a drug specific study undertaken by each sponsor.
16 Also, they would need to be species specific only since many
17 drug classes could be tested on the same isolates, and many
18 pathogens could potentially be isolated from a single
19 sample.

20 [Slide]

21 In addition to other scientific data, the post-
22 approval monitoring programs could provide a critical early
23 warning system for detecting and evaluating the emergence of
24 resistance under actual use conditions. On-farm studies
25 would allow the agency and the drug sponsor to monitor for

1 established resistance and monitoring thresholds as are
2 described in the framework document.

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

12 [Slide]

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

1 now.

2 [Slide]

3 On-farm studies would provide very useful
4 information also if resistance should reach a predetermined
5 threshold. On-farm studies could conceivably identify a
6 more precise location where resistance was developing, for
7 example, in a certain geographical location for a specific
8 drug of a class, or in response to use of a particular
9 dosage form. Then, mitigation or regulatory action would
10 have to be taken only on the particular use that is causing
11 the resistance to develop.

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

19 [Slide]

20 To summarize -- and I know this is a brief
21 presentation but I will answer questions -- although the
22 national antimicrobial resistance monitoring system can
23 provide a broad overview of resistance trends for both human
24 and veterinary enteric pathogens and information on several
25 drug classes, it cannot provide demographic and drug-related

1 and non-related risk factor information on the animal side
2 of the system.

3 [Slide]

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

13 [Slide]

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

22 The advantages to having these studies instituted
23 immediately post-approval are an increased insurance that
24 resistance and monitoring thresholds will not be exceeded;
25 that data from on-farm studies will allow us to more

1 precisely determine why and how resistance is emerging; and
2 that mitigation strategies can be implemented in a timely
3 manner. The disadvantage is the cost associated with the
4 studies, potentially in situations where a problem will
5 never arise.

6 Are there questions?

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

10 DR. TOLLEFSON: The main advantage -- I would
11 consider a stockyard on-farm -- the major advantage is to
12 try to pick up the contextual information surrounding the
13 sample. In the national program when we collect the
14 slaughter isolates, for example, we get species and the
15 sample. We get a broad geographical location but nothing
16 else. So, we don't have any kind of information on the
17 sample that could rule out drug, non-drug causes to that
18 resistance development. If you have a program in place
19 where you are monitoring on-farm -- actually, the collection
20 of the sample should probably be close to slaughter because
21 we may not be interested in what happens earlier,
22 conceivably you would have at least a mechanism to collect
23 the information on the risk factors, to find out if, say, a
24 poultry house or the group of animals was treated with drugs
25 what other husbandry practices could be going on; not

1 cleaning up the farm and the environmental concerns that you
2 had mentioned in response to Dr. Miller's presentation.
3 That is what we are thinking of. We don't have any means of
4 doing that in the national program.

5 DR. STERNER: Yes, Dr. Lein?

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

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

25 The on-farm studies, as we start to look at these,

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

15 The environment changes so quickly. I was just at
16 a herd the other day doing testing, and if you look at the
17 amount of bird contamination that comes into that herd --
18 and I know as we work with the poultry industry, and this
19 would be true of any industry, the amount of rodent
20 contamination -- it is quite interesting, how that changes.
21 So, the monitoring is going to be something quite
22 interesting to look at.

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

25 DR. LEIN: Yes.

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

3 DR. STERNER: Dr. Angulo?

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

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

20 DR. HASCHEK-HOCK: I just wanted to follow up on
21 what Dr. Lein said about on-farm surveys versus
22 slaughterhouse surveys because recent studies at the
23 University of Illinois have shown that transportation
24 markedly increases shedding of Salmonella in animals that
25 were not previously shedding. There is also a study showing

1 that food withdrawal can also affect shedding. So, I think
2 that those factors are really important in this discussion.

