

1 continuing it to a logical workable endpoint.

2 If the objective is food safety, then, let's
3 develop a process that will change the framework to meet
4 these needs. As Dr. Bell said, we need to think outside the
5 box and change the proposal, so that it can work. If the
6 agency understands what they are proposing, then, they are
7 intending to eliminate the use of antimicrobials in food
8 producing animals.

9 It is our contention that this will actually have
10 the opposite effect on both our animal welfare, the
11 environment, and food safety than what we actually are
12 intending for this.

13 What do I mean by that? We will not be able to
14 quickly and effectively address animal disease, and there
15 will be more manure produced, and alternatives like heavy
16 metal feed additives that will contaminate the environment.

17 The framework will eventually increase food safety
18 risks because of our loss of ability to effectively treat
19 disease. The agency has repeatedly and publicly said that
20 one of the best ways to ensure food safety is to ensure the
21 availability of a variety of effective products. We agree
22 with this position. Has the agency changes its position?

23 We believe that eliminating or limiting product
24 availability will increase resistance, not decrease it,
25 because we will be forced to rely on, at best, a very

1 limited, narrow supply of products.

2 Finally, all of these factors will have an effect
3 on the ability of our pork producers to make a living and
4 stay in business. If these outcomes are not the agency's
5 intent, then, it should reevaluate the framework. Input
6 from all stakeholders is needed to do the job right.

7 The VFD process set a precedence for cooperative
8 effort that led to reasonable outcome in which all
9 stakeholders could claim some ownership. This was a
10 successful example of Dr. Bell's outside-the-box thinking.
11 It was said then that the VFD process was a model for a new
12 FDA paradigm, listening to stakeholder input.

13 The agency worked with its constituents openly and
14 cooperatively, and this is what we need in this case.
15 Points that we need to consider include strengthening the
16 monitoring program. We support a scientifically defensible
17 NARMS program.

18 One possibility that NARMS is planning is to take
19 more samples in the packing plants and monitoring that
20 pathogen resistance. This could make the program similar to
21 the residue monitoring program including adequate and
22 anonyne safeguards.

23 There are other possibilities also and they should
24 be carefully considered. We need to have reasonable
25 discussions about the alternatives. The point is to

1 dedicate the money and resources available to make a NARMS
2 program that is statistically significant and meaningful.

3 We think that the AHI proposal of advisory panels
4 is sound. This would give stakeholder input and ownership
5 of the process. Then, we could use that data to design
6 focused studies to help the advisory panel and the agency.

7 Why is there so much concern about the framework?
8 The second footnote in the introduction says that after
9 evaluating input on the framework, the agency will take
10 appropriate procedural steps to develop and implement any
11 resulting policies.

12 It assumes that the framework is the correct
13 approach. It doesn't acknowledge that the agency could
14 review the proposal and decide whether it is appropriate as
15 it is, whether it should be amended, or whether it should be
16 completely reworked.

17 It says the agency will take appropriate
18 procedural steps to develop and implement policy. The
19 footnote says the agency is interested in stakeholder input,
20 but it does not suggest that it will listen to or act upon
21 that input, and the language of the document is all that we
22 have to go on.

23 We, as pork producers, do not want to be
24 obstructionists to developments of food safety, and we have
25 a very good history to show that we are not obstructionists.

1 A few of those examples are we have actively
2 participated in the national and international discussions
3 and the development of the AVMA's judicious use principles.
4 We have committed our own producer checkoff money to funding
5 research.

6 Last summer alone, we awarded over \$200,000 to
7 antimicrobial research. I earlier mentioned our extensive
8 pre-harvest food safety research. This is a lot of producer
9 dollars going into research for both antimicrobial
10 resistance and pre-harvest food safety.

11 We have formed a pharmaceuticals issues task force
12 with the AASP. The intent is to examine the science of
13 resistance and how it affects the pork industry and human
14 health. We haven't accepted poor quality assurance program
15 that is used by the industry. Over 40,000 producers have
16 gone through the program. Major packers are not asking for
17 this, but now are requiring producers to be at PQA level 3.

18 We are preparing a revision that will include
19 judicious use and resistance information. I am very pleased
20 to report that our PQA program is working. Education works
21 with our producers. The evidence is in the decreased
22 residue incidence since the PQA's inception. Our producers
23 are voluntarily being involved in this program and getting a
24 lot of good out of it, and producing a safer product because
25 of it.

1 There is a necessary caution and deliberation
2 because our constituents' livelihood depends on the outcome
3 of this issue. We are talking about real life people who
4 are doing their absolute very best to provide the safest
5 product possible to you.

6 Multiple scientific bodies have said that there is
7 a need to gather more information to make an informed
8 decision, and that this is not an imminent hazard.

9 As the chairperson of the Pork Safety Committee
10 and a member of the NPPC board of directors, I have to go
11 back and give the producers the scientific justification for
12 spending their tax dollars on this program, and right now I
13 don't have that information.

14 We have been trying to help gather the needed food
15 safety information. We owe to our constituents the
16 consideration of risk assessment for risk management.

17 Again, I would like to thank you for the
18 opportunity to give the pork producers' view on the
19 framework, and I offer our help and resources in working
20 with the agency and the other stakeholders towards
21 developing a doable, reasonable system that we can all
22 consider successful.

23 Thank you.

24 DR. STERNER: Are there questions from panel
25 members for Ms. Determan?

1 [No response.]

2 DR. STERNER: Thank you very much.

3 Perhaps our next speaker will avail himself of the
4 answer to the question that I posed to the AHI people with
5 regard to the risk assessment report. Dr. Lester Crawford
6 goes back with CVM many years as a former director, in fact,
7 I think he is responsible for the name Center of Veterinary
8 Medicine, if my memory serves me correctly.

9 Dr. Crawford.

10 **Dr. Lester Crawford**

11 DR. CRAWFORD: Plead guilty to all that.

12 With respect to funding, our university and our
13 center are underwritten by industry, government, and also
14 foundations, and the study that I will mention is
15 underwritten by the Animal Health Institute.

16 I appreciate the opportunity to be here and also
17 would like to congratulate the agency for conducting this
18 hearing and also to responding to the current concern about
19 antibiotic resistance.

20 I would like to begin by talking a little bit
21 about my personal involvement over the years with risk
22 assessment on products like this. The question was earlier
23 posed what would risk assessment do for us, and are there
24 any regulatory issues that have been adjudicated or
25 addressed by risk assessment.

1 In fact, of course, there are. When I was with
2 the agency, starting in the middle seventies, and then off
3 and on for some years, we did risk assessments on
4 diethylstilbestrol, which eventually came off the market as
5 the result of a fairly comprehensive look, and also
6 nitrofurans, which came off the market after an 8,400 page
7 outlook.

8 Those were then the subject of special studies by
9 the National Academy of Sciences, as previously mentioned,
10 and an engaging series of consultations, many conferences,
11 and also a pamphlet, the risk assessment with respect to
12 regulatory responses was memorialized by the Academy in a
13 series of publications using those two and two more that
14 were done in other parts of the government as examples of
15 what was to come.

16 The Deputy Associate Commissioner for Scientific
17 Affairs in FDA, Dr. Joe Rodericks, was the author of many of
18 those papers and also co-chairman of the NAS study.

19 Following that, there were some more Academy looks
20 at risk assessment, and as many of you in the room know, out
21 of that grew HACCP, which is considered on-the-farm or in-
22 the-plant risk assessment, and certainly regulatory
23 decisions are made by that always.

24 And then in 1988, both FDA and USDA exceeded and
25 funded an external risk assessment which involved a number

1 of agencies and also some universities and others of
2 *Listeria monocytogenes*, which formed the basis of the
3 current policy, which is still being employed.