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

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

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

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

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

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

12 **Need for Addressing Issue and Benefits of Establishing**
13 **Threshold Levels**

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

21 Antimicrobial resistance develops as a consequence
22 of antibiotic use in hospitals, in the community and on
23 farms. Although there is some overlap, the pathogens that
24 acquire resistance and are transmitted in each of these
25 settings tend to be different so that efforts to prolong the

1 useful life of antibiotics must focus on each of these
2 settings. Our focus today is on farms.

3 CDC recognizes that the use of antibiotics in
4 agriculture is important to enhance food production.
5 However, antibiotic use on farms can pose a risk to human
6 health due to development of resistant bacteria that can
7 infect humans. Resistant bacteria can be transmitted by
8 food, contact with infected or colonized animals, or
9 resistance to genes that emerge in animal strains can be
10 transferred to human pathogens. Judicious use of
11 antibiotics is, therefore, an important preventive and
12 control measure.

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

24 Much of the difficult work remains to be done as
25 specialty groups take the general principles and develop

1 specific recommendations for their members. This is a
2 pioneering and important effort, but it only applies to the
3 therapeutic use of antibiotics under the control of
4 veterinarians and, as we know, much antibiotic use on the
5 farm is neither therapeutic nor under the control of
6 veterinarians.

7 Partly to fill these gaps, and partly because
8 compliance with voluntary measures may vary, we very much
9 need a regulatory framework that ensures the availability of
10 safe and effective drugs for treatment of human disease and
11 for food production.

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

23 Now, it has been very difficult to arrive at a
24 consensus between the human and animal health communities.
25 We all pay homage to the scientific data. However, the

1 problem is that people with different perspectives interpret
2 the same body of information differently. Physicians in
3 human medicine who deal everyday with drug resistant
4 infections may not appreciate the difficult problems in food
5 animal production. People who wrestle everyday with how to
6 produce food economically may never have stood at the
7 bedside of a critically ill patient with invasive Salmonella
8 or other serious infection, hoping that the antibiotics will
9 work and having to deal with the consequences when they did
10 not work. These differences in professional experience and
11 perception inevitable affect how people interpret available
12 information on the issue. In addition, of course, some
13 people with major economic interests at stake may find it
14 difficult to adopt a position contrary to those interests,
15 no matter how much scientific data may be available and what
16 it may show.

17 So, although more scientific data may help to
18 narrow the gaps, I am starting to wonder if there will ever
19 be a true scientific consensus shared by both the animal and
20 human health communities. I am starting to think that we
21 are reaching the point of diminishing returns from expert
22 committees and scholarly reviews. It seems that if we know
23 the percentage of human versus animal health experts on a
24 particular committee, or writing a particular report, we can
25 often pretty much predict what the report will say. These

1 reports in general have not changed people's minds anyway.
2 They have been basically used by partisans of various
3 positions to wave at each other and selectively quote
4 passages from.

5 In frustration, some people on both the human and
6 the animal side have given up hopes of truly working
7 together. They have sought to impose solutions through
8 legislation or other types of congressional intervention.
9 These strategies may occasionally produce short-term
10 victories. However, these victories just galvanize the
11 opposition to fight harder, and are really not a long-term
12 strategy for the long-term goals of ensuring safe and
13 effective antibiotics for the treatment of human disease and
14 for food production.

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

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

1 outside the box for solutions.

2 I just want to reiterate that, you know, I have
3 heard people say that we need more research; if we just wait
4 for this upcoming scholarly review, then everything will
5 become clear; if we have one more meeting or blue ribbon
6 commission, that will lead to consensus. I am starting to
7 hear talk about waiting for scholarly risk assessments. You
8 know, all of these approaches do have some value, but I am
9 not sure that they are going to produce consensus at all.
10 The risk assessment scholarly reviews inevitably depend upon
11 assumptions and weighting factors, and whatever the results
12 are they are going to be challenged by the other side.