4 The risk assessment that we are doing, we start
5 out, as you do in all risk assessments, and as all of you
6 know, we create a fence around the problem, and with ever
7 narrowing concentric circles we tried to get to a doable
8 assessment that still will have sufficient validity and
9 breadth to add some light to the issue.

10 In our case, after starting out fairly broad, and
11 with the impaneling of an advisory committee, some of whom
12 are here in the room, we narrowed our study down to
13 fluoroquinolones as they are used in beef cattle.

14 It happened that during the time we were putting
15 the early analyses together, that one of those compounds was
16 approved for use in beef cattle in the United States. It
17 was a watershed event as far as public health mensuration is
18 concerned because there was no fluoroquinolone used in beef
19 cattle prior to that time, and then from that point there
20 was. So, it lent itself very well to what we were doing.

21 Then, we started looking for target organisms to
22 assess, and after some fits and starts we narrowed down
23 *Campylobacter jejuni* and also *Salmonella typhimurium*,
24 Definitive Type 104.

25 Our look at the literature has revealed that we do

1 have sufficient information upon which to conduct these risk
2 assessments. The first study is out to the internal review
3 committee, and will be submitted for publication shortly.
4 It comprises an analysis of the effects on Campylobacter.
5 The second will be the Salmonella study. The first one
6 should be published by late spring or early summer, the
7 second one by early fall or late fall.

8 As to what they will say at this point, obviously,
9 it is premature. I would mention, though, that just this
10 past week, I visited colleagues who are doing a broader
11 study in the United Kingdom, at the Central Veterinary
12 Laboratory at Weybridge, where they have considerable risk
13 assessment expertise, and we are going team with them in
14 terms of trying to provide them with what we have and also
15 hopefully learn from the study that they are doing.

16 As you know, risk assessment is an ever-changing
17 field. The question is are your assumptions sufficient and
18 valid, and also, on a topic like this, you know, how fast
19 can you complete it.

20 A risk assessment in a field like this, that takes
21 three years, it is probably excessive. We are mindful of
22 that, and we hope to accomplish what we are doing in a year
23 and a half or, in other words, about another six to nine
24 months, but that is certainly using all the resources that
25 you have, and also you have to, in our case, avail

1 yourselves of outside consultation and also professional
2 risk assessment groups, which we are and have done. So,
3 more to come in that respect.

4 Also, here, there has been some conversation about
5 when will it be done and why should we wait for it, and what
6 is the necessity of waiting, and so forth, and since FDA
7 first started trying to regulate these issues in the
8 seventies, and particularly when I was on board in '75, '76
9 and then again in '78 through '80, things changed.

10 Diane Fagerberg talked about her excellent study
11 and some of the conclusions that she came up with.
12 Incidentally, Diane, with respect to your slides, I was around
13 when those were first shown. I hope I haven't faded as much
14 as your slides have, with all due respect.

15 So, I don't think we are in a position to tell
16 anyone, certainly no regulatory agency, to wait until we
17 finish our study. That is not our position at all. As you
18 know, there are key meetings that are coming up. The World
19 Health Organization is having one March 15 through 19 on the
20 transmission of resistance through food, not on their
21 veterinary public health side, but on their food safety
22 side.

23 Also, OIE, the international veterinary parliament
24 is having a similar meeting a few days later. So, those I
25 think would be worth incorporating, but we are not standing

1 as a barricade the you and your deliberations. I think you
2 have plenty to do without that.

3 Thank you.

4 DR. STERNER: Questions from the panel for Dr.
5 Crawford? Yes, Linda.

6 DR. TOLLEFSON: Lester, can I just a question for
7 clarification? The Georgetown risk assessment is looking at
8 use of fluoroquinolones in feed lot cattle?

9 DR. CRAWFORD: Yes.

10 DR. TOLLEFSON: Is that all you are going to look
11 at?

12 DR. CRAWFORD: Yes, precisely.

13 DR. TOLLEFSON: Thank you.

14 DR CRAWFORD: We don't believe in extra-label
15 uses, so that is what we are confining ourselves to. I
16 don't know where that term ever came from anyway.

17 DR. STERNER: Other questions for Dr. Crawford?

18 [No response.]

19 DR. STERNER: Moving on then, Joel Brandenberger
20 is from the Coalition for Animal Health, and he is allotted
21 10 minutes.

22 **Joel Brandenberger**

23 MR. BRANDENBERGER: Thank you all very much. I
24 know it is late in the day, so I thought I would come talk
25 to you all about something you haven't heard about to this

1 point, risk assessment.

2 My name is Joel Brandenberger, and I am speaking
3 here today on behalf of the Coalition for Animal Health.
4 The Coalition is comprised of more than a dozen
5 organizations. We represent every major livestock and
6 poultry association in the U.S., as well as the commercial
7 feed industry, veterinarians, and animal pharmaceutical
8 companies.

9 We were formed in the mid-1990s to promote public
10 policies that ensure the availability of the widest possible
11 variety of safe and effective animal drugs to help treat
12 those animals in our members' care.

13 We have worked with FDA on several issues in the
14 past, but most notably a few years back to reach consensus
15 on the Animal Drug Availability Act of '96. That effort
16 remains a model of how stakeholders and CVM can work
17 together to address complex and difficult issues, and we
18 hope that maybe we can enjoy the same cooperation as we
19 address the antimicrobial resistance issue that is before us
20 today.

21 The Coalition, first of all, wants to commend CVM
22 for bringing the committee together to discuss the
23 scientific evidence regarding the use of antibiotics in food
24 producing animals and antimicrobial resistance.

25 It is a complex issue, one that deserves the

1 committee's attention, and the Coalition is pleased to be
2 able to comment on the proposed framework.

3 A lot of the Coalition members have been here
4 today or will be here later offering individual
5 presentations. These remarks that I am making are designed
6 strictly to highlight our areas of common concern and
7 interest.

8 The Coalition members share FDA's and the public
9 health community's concern about antibiotic resistance
10 whether in humans or animals. The safety of the food supply
11 is of the utmost importance the all of us, and as is the
12 continued effectiveness of antibiotics.

13 We hope to continue working with FDA and all
14 relevant government agencies to ensure we are providing the
15 safest possible products to our consumers while minimizing
16 the incidence of illness and other suffering and farm
17 animals.

18 Our policy toward the framework needs to be clear.
19 The Coalition for Animal Health will find it difficult to
20 support any change in the policy for approving antibiotics
21 in food producing animals if that change is not preceded by
22 a comprehensive assessment of the actual risk posed by
23 antibiotic use in farm animals or the risk of resistant
24 bacteria in those animals.

25 This position should not be misinterpreted as

1 indifference on the part of the Coalition toward the
2 antimicrobial resistance issue or unwillingness to work with
3 FDA toward policy change. The Coalition shares the goal FDA
4 stated in the recently released framework document. We are
5 absolutely committed to protecting the public health and to
6 ensuring the use of antimicrobial drugs in food producing
7 animals does not result in adverse health consequences to
8 humans.

9 We also are pleased that FDA agrees with the
10 Coalition that the use of antimicrobial drugs in food
11 producing animals is important to promoting animal health
12 and providing an abundant and affordable supply of meat,
13 milk, and eggs.

14 Coalition members also would agree that this is an
15 appropriate time to examine the antimicrobial resistance
16 issue in further detail and to contemplate potential changes
17 in the FDA approval policy for antibiotics.

18 We understand the seriousness of the issue, as
19 well as the need to develop appropriate measures both to
20 protect the use of antibiotics in humans and minimize the
21 negative consequences to animals and the food supply.

22 There is no doubt bacteria can develop resistance
23 to some antibiotics whether they are used in humans or
24 animals or both. However, the likelihood and extent to
25 which antibiotic resistance occurs in the farm setting and

1 is then transferred to humans has been neither adequately
2 assessed nor established, and that is the crux of the
3 Coalition's concern.