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

25 So, we are now looking at a novel FDA proposal.

1 FDA is really to be congratulated in stepping outside the
2 box to develop this proposal. This is pioneering,
3 innovative thinking. It needs tuning. It will be difficult
4 to implement, but it is a framework offering the hope of the
5 way forward. If it really works it could be offered as an
6 alternative to more draconian measures proposed or
7 undertaken in other countries. If we have a framework in
8 the United States that both the FDA and CDC state meets the
9 needs of protecting the public health, that will be a strong
10 argument in any trade dispute where public health is an
11 issue.

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

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

24 Well, if this FDA proposal fails I predict we will
25 all be back here in a few years, looking at each other, in

1 the same predicament but with a dramatically increased level
2 of bitterness as people point fingers as to why it failed.

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

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

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

1 comparison, the background rate of invasive meningococcal
2 disease in the United States is 1 case per 100,000 people
3 per year. If a population such as a school or a community
4 has an annualized rate of 30 per 100,000 in a specific time
5 period, CDC recommends mass vaccination. Sometimes in a
6 small community or college that can only amount to a few
7 cases but the idea of having this threshold saves a lot of
8 time and effort, and streamlines things and provides
9 guidance, and we have found it to be very effective.

10 Currently, for animal drug approvals the only
11 public health safeguard is the approval process itself.
12 This process can only predict what may happen after a drug
13 is marketed. After approval, if a problem develops the
14 burden is on the FDA to prove that the drug is unsafe. This
15 process can be lengthy and difficult and meanwhile the
16 consequences mount. Therefore, the FDA needs to be cautious
17 in approving new animal antibiotics. If resistance
18 thresholds were established prior to approval in sentinel
19 organisms, for example Salmonella, and if rates exceeding
20 these thresholds more or less automatically resulted in
21 corrective actions, including ultimately withdrawing the
22 approval, CDC would be less concerned about seeing certain
23 antimicrobials approved for food animal use. The AVMA
24 prudent use guidelines would be an essential component part
25 of this framework, providing guidance for veterinarians to

1 use the antibiotics in a way to minimize the likelihood of
2 crossing the thresholds.

3 Prestablished thresholds are important to focus
4 preventive efforts and to allow prompt mitigation of hazards
5 if the thresholds are exceeded, that is, without an extended
6 period of discussion while resistance rates continue to rise
7 and the antibiotic becomes progressively less effective.

8 Monitoring thresholds should also be applied to
9 certain currently approved antibiotics, regardless of
10 whether they may be therapeutic or subtherapeutic, with
11 threshold levels requiring corrective action determined by
12 increases in resistance rates for sentinel organisms. The
13 thresholds must be scientifically based and determined on a
14 drug by drug basis.

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

19 Since CDC is primarily concerned with human
20 disease, we are most concerned about resistance in human
21 isolates. We would advocate that thresholds based on
22 resistance data from human strains derived from animals be a
23 major determinant of regulatory action. For example, CDC
24 estimates about 2,500 cases per year of invasive Salmonella
25 infections in the United States. At the present time,

1 fluoroquinolones are often the drug of choice for invasive
2 Salmonella infections. If the rate of fluoroquinolone
3 resistance in invasive Salmonella from humans rises to 1
4 percent that will place about 25 patients per year at risk.
5 Treatment failures will be expected. A resistance rate at
6 that level would be of great concern, particularly if the
7 trend was upward. These isolates would be from patients who
8 are not travelers, without pets, not taking antibiotics, and
9 there really wasn't much reason that they could have
10 developed this other than from food animal origin in the
11 U.S.

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

20 In closing, I just want to reiterate one more time
21 the importance of taking the framework proposed by the FDA,
22 making constructive suggestions to improve it and then
23 really rolling up our sleeves to work together to make it
24 work. Thank you.

25 DR. STERNER: Thank you, David. I will

1 editorialize for just a moment. I hope that panel members
2 were listening very carefully to a very astute insight into
3 the people and politics of what is really a very divisive
4 issue within the professions. Thank you. That was really
5 remarkable, David.

6 Are there questions for Dr. Bell from the panel?

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

11 DR. BELL: Human isolates.

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

18 DR. BELL: I think my colleague, Dr. Angulo, could
19 speak to the scientific data issues with a greater depth of
20 expertise than I could. We believe that the great majority
21 of Salmonella cases in humans in the United States are
22 attributable to Salmonella derived from food animals.
23 Taking a level of resistance in animals and predicting what
24 would be the human level of resistance, and how to model
25 that, I think might be difficult. But if we start --

1 perhaps not start, if we use as a major determinant the
2 threshold of Salmonella resistance in human cases-- and
3 these human cases would not have pets, or have traveled, or
4 have any other realistic explanation -- we could be
5 confident in attributing that this was resistance resulting
6 from drug use on the farm. I don't know if Fred wants to
7 add to that.

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

17 It is true that we cannot say with certainty with
18 a single case where the resistant infection that that person
19 got came from, but when you use epidemiology and look at a
20 population basis, we can say with extreme confidence that
21 the dominant factor contributing to antimicrobial resistance
22 in foodborne pathogens is use of antimicrobials in food
23 animals. That is an important background statement. It is
24 actually not one of the discussion points of this committee
25 but it is an important epidemiological certainty.

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

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

17 DR. STERNER: Dr. Galbraith?

18 DR. GALBRAITH: David, given some of the
19 regulatory traditions of the federal government, I am
20 curious what you would say about the justification for human
21 indicators and thresholds as opposed to a more conservative
22 approach.

23 DR. BELL: I am not sure I understand the
24 question. What would be the more conservative approach? I
25 apologize, I just don't -- in the background of regulatory

1 tradition, I am not sure what you mean by that.

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

7 DR. BELL: Well, I am not knowledgeable about
8 regulation of pesticides. I think one of the problems that
9 we face here is that we need antibiotics in animals. When
10 antibiotics are approved for use in animals we can't really
11 predict what level of resistance will result; how soon it
12 will result. I support Dr. O'Brien's comments in that
13 regard. So, we would be willing to take a chance, if you
14 will, recognizing the legitimate needs of antibiotics on the
15 farm, as long as there was a good surveillance system that
16 picked up the first signs of adverse human consequences and
17 there was a system already in place to mitigate the hazard.
18 Otherwise, I don't see any other way out of these endless
19 arguments of what would the risk be from approving a drug to
20 be used on the farm. We can't predict it. There is a fair
21 amount of data based on studies in laboratory animals
22 indicating at what level a chemical in the environment would
23 pose a hazard, and so we don't need the human cases to
24 develop; we can monitor the level of chemical in the
25 environment. But in this kind of situation I think it is

1 different.

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

9 **Risk Assessment**

10 DR. MCEWEN: Well, I certainly hope so. While we
11 are getting to the slides, I would just like to echo the
12 Chair's comments. We really have heard a lot of references
13 to risk assessment this morning. Dr. Friedman talked about
14 the need for balance and making decisions in the face of
15 uncertainty; that it is a prescription for formal risk
16 assessment to do that sort of thing. Dr. Lurie talked about
17 risk assessment being an imperfect science. I think that is
18 something we have to work on. Dr. Sundlof talked about the
19 complexity of this issue of antimicrobial use in animals,
20 and simple answers don't seem to work anymore, and I think
21 that is a compelling for risk assessment. Dr. Miller talked
22 about the possibility of using a risk assessment approach to
23 achieve the goals of the framework document, and I would
24 like to echo that. Dr. Tollefson referred to some issues
25 that I would fully endorse, and am excited about, in terms

1 of the post-approval monitoring that could provide data to
2 use in risk assessments. Of course, Dr. Bell set the stage
3 up very well in describing some of the problems we have had
4 with risk assessments in other areas where they have been
5 used perhaps to obfuscate problems or issues of delay
6 processes. I think we don't want to see that but there are
7 other aspects of risk assessment that can be quite useful.
8 So, with that kind of introduction, if I could have the
9 first slide, please?