4 Neither FDA nor any credible scientific
5 organization has conducted a comprehensive risk assessment
6 with regard to this issue. We don't see how FDA or any
7 other agency for that matter can look at data and studies
8 that are incomplete or contradictory and come to the
9 conclusion that the recommendations in the proposed
10 framework represent the best possible public policy solution
11 to the danger of antimicrobial resistance.

12 FDA cannot give in to the temptation to regulate
13 based on scare headlines and studies that have yet to stand
14 the test of peer review.

15 We would remind everyone here that three recent
16 reports from the National Research Council, the Institute of
17 Medicine, and the World Health Organization do not come to
18 the same conclusion that FDA did in this proposed framework
19 document. All agree that there is cause for closer
20 scrutiny, but all recommend additional data to determine the
21 appropriate course of action.

22 Indeed, the 1998 NRC report on "The Use of Drugs
23 in Food Animals: Benefits and Risks" acknowledges the
24 possible link between antibiotic use in farm animals and the
25 development of bacterial resistance in humans, but the

1 report says, "Information gaps hinder the decisionmaking
2 process for regulatory approval and antibiotic use in food
3 animals. A data-driven scientific consensus on the human
4 health risk posed by antibiotic use in food animals is
5 lacking."

6 According to the NRC, "Until more accurate data on
7 antibiotic use, patterns and rates of resistance transferred
8 to human, occurrence of actual disease emergence, and
9 mechanism of resistance are available, actions aimed at
10 regulation antibiotics cannot be implemented through a
11 science-driven and well validated and justified process."

12 Let's put it simply. Really, what we are saying
13 here, if we are only contributing 10 percent to the
14 resistance problem, we don't want 75 percent of the solution
15 put on our backs. That is really our bottom line.

16 Dr. Crawford just talked about the study that
17 Georgetown University, Center for Food and Nutrition Policy
18 is conducting, and we think this is a model and a step in
19 the right direction to determine the actual risk and
20 subsequently develop an appropriate plan of action.

21 I think it is important to look just real briefly
22 at what we don't know here. While some animals
23 unquestionably carry resistant bacteria, we have very
24 limited information about how many animals with such
25 bacteria ever make it to the processing plant.

1 We have no clear idea how much resistant bacteria
2 actually survives all the critical control points in modern
3 food processing and packaging and we have very little data
4 about how much of that bacteria survives because of
5 mishandling or undercooking of meat and poultry products by
6 the end consumer.

7 While science is still trying to determine how
8 many people actually get sick each year from food-borne
9 illness, we do know that to date no death from food-borne
10 illness ever has been connected to a resistant bacteria
11 derived from the use of antibiotics in animals.

12 Given this dearth of information, how can we be
13 sure the policies in the proposed framework actually will
14 reduce the incidence of antimicrobial resistance?

15 What is far more certain, unfortunately, is that
16 these policies will reduce the availability of
17 antimicrobials to food animal producers, and we have got to
18 remember that there also is a risk associated with narrowing
19 the spectrum of available antibiotics.

20 I saw an article recently where Dr. Mitchell Cohen
21 from CDC was quoted as saying one of the reasons why we saw
22 antibiotic resistance rise in recent years is because of the
23 lack of antibiotic development on the human side in the
24 1980s, and that doctors now have fewer alternative available
25 to counter drug resistant infections.

1 So, my question here is what do we think is going
2 to happen if livestock and poultry producers have fewer and
3 fewer and antibiotics to utilize and drug companies find the
4 regulatory cost of bringing new antibiotics to market
5 prohibitive. We are going to have the same problem begin to
6 develop on the animal side.

7 But -- and I think this is the important thing
8 here -- the Coalition understands it isn't enough just to
9 come to you all and say do a risk assessment. You have been
10 hearing that all day, and you are probably going to hear it
11 more before you are done.

12 So, what we want to promise is that we will work
13 tirelessly with FDA, everybody in the Coalition, to develop
14 an affordable risk assessment plan that provides -- and this
15 is the important part -- in the shortest time frame possible
16 all the data needed to make science-based policy changes,
17 and we will go one better than that, too. When a consensus
18 analysis of that data is complete, you have got our pledge
19 to work with the agency to make all changes dictated by the
20 risk assessment.

21 I am going to talk real briefly about some of the
22 specific concerns we have in the proposal because we do find
23 it troubling that the framework appears maybe to ignore some
24 proactive steps that are being taken right now by
25 stakeholders in this process.

1 On the meat and poultry processing industry side
2 where I come from, for example, we are in the midst of a
3 significant effort to control pathogens in food supply. We
4 are in the middle of implementing the new HACCP inspection
5 system in the plants, and we think that will minimize
6 exposure to food-borne pathogens.

7 In addition, other steps are being taken including
8 steam pasteurization and educational campaigns to reduce the
9 incidence of food-borne illness, all of which must be taken
10 into consideration in a risk assessment.

11 We are also troubled that the framework doesn't
12 seem to really fully recognize or consider the efforts that
13 are underway by the nation's producers and veterinarians to
14 develop judicious use principles for industry.

15 The first phase of that is already through. The
16 next phase is scheduled to move forward very quickly. I
17 think AVMA has done an outstanding job of leading that
18 effort.

19 We are a little perplexed, I guess would be the
20 best way to put it, that instead of working with producers
21 and the industry to ensure these principles properly address
22 the issue and are fully implemented out there, less than
23 eight months into sending us off on that quest, we have
24 suddenly got this major change in the regulatory approval
25 process before us, and that confuses us maybe even a little

1 more because the educational approach is not only considered
2 acceptable, but is being emphasized in human medicine.

3 Animal and human medicine are different, we
4 understand that, but there are similarities, and the animal
5 and human medical approaches right now do not appear very
6 consistent.

7 DR. STERNER: Joel, your time has expired.

8 MR. BRANDENBERGER: Okay. Fair enough. Thank you
9 very much for the time and for the opportunity. I would be
10 happy to answer any questions.

11 DR. STERNER: Dr. Bell, I have not made this
12 exception for anybody else. I regret, you will have the
13 opportunity if Joel is here in the morning, to press your
14 question.

15 MR. BRANDENBERGER: I may not be here in the
16 morning, so I will be around for a while this evening.

17 DR. STERNER: Our next scheduled speaker is Clyde
18 Thornsberry from MRL Pharmaceutical Services. He has 15
19 minutes scheduled to him.

20 Clyde.

21 **Dr. Clyde Thornsberry**

22 DR. THORNSBERRY: I promise to give you back some
23 of those minutes.

24 Let me say first that MRL doesn't have anything to
25 do with residue levels.

1 DR. STERNER: Could you give us your affiliation
2 or your disclaimer first?

3 DR. THORNSBERRY: Yes, I am about to. My name is
4 Clyde Thornsberry. I work for MRL Pharmaceutical Services.
5 Fortunately, we have lots of contracts with most of the
6 pharmaceutical companies that make antibiotics for animal
7 health service, and fortunate I say because they can pay for
8 me to come here and do this.

9 Before I go on to what I really came to talk
10 about, I want to say to David Bell that the first half of
11 your talk was the most remarkable talk, and it's about time
12 someone said what you said.

13 I totally agree with you. I don't think that any
14 scientific or nonscientific studies are likely to change the
15 status quo. We do, because this is totally a political
16 process, and, in fact, I thought that is why Monica was
17 here, but it is a political process, and I agree with you
18 there has to be bridges built and spanned, but -- you may
19 not like this one -- I would suggest to you that CDC build
20 some bridges, because if you ask a lot of these people
21 around here, CDC is the biggest bully on the block. But I
22 totally agree with you, and thank you for saying that.

23 The other, to take that a little bit further, I
24 might even go further than David and say to the FDA get rid
25 of every one of your consultants, put your program into

1 action because if it's untenable, you will hear about it,
2 because some congressional aide will be sitting on your
3 desk, because one of the things that FDA does is they are
4 always responsible to somebody, very unlike most of the
5 other government organizations that we know about.

6 But anyway, that is not why I came. I want to
7 thank you for letting me address the committee and the rest
8 of you, and as some of you know anyway, my group and I have
9 been interested in surveillance of antimicrobial resistance
10 for a long time wherever it is, whether it's human or
11 whether it is an animal population, and that is my main
12 reason for being here.

13 Upon reading the framework document, I certainly
14 wish to compliment the FDA for recognizing that surveillance
15 of resistance is the basis for most any actions that you
16 would ask for or objectives that you would intend to reach.

17 If I understand the document correctly, the major
18 steps which you wish to take, is to determine how many drug
19 resistant enteric bacteria exist and the effect of changes
20 in pathogen load on the host.

21 I suspect the first one could be done, I think
22 that the second one might be more difficult, but I think
23 that if you read the document, you come to the ready
24 conclusion that this is a microbiological problem.

25 I thought it was very interesting as I looked

1 around this table, I see only two card-carrying
2 microbiologists, and if the rest of you are, forgive me, but
3 I only know two of you that are, and I think this is a
4 microbiological problem, and I think one of the ways that
5 this must be approached is from a microbiological viewpoint.

6 I also wish to compliment the FDA and their sister
7 organizations for promulgating the NARMS program as a
8 sentinel surveillance system in animal health, but even as I
9 applaud you, however, I do not believe that you have
10 developed an ideal or an adequate program.

11 Before I express my reservations and concerns, let
12 me elucidate a bit on items which are discussed or alluded
13 to in the framework document.

14 First, in the document, there are many references
15 to inducing antimicrobial resistance. Although this is
16 correctly explained in some areas of the document, I believe
17 that the naked references to inducing resistance could
18 create some false impressions.

19 Antibiotics do not cause resistance, but rather
20 select for resistant mutants as indicated. I think this is
21 a fundamental principle that must be remembered.

22 Second, let's discuss a bit about the factors that
23 influence the number of drug resistant strains that we find
24 in a host or in an institution, and I should say that those
25 of you who know me, also know that I am a human

1 microbiologist, not an animal microbiologist, so much of
2 what I have reference to will be in humans.

3 Let me mention four things that I think have to do
4 with the number of resistant strains. The first is that
5 obviously, we have resistant mutants and have created a
6 selective pressure with a drug to which the mutant is
7 resistant.

8 The second effect of infection is the effect of
9 infection control. Now, obviously, that is a human term,
10 but I think it can be transferred to the animal health
11 system, and horizontal transfer -- and both of those have
12 been talked about today -- I want to talk about horizontal
13 transfer in terms of patient to patient, and not bug to bug,
14 and it is probably certainly better understood in humans
15 than in animal environments, but there are many, many cases
16 in many hospitals in the United States where the resistant
17 rate for a bug and a drug far exceeds 50 percent, yet, the
18 national prevalence of resistance is less than 10 percent.

19 It is easy to blame this on antimicrobial abuse,
20 but in reality, in most cases it is the failure of the
21 infection control programs to control spread of any
22 infections.

23 The third factor that affect the number of
24 resistant strains, and probably the least understood
25 although it has been mentioned several times here today and

1 was talked about by Linda to some degree this morning, it
2 involves the number of drugs to which a strain is resistant.

3 This can be best demonstrated with methicillin-
4 resistant staphylococci. As you know, MRSA are resistant to
5 almost every drug except vancomycin. As a result, every
6 drug is a selective agent for itself and for every other
7 drug except vancomycin. It does not have to be
8 Ciprofloxacin that selects for resistance to Ciprofloxacin,
9 it can be penicillin, it can be a cephalosporin, it can be a
10 tetracycline. It can be any of this list of 40 or 45 drugs.

11 Today, in the U.S. human hospital population, MRSA
12 population, 80 percent will be resistant to
13 fluoroquinolones, but if you look at the methicillin
14 susceptible population, or that is, MSSA, less than 50
15 percent are resistant to fluoroquinolones.

16 This is because the MSA strains, the only
17 selective agents are probably fluoroquinolones and a
18 penicillin. A similar but less severe situation exists with
19 *S. typhimurium* DT104, but not to the level seen with the
20 MRSA, because in DT104, if you get fluoroquinolone
21 resistant, the fluoroquinolone will be no more selective
22 than the other four or five drugs that it is resistant to.

23 So, if you are talking about getting rid of one of
24 these, you are talking about getting rid of six drugs,
25 because every one of them is a selective agent.

1 Lastly, the rapidity with which resistance
2 develops is a bug, and a bug and drug varies greatly between
3 species and between drugs. Certain species seem to have a
4 capacity to circumvent these pressures, which leads to a
5 resistant population.

6 For example, in the human side, we have used
7 gentamicin for several decades, and we have used ceftazidime
8 for almost two decades, yet, the incidence of resistance in
9 *Pseudomonas aeruginosa* for each of those drugs is about 10
10 percent.

11 Clearly, *Pseudomonas aeruginosa* does not develop
12 resistance very rapidly to those agents.

13 In addition to determining the level of resistance
14 in drugs and bugs, these factors also may influence what are
15 considered Category I drugs. It would seem to me that if
16 one of the criteria here is lack of selective pressure,
17 then, if you were talking about MRSA type resistance, you
18 are talking about making almost every drug a Category I
19 drug.

20 So, I think you are going to have difficulty
21 fitting many of these agents into the Category I.

22 But anyway, let me get back to what I really came
23 for and what I asked the time for, and talk about
24 surveillance. Although I am happy that the FDA recognizes
25 the value of resistance surveillance and that they have

1 their own surveillance system, I do not believe that what
2 you are recommending or what you are doing is adequate.

3 I strongly believe that resistance surveillance
4 should be done for its own sake, and should not be hidden as
5 a part of the food safety program. Let them exist
6 independently. I further believe that the surveillance
7 should include the vast majority of organisms and
8 antimicrobials that are used in animal health, and that
9 strains should come from all stops between the farm and the
10 butcher shop.

11 In the past, I have advocated programs in which
12 the organisms are collected throughout the country and
13 tested in a central laboratory. I still think that is
14 probably the most viable and the best way to do it, but with
15 the adoption of the NCCLS methods that Tom talked about, by
16 more and more veterinary labs, and the availability of good
17 results from a standardized method, I believe that we could
18 also begin to do electronic surveillance as we have done in
19 human medicine.

20 The central lab program should, of course, be done
21 annually, and the electronic system would be a continuous
22 program which would do surveillance every day, every week,
23 every year.

24 It is only with these kind of data, I think, that
25 you can answer all the questions and do it in timely manner.

1 Let me give you an example or two before I quit.

2 There is much concern expressed about
3 fluoroquinolone resistance in E. coli, including here today.
4 In the U.S. in 1998, we used almost one billion dollars
5 worth of Ciprofloxacin in the United States alone. If you
6 ask me where I got that number, I would have to think about
7 it, but it is not in confidence, but almost a million
8 dollars of Cipro was used, and yet the resistance of human
9 isolates was 2.2 percent.

10 Is E. coli the best enteric organ to use in
11 indicator species? Maybe not, because P. mirabilis had 5.8
12 percent resistance. There were no fluoroquinolone resistant
13 Salmonella in 1998.

14 So, should we be concerned about fluoroquinolone
15 resistance in Pseudomonas aeruginosa? Probably so, since it
16 is now about 23 percent. Is it increasing? Probably,
17 because last year it was 20 percent. A year before that it
18 was 18. So, my point for bringing this up is if you know
19 that you have a drug and a bug that is increasing every year
20 about 2 percent, is that a point at which you, as an FDA,
21 would make a move to stop or would you say that that is
22 okay?