10 [Slide]

11 I hope you can read that at the back. As a
12 researcher in the area of epidemiology of food safety issues
13 on the farm, as I teach veterinary students in public
14 health, I have been interested in risk assessment for a
15 number of years. And, I should thank you very much as a
16 Canadian for having me down here to talk about this topic.
17 I feel a little bit awkward in a sense engaging in
18 discussions that have to do with U.S. policy, but I hope you
19 will understand, and I will try not to step out of bounds.

20 [Slide]

21 This is a little outline of the talk, basically a
22 brief background on risk assessment. I know a lot of people
23 here know a lot more about risk assessment than I do,
24 especially folk on the chemical side of things but I will
25 just touch on a few sort of salient points. I will talk

1 about the needs and possible uses for it on farms. I think
2 that is a very germane issue to today's topic; then a little
3 bit about some general model structures, what is being used
4 on the microbial side in other fields which I think also is
5 relevant. And, I will touch on some data needs.

6 [Slide]

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

11 The history of this -- the U.S. has made very
12 major contributions to the whole field of risk assessment.
13 As everybody knows, part of the total risk analysis
14 packaging includes risk management and risk communication,
15 and I won't touch on those topics today. I like to think of
16 the beginning, starting with the issue of trying to assess,
17 as was just mentioned a few minutes ago, the risks from
18 contaminants in the environment, emissions, pollutants and
19 other things of that nature where, because of the nature of
20 the problems these hazards might cause, we don't have actual
21 counts of human disease. So, there needs to be a surrogate
22 way of looking at it. So, the EOA, as I understand the
23 literature, has provided a lot of background there.

24 We also know that it has been used to assess risk
25 for food additives, especially veterinary drugs in today's

1 context. It is used in the engineering field to look at
2 safety of public facilities. On the animal health side of
3 things, risk assessment is being embraced more fully in the
4 way of addressing the hazards that may be associated with
5 importation of animals from other countries. Importantly,
6 in the upper right-hand corner is the sort of recent
7 burgeoning of information having to do with microbial food
8 safety and risk assessment, and I will touch on that in
9 greater depth.

10 [Slide]

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

21 [Slide]

22 The one sort important follow-up and, again, this
23 slide isn't going to show up very well, is that this
24 document used a risk model. A lot of people have referred
25 to that. The point I am trying to make here is that there

1 is a variety of ways of conducting developing risk models.
2 This one was based pretty much on CDC type data where you
3 have information on outbreaks of Salmonella, and that sort
4 of thing, and they used a sort of default approach to try to
5 portion out the number of cases that may happen as a result
6 of drug-resistant salmonellosis that could happen as a
7 result of use of these drugs in food animals.

8 The type of risk assessment model I would propose
9 is different than this. This would be a vehicle for
10 validation. It would be useful for other purposes. It
11 underpins the type of estimates that Dr. Bell referred to a
12 few minutes ago. Estimated 2,500 cases per year would be
13 developed through this type of modeling approach. The type
14 that I would foresee or others have suggested would be quite
15 different.

16 [Slide]

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

25 The book on the far right, and again you can't

1 read the title, is called The Red Book. It laid out for
2 readers like me in other countries, and everybody else, the
3 basics or concepts for risk assessment. The other books
4 sort of grew out of that.

5 [Slide]

6 This sort of outlines what I would call the NRC
7 model for risk assessment. There are four basic levels:
8 hazard identification, to which Dr. Sundlof referred, is on
9 the left; dose response assessment or hazard
10 characterization; exposure assessment and risk
11 characterization, the sort of classic setup, and that is
12 what I think would be sort of useful here.

13 [Slide]

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

19 One of the issues around the role of risk
20 assessment and food safety, food microbiology is that we
21 have known for a long time that end-product testing is
22 really not the answer to try to solve the problems, and we
23 have to engage more in process control. That is where the
24 HACCP program has come in. One of the problems with
25 developing that sort of program is that we don't really have