23 Clearly, if we have the right kind of
24 surveillance, we can answer those questions. So, I would
25 urge that we do resistance for resistance sake, and use the

1 data where they are needed, be it food safety or the need to
2 develop methods of intervention of resistance.

3 Thank you very much.

4 DR. STERNER: We have a brief period of time, a
5 window of opportunity for questions of Dr. Thornsberry.

6 [No response.]

7 DR. STERNER: Hearing none, at this point we will
8 press on relentlessly.

9 DR. LEIN: One, if I could.

10 DR. STERNER: Donald.

11 DR. LEIN: Dr. Thornsberry, what about
12 fingerprinting something like Salmonella basically to be
13 more exact what we are finding as we look from the animal to
14 the butcher shop that you are talking about?

15 DR. THORNSBERRY: I think the way that that has to
16 be approached is that you use your surveillance system to
17 identify where you have the problem, and then I think that
18 becomes a side research issue, because, you know, I think it
19 would probably be too difficult and expensive to do.

20 DR. LEIN: And use the antimicrobial resistance
21 patterns.

22 DR. THORNSBERRY: To identify, yes, but obviously,
23 the fingerprinting would be better.

24 DR. LEIN: Thank you.

25 DR. STERNER: Our next public speaker is Harless

1 A. McDaniel. I don't know what the acronym AVID is. You
2 have 10 minutes, and I assume you will explain that to us
3 after you give us your disclaimer.

4 **Harless A. McDaniel**

5 MR. MCDANIEL: No funds from any drug company, and
6 no funds for paying any expenses to attend this meeting.

7 AVID is an acronym for American Veterinary
8 Identification Devices. However, I hope that my comments
9 today apply more across the board to the electronic animal
10 identification technology, as well as the database
11 development and management for animal production records.

12 I urge the Center for Veterinary Medicine to
13 provide leadership to the livestock and poultry industries
14 by developing a database format for electronically compiling
15 and submitting information on use of antimicrobials and
16 other regulated products in food animals prior to and during
17 slaughter, throughout slaughter.

18 This process would provide CVM and other agencies,
19 as well as industry organizations, industry needed about
20 animal slaughter for human food. Many animals, not many
21 poultry, but certainly quite a number of cattle and quite a
22 few hogs now are being electronically identified and
23 produced using software management programs.

24 Computerized management reduces production costs
25 by 15 to 23 percent according to several experts, not me.

1 Data on feed, treatment, and other production activities are
2 available and could be electronically compiled and submitted
3 to a central database if an appropriate program can be
4 developed including definitions and so that everybody is
5 talking about apples and oranges, or whatever it is, and the
6 information becomes so much more meaningful if we have
7 national and perhaps even worldwide standardized
8 definitions.

9 Now, the database to me is far more important than
10 your electronic identifiers or readers, or any other
11 component in the system, and the database should extend from
12 conception through the entire slaughter, sampling process,
13 so this is the data for one animal and everything that is
14 known about this animal or, in the case of poultry and
15 perhaps some pigs that are produced in the same lot, in the
16 same environment, of the same genetic stock, you may be
17 talking about electronic identification for a sampling of
18 these animals, or even in the case of poultry where they are
19 all from one premise, you don't have to put it on any
20 animal, but you just put it into the computer.

21 Certified production data could be useful for
22 export and domestic marketing, plus a variety of other uses.
23 It could be developed so production premises could be
24 located, the premise data compiled, coupled with the
25 individual animal identification could be used to evaluate

1 exposure to infectious diseases of animals or human if
2 diseases, such as mad cow disease occurred in this country.

3 Other less devastating animal disease outbreaks or
4 in this case antibiotic resistance could be managed quickly
5 without costly disruptive programs.

6 European Union has spent millions of dollars
7 developing an animal identification system to be coupled
8 with a database also under development. In 1998, the animal
9 identification part of this alone, the budget exceeded \$25
10 million. So, they are several years ahead of us.

11 We might not have to do all the work to develop an
12 identification system, definitions, database management,
13 electronic, and so forth, and so on. I suggest that we
14 might find that much of this has already been done by the
15 Europeans, and the more of this that we could standardize
16 would be a great asset to the global marketing of animals
17 and animal products.

18 I included in my submission the name, address, and
19 so forth, for the European organizations that are managing
20 the animal identification project, and I believe the same
21 people are also involved in the database development.

22 That concludes my prepared remarks.

23 DR. STERNER: Are there questions from any of the
24 panel members? Yes, Dr. McEwen.

25 DR. McEWEN: Just a comment. I would like to say

1 that I think the sort of traceback studies that Scott
2 Holmberg did, and John Speka, and others, on resistance
3 issues would have been made a lot easier if there had been
4 an I.D. system in place, and so I would like to endorse the
5 concept as a way of helping to address some of the issues
6 that we are talking about today.

7 DR. STERNER: Other questions or comments from
8 panel members?

9 [No response.]

10 DR. STERNER: Thank you.

11 Our next speaker is one of my feathered friends,
12 Dr. Dennis Wages, who is here to represent the American
13 Association of Avian Pathologists. Dennis, you have 10
14 minutes, and the meter is about to run.

15 **Dr. Dennis Wages**

16 DR. WAGES: Thank you. Sorry about the cold. I
17 usually can tell people that my voice will never get any
18 worse, but I think today it might.

19 First, I guess Animal Health Institute has paid my
20 expenses to this meeting, but I do not have any financial
21 interest nor am I supported in my research at North Carolina
22 State University by any of the pharmaceutical companies.

23 Today, I wear the hat of a poultry clinician, a
24 teacher at the College of Veterinary Medicine, specializing
25 in poultry medicine, as well as chairman of the Drugs and

1 Therapeutics Committee representing the American Association
2 of Avian Pathologists, which represents both turkey and
3 chicken veterinarians.

4 Since the Swann report in '69, and in the much
5 publicized Holmberg report of the Salmonella smoking gun in
6 the early eighties, poultry veterinarians have realized the
7 importance of a safe and an economic, healthy source of
8 protein for the United States and the world.

9 Since that time and those reports, without fanfare
10 and without publicity, the poultry integrators and poultry
11 veterinarians withdrew penicillin, tetracycline, and
12 sulfonamides from low-level or growth-promoters in their
13 operations.

14 We, not like our counterparts in swine and cattle,
15 had alternatives. We had the bacitracins, the
16 virginiamycins, as well as some of the antimicrobials that
17 were not used in human medicine.

18 Little did we know that today, 20 years later or
19 25 years later, we would be looking at two of those, being
20 bacitracin and virginiamycin, which are on the cutting stone
21 in our European neighbors to be pulled off the market for
22 the potential for cross-resistance.

23 So, we don't know now what is going to happen 20
24 or 30 years from now, and our decisions may reflect that
25 ambiguity, if you will, on what might happen.

1 From 1994, I have agreed and I have spent many
2 occasions defending the use of fluoroquinolones in poultry
3 and other food animals. As this meeting has shown, and
4 other meetings like it, to say this is a controversial issue
5 would be the understatement. Prescription only, detailed
6 records, HACCP, food safety initiative, FoodNet, post-
7 approval monitoring, and I will say HACCP two or three
8 times, the committees on judicious therapeutic antimicrobial
9 use, and now the WHO initiative for the code of therapeutic
10 use are all vocabulary terms that we know well because of
11 fluoroquinolone use in food animals.

12 All of the above programs that I have mentioned
13 are in stages of development. HACCP is in place, FoodNet,
14 food safety initiative is in place, and I guess my first
15 question when I saw the framework is why another one.

16 I think at some point in time we must look at
17 merging or marrying these programs together. It appears
18 that we have the framework and the nidus in place with HACCP
19 and the antimicrobial monitoring that is going on, NARMS, I
20 omitted, we have these in place to be able to integrate this
21 type of a framework document to better suit our needs.

22 I am afraid that if we don't integrate what we
23 have got, then, four, five, six, 10 years from now, when the
24 budgets are cut, what program is going to be pulled, and it
25 is going to leave the rest of them naked.

1 As far as concern on the document itself, and I
2 can echo a lot of things that have been said from my food
3 animal counterparts, and probably will be said, that I look
4 at the categorization of drugs and I feel a little bit of an
5 apprehension.

6 First of all, there doesn't seem to be any way to
7 improve your categorization. If you are pulled into a
8 Category I, it doesn't seem like there is very much way that
9 you can go to a level 2 or 3, and it seems if you are a
10 level 2 or 3, the only place to go is up, and up is bad.

11 I shudder to think at some of the comments that
12 were made for veterinary medicine to prove that it does not
13 cause the problem. I am not a statistician, and I am not a
14 Rhodes scholar, but to prove a negative has never been very
15 high on my list to be successful and to prove that we cannot
16 or will not or cannot do something would be very detrimental
17 to the antimicrobial industry and to our animals.

18 Another thing that bothers me about the
19 antimicrobial categorization is there is nothing on there
20 about the importance of those antimicrobials in the food
21 animal itself.

22 Folks, from 1988 or in the eighties when
23 [noctafurzone] was pulled off the market and was the only E.
24 coli drug I had left, and the poultry industry had left to
25 treat E. coli, I had nothing to treat E. coli infections

1 until the fluoroquinolones were approved, not that I had an
2 option, not that I could combine drugs, I had nothing, and
3 so the fluoroquinolones were a godsend to us.

4 But even though you would think that with such an
5 impact on E. coli infections, when you are only dealing with
6 5 to 6 percent of the flocks in our industry getting sick,
7 an 18-month survey period has shown that in the broiler
8 industry, only 1.2 percent of our flocks are treated with
9 fluoroquinolones.

10 Yes, they are important, yes, they minimize the
11 disease impact going into the plant, but, no, we don't over-
12 abuse them in our opinion.

13 So, those are some problems that I see with the
14 categorization. On-farm monitoring, I think that if you are
15 going to do on-farm monitoring, it has got to be focused. I
16 think if you do a national on-farm monitoring, that in my
17 opinion could be disastrous.

18 I think if you are looking at the on-farm
19 monitoring to actually try to point out where the resistance
20 and if transfer resistance from either food-borne bacteria
21 to non-food-borne bacteria, and the antimicrobial resistance
22 resulting, if that is going to be found and finger-pointed,
23 I think you need to have a very focused attempt, and not in
24 this global picture.

25 Also, I think we have kind of missed the boat on

1 something that may have already told us a lot. One of the
2 big questions and concerns is veterinary use of
3 antimicrobial as it impacted the treatment of food-borne
4 pathogens. We have a perfect example with erythromycin.

5 My understanding is even though we screened humans
6 with fluoroquinolones for nonspecific diarrhea disease, once
7 we find that it is a Campylobacter, erythromycin is the drug
8 of choice. Erythromycin has been used very heavily in
9 turkeys for 30 years. It has been used in chickens, not as
10 heavy, but if you are looking at a trend, let's track
11 erythromycin and the resistance that has even been developed
12 or not developed in Campylobacter.

13 It may be something that is sitting right there
14 that we haven't utilized, we have been looking at
15 fluoroquinolones.

16 Campylobacter, Salmonella, and E. coli are target
17 organisms. Five years from now listeria may be the target
18 organism for food-borne illnesses that we need to be
19 concerned with.

20 I guess one thing that I think of that probably
21 hasn't been expressed in the food document is if you can
22 take something out of the equation to minimize exposure to
23 humans, I think irradiation and stopping the exposure of the
24 humans potentially to that food-borne pathogen as the comes
25 off the carcasses, an important area of consideration.

1 It doesn't stop cross-contamination. It doesn't
2 stop the cross-contamination from the alfalfa sprouts and
3 the vegetables, but it may go a long way in helping us out.

4 Everywhere that I find information that tells us
5 antimicrobial cross-resistance doesn't occur, I find
6 information that says that it does, so it is conflicting.

7 I guess to close, I would like to say that I am
8 personally convinced that the intent of the framework
9 document that has been presented is not to deter the
10 development of new animal drugs in veterinary medicine, but
11 I think the reality, if I am sitting back in the back of
12 this auditorium, and I am an R & D person for a
13 pharmaceutical company, that is exactly what this framework
14 document will do.

15 If I have my options and I have the potential of
16 putting a small animal drug on the market or an equine drug,
17 or a food animal drug, I will guarantee you with some of the
18 framework documents and the hoops and the barriers that we
19 have to go through or would have to go through, I would not
20 do it, especially to potentially treat 1.2 percent of the
21 broilers or the turkeys that we are talking about.

22 I say let the programs talk. I think that when
23 you look at a framework and a document, such as this, that
24 not only can VMAC be involved in it, but you need to
25 integrate a lot of the other stakeholders before you present

1 this framework to the public, and maybe some of the
2 controversy can be laid to rest.

3 Thank you very much.

4 DR. STERNER: Thank you, Dennis.

5 Our next speaker is from Iowa State University,
6 Dr. Mike Apley, his presentation representing the Academy of
7 Veterinary Consultants, and if you will start with your
8 disclaimer also, Mike.

9 **Dr. Mike Apley**

10 DR. APLEY: My name is Mike Apley, and my expenses
11 to this meeting are being paid by the Academy of Veterinary
12 Consultants, whom my comments today represent.

13 I am on the faculty at the Iowa State University
14 College of Veterinary Medicine, working in the areas of food
15 animal production medicine and clinical pharmacology.

16 The Academy of Veterinary Consultants, or AVC, is
17 a group of approximately 400 veterinarians involved in beef
18 cattle production systems. Our objectives include to
19 promote the profession and maintain high standards under
20 which the members conduct the services of the public by
21 holding meetings for the exchange of ideas and the study of
22 the profession of herd-health consultation, and to cooperate
23 with veterinarian agriculture organizations and regulatory
24 agencies.

25 The commitment of the AVC to the issue of

1 antimicrobial resistance has been demonstrated by recent
2 presentations at our meetings by Dr. Angulo from the CDC,
3 Dr. Thompson from the CVM, and Dr. Lieberman from the CSPI.

4 We applaud the recent visit of Drs. Bell, Webber,
5 and Angulo to Colorado feed lots where they were introduced
6 to our production system.

7 The AVC is committed to animal health, public
8 health, and the viability of the beef industry. The
9 delivery of a safe wholesome product to the consumers is our
10 ultimate goal. The AVC recognizes, as do producers, that
11 this is a vital component of the longevity of the food
12 animal industry.

13 In keeping with the requested topic of this
14 meeting, we would offer our comments on a proposed framework
15 document. This framework document requires us to emphasize
16 our animal obligations in order to achieve balance in the
17 approach.

18 As written, the document contains the potential to
19 severely compromise our ability to fulfill our obligations
20 to animals and animal health. While the AVC agrees that the
21 relationship between antimicrobial use in animals and humans
22 must continue to be close examined, we must also remember
23 that antimicrobials are a major component of delivering a
24 safe product to our consumers.

25 Upon initial reading by one concerned with issues,

1 as the AVC is concerned about, the agency appears to have
2 assumed the stance of if we can conceive it, you must
3 disprove it.

4 While the widespread application of the
5 precautionary principle to this issue may be expedient, we
6 must also consider the potential negative impacts on public
7 and animal health.

8 In document Section II, the introduction, the
9 following statement in the document, we would like to
10 propose comments on. I will read the statement.

11 "In addition, bacteria can become resistant
12 indirectly when resistance traits are passed on from other
13 bacteria by mechanisms which allow the exchange of their
14 genetic material. In this way, resistance can be
15 transferred between nonpathogenic and pathogenic bacteria
16 and from bacteria that usually inhabit the gastrointestinal
17 tract of animals to those that infect humans."

18 The reference for that was Dr. Levy's article,
19 1998 article, Multi-Drug Resistance, a Sign of the Times.

20 This concept is brought up later in the
21 introduction, as follows:

22 "Alternatively, the bacterial resistance genes can
23 be transferred to pathogenic bacteria in the human
24 gastrointestinal tract or in the environment and these newly
25 resistant bacteria may then cause human infections in the

1 immunocompromised host."

2 While this statement is conceptually understood, I
3 could not come to grips with that reference being the source
4 for that statement. We have had an excellent presentation
5 on this subject earlier today that outlined many
6 possibilities, but in my opinion, few certainties.

7 We do not dispute that pathogens in food animals
8 with altered susceptibilities may be passed to humans
9 through improper hygiene, whether personal or in the food
10 preparation system. In fact, preventing the zoonotic
11 transfer of pathogens and minimizing any bacterial transfer
12 to the absolute lowest point possible is a major effort on
13 the part of the producer and slaughter industry.

14 However, we encourage the agency to carefully
15 examine the concept of indirect transfer of altered
16 susceptibility from nonpathogenic food animal isolates to
17 enteric pathogens in human for a specific drug pathogen
18 combination before using this concept as the basis for
19 policy.

20 Adoption of this concept is reality without
21 justification for each application. It would allow the
22 hypothetical linkage of almost any drug use in animals to an
23 important therapeutic application in humans.

24 A major assumption that will be necessary to
25 enable this document is some idea as to the amount of change

1 in susceptibility required to have an adverse effect on
2 human therapy or to at least have an idea of how to
3 determine this threshold for effect.

4 Committing to fulfilling the requirements of this
5 framework document with no direction in this area relies on
6 a very optimistic view of the relationships we will be able
7 to work out agreements on.

8 This framework relies on developing information
9 for much of which the agency does not possess reasonable
10 methods of discovery at this time. This framework
11 establishes required decisions and policies that, by their
12 design, will require subjective judgments on the part of the
13 agency.

14 We appreciate the opportunity to comment today and
15 ask that the agency continue this transparent method of
16 development.

17 In the section on importance in human medicine, we
18 realize the agency cannot consider animal welfare in the
19 pursuit of human food safety, however, we ask the agency to
20 consider the point that some antimicrobials may be very
21 important in controlling pathogen occurrence, and by this
22 manner have a positive effect on food safety.

23 Regarding the Category I criteria, we would ask
24 the agency start by indicating anticipated cross-resistance
25 categories. We encourage the agency to safeguard against

1 errors based on overgeneralization. As a pharmacologist, I
2 routinely run into misconceptions based on generalized
3 concepts concerning antimicrobial drug groups.

4 We propose the agency designate a review period
5 after which a drug standing in human medicine is reviewed.
6 Under the current proposed framework, it is hard to envision
7 a drug ever moving down a category unless a periodic review
8 inviting public comment is required.

9 The "new class statement" should be better
10 defined. As written, the agency has wide latitude as in no
11 definition for designating a novel drug class as having
12 potential for long-term therapy in human medicine.

13 Other definitions required are those for a rare
14 mechanism of action and/or the nature of resistance
15 induction is unique, as well as resistance is rare.

16 The issue of category placement is extremely
17 complex in itself. We would anticipate a transparent
18 process whereby the reasons for each drug placement would be
19 disclosed and comments would be received.

20 In the part of the document that addresses
21 evaluating the potential exposure of humans, the following
22 example from the agency document is referred to in the
23 comments below. This is a section from the document.

24 "An antimicrobial drug administered in drinking
25 water ad libitum is used for 7 days to treat E. coli

1 infections in a herd of swine and the drug has been shown,
2 in vitro, to induce resistance to an antimicrobial used in
3 humans to treat food-borne pathogens such as Salmonella
4 species. This drug is administered to all of the animals in
5 the herd in the production class that is susceptible to the
6 disease when a disease outbreak occurs. However, outbreaks
7 occur in only a small fraction of the herds brought to
8 market."

9 Pivotal determinations required for categorization
10 of exposure for this example include what is a small
11 fraction of the population, what is the definition of
12 resistance, and what in vitro standards are to be applied,
13 does the change in susceptibility patterns constitute
14 resistance.

15 Additional questions from this section of the
16 document include what does the agency intend to use for the
17 definition of a significant baseline incidence. Obviously
18 the 6 to 21 days for a medium exposure drug is put out for
19 discussion, which you are welcome to take part in.

20 We do not hold these up as reasons that such
21 evaluations are impossible, but as examples of the
22 complexity of the documents that will require multiple
23 inputs.

24 Regarding microbial safety, the agency requests
25 comments on whether and when it would be appropriate to set

1 resistance thresholds on human data, animal data, or both.
2 By setting resistance thresholds based on human data, the
3 agency would be contending that the vast majority of
4 resistance development for that pathogen drug combination is
5 due to antimicrobial use in animals.

6 The agency is confident that the majority of human
7 Salmonella infections are of food origin. How would this
8 framework address other pathogens? For example, vancomycin
9 resistant enterococci has been referred to as a pathogen
10 "that may now be essentially untreatable in the United
11 States."

12 The relationship between animal use of the
13 glycopeptides and appearance of VRE in humans in Europe is
14 used extensively through the framework document as
15 justification for this approach.

16 Under the proposed framework document, it appears
17 that if glycopeptides were used in U.S. food animals, the
18 current VRE incidence in the United States would be at least
19 partially attributed to food animal use.

20 I can see no provision in this document to attempt
21 to discern between effects of widespread use or misuse in
22 human medicine and use in veterinary medicine. The food
23 animal industry must prove that use in animal agriculture is
24 not the cause.

25 This is the doctrine of -- and excuse my Latin --

1 res ipsa loquitur where the agency is stating that it is so
2 obvious that food animals are at fault, that it is up to the
3 industry to prove they are innocent.

4 The AVC asks for a description of how the agency
5 would examine would causes of this resistance from both
6 animal and human use.

7 Along this line, I was troubled earlier today by
8 the somewhat cavalier discussion of the mean of resistant
9 human Campylobacter in Spain. According to my information,
10 this country has a high prevalence of endemic Campylobacter
11 in humans, has multiple generic an illicit versions of
12 fluoroquinolones available to humans on an over-the-counter
13 basis, and in some areas, has a sewer system far below that
14 which we are accustomed to in the United States.

15 Does this mean that animal use has no bearing on
16 human Campylobacter isolates in this country? No, however,
17 discussing this resistance level in conjunction with animal
18 use, with no discussion of possible human contributions, is
19 misleading.

20 For animal data, the source of isolates must be
21 carefully considered. The agency must commit to identify
22 point sources contributing to a change in susceptibility
23 detected in a nationwide monitoring program, and addressing
24 control efforts at these point sources rather than utilizing
25 a blanket approach, and we have discussed that today.

1 We are not convinced that routine on-farm
2 monitoring would yield the most useful information on a
3 routine basis. However, this may be useful if problems are
4 identified with a specific drug-pathogen combination.

5 It appears that the agency depends on sponsors to
6 foot the bill for this program. Given the small size of the
7 veterinary market and the extensive financial commitments
8 required to fulfill obligations imposed by these higher
9 categories and exposures, this will directly affect
10 decisions by companies to pursue new animal drug approvals.

11 Other concerns include drugs for which patent
12 protection is expired, that now compete with numerous
13 generic forms. The financial requirements of being placed
14 in a high human importance category as currently established
15 may lead to the demise of these compounds due to no company
16 wanting to fund programs for the benefit of their
17 competitors.

18 To some, the loss of new and currently approved
19 products appear to be laudable outcomes of the framework
20 document, however, to those directly responsible for animal
21 health, and who do not just see animals as numbers on
22 computer screens, it is a frightening proposition.

23 The AVC implores the agency to proceed with the
24 realization that the goals of this document will not come
25 without a cost to the veterinarian's ability to address

1 disease.

2 The ultimate result of this framework document is
3 best illustrated by combining the following excerpts. The
4 agency notes that the ability to set scientifically based
5 resistance and monitoring thresholds depends on at least two
6 factors. One is the ability to demonstrate that a
7 particular resistance threshold is adequately protective of
8 the public health, and two, the ability to detect when the
9 resistance of monitoring thresholds are reached. In the
10 absence of either factor, the agency presumably would not be
11 able to approve new uses of antimicrobials in food producing
12 animals when such approval is dependent upon setting and
13 monitoring such thresholds.

14 Another excerpt is that while the agency believes
15 that some level of resistance transfer from animals to
16 humans due to use of a Category II drug -- this is reference
17 to Category II -- in animals may be shown as safe, it does
18 not have data and information currently that would enable it
19 to establish such levels.

20 By combining these statements with the stated
21 intention of applying these principles to future and
22 existing approvals, the agency is now effectively linking
23 the existence of all food animal approvals to the creation
24 of thresholds for which it states it does not have data or
25 information to establish.

1 The current document is based on evaluating the
2 potential impact of antimicrobial use in food animals, on
3 therapeutic efficacy, and human medicine. How has the
4 agency performed recently in this area?

5 In order to evaluate the potential human health
6 impact of an antimicrobial use in veterinary medicine, the
7 agency must follow the principles of a risk assessment. We
8 have heard enough about those today, that I will try not to
9 say that word again.

10 The Center for Veterinary Medicine was unable to
11 reach a consensus resulting in a risk assessment for recent
12 drug approval. This attempt risk assessment was conducted
13 only within the Center. We would ask that the Center
14 propose a process to come to a consensus on the contentious
15 issues in the framework document with the additional
16 participation of outside parties.

17 The proposed framework document is a excellent
18 document for the purpose for defining areas where little
19 information is available. As a basis of policy, it could --
20 I emphasize could -- serve to severely impact the ability of
21 veterinarians to fulfill their obligations to food animals.

22 This impact would be the cost if -- I emphasize if
23 -- the agency errs significantly on the side of caution in
24 multiple areas where the agency will be forced to make
25 decisions based on limited data.

1 The AVC looks forward to further cooperation
2 between the Center for Veterinary Medicine and AVC members
3 as we work together to protect human and animal health.

4 We thank you for the opportunity to comment.

5 I would like to close with a comment on the
6 earlier statement the guidelines didn't work in human
7 medicine, and good luck on getting them to work in
8 veterinary medicine. It just so happens that I am the guy
9 that is the director of our attempt to create for veterinary
10 medicine.

11 Our web-based database will be designed to allow
12 the veterinarian to rapidly access dose regimen information
13 based on empirical therapy, as well as for therapy with the
14 benefit of culture and susceptibility testing.

15 We intend to be quick, be brilliant, and be gone,
16 basically, what a good speaker does and I am fixing to do.

17 Four veterinary organizations and one producer
18 organization fund our project. In 1988, as a young
19 veterinarian, I was introduced to Ciprofloxacin by a local
20 physician when I was handed a handful of Cipro samples for a
21 fever of unknown origin. I, along with the veterinary
22 profession, remain committed to doing better than that.

23 Thank you.

24 DR. STERNER: Thank you, Michael.

25 Questions from the panel members? Dr. Angulo.

1 DR. ANGULO: Mike, I am encouraged because I
2 didn't hear the word that you were opposed to the framework.
3 By you not saying you are not opposed to the framework, can
4 I assume that you endorse the framework?

5 DR. APLEY: You know, Fred, the only thing I can
6 say is if you wouldn't have asked something, I would have
7 gone away crushed, because I was hoping to get Fred wound
8 up.

9 I don't if it's support as much as it is a
10 reality. Myself, and I think I speak clearly for the AVC,
11 we are very anxious to come to some conclusions on this
12 subject, and we are anxious to get us working together like
13 Dr. Bell stated earlier.

14 Our biggest concern is what I tried to cover
15 through this whole prolonged yak here was we are very
16 concerned that our ability to adequately express health
17 concerns in animals, including food animals, be preserved,
18 and as a veterinary organization, our interest is actively
19 reviewing this document and seeing how it would impact us.

20 I think there has to be some type of organized way
21 to approach it. That, I would agree with. I think there
22 are a lot of ways we could make the framework better.

23 DR. STERNER: Dr. Bell.

24 DR. BELL: Mike, I want to thank you for your
25 thoughtful comments, and I just have a question. It really

1 didn't sound to me, Fred, like he was supporting the
2 framework.

3 DR. APLEY: Fred is an optimist.

4 DR. BELL: Well, me, too, actually. My question
5 is are there a list of specific suggestions that you could
6 make, either now or in the future, specific modifications in
7 this framework that would enable you to take a more positive
8 role in it?

9 DR. APLEY: I think we could boil this down and
10 have some other suggestions, yes. I took a part out because
11 I thought it sounded a little too flippant.

12 Dr. Sterner will fully understand this. I spend a
13 lot of time in a truck and with dirty boots and grew up in a
14 veterinary practice, and you have to understand the
15 veterinarian does not like to wake up in the morning and the
16 first thing you hear is, "We are from the government, and we
17 are here to help you."

18 If the question is do we trust the agency, the
19 answer is, well, conditional. I don't mean that to be
20 insulting, but we are going to approach this with a very
21 jaded eye, but we do want to see progress. So, I would be
22 glad to put together a list.

23 I think we gave several constructive things in
24 there, interactions we would like to see, and areas of the
25 document we sure want to be transparent.

1 DR. STERNER: Thank you for your candor, Michael.
2 Coming from Michigan and the home of the Michigan
3 militia, I am not sure that the answer would be quite the
4 same about I am from the government, and I am here to help
5 you.

6 Our next speaker does, in fact, come from
7 Michigan. Dr. Robert Walker from Michigan State University
8 who was referred to earlier, who heads up the Campylobacter
9 International Committee, is next on our agenda.

10 For those of you whose rear ends are at a true
11 endpoint, I will tell you that we have, by my count, just
12 three more speakers, so the end is in sight, or the train is
13 at the end of the tunnel, one of the two.

14 Dr. Walker, would you state your affiliations.

15 **Dr. Robert Walker**

16 DR. WALKER: I am a Professor of Microbiology at
17 Michigan State University. I do perform pharmacodynamic
18 studies for numerous pharmaceutical companies. My expenses
19 to this meeting have been paid for by the Animal Health
20 Institute.

21 I think it is unrealistic -- this is from my own
22 perspective -- unrealistic to expect a pharmaceutical
23 company to develop a class of antimicrobial agents that is
24 not or will be not be used for human need or human use,
25 human medicine.

1 I also think it is unrealistic to expect any
2 producer group to produce the quantity of meat needed to
3 feed our growing population without the use of anti-
4 infective drugs.

5 I therefore believe that it is necessary for us to
6 use the drugs that we have or will develop more
7 intelligently, both in human and in veterinary medicine.

8 [Slide.]

9 So, because I only have a couple minutes, I will
10 bypass the goal that FDA has put out, and you all can read
11 that.

12 [Slide.]

13 From my reading these documents or this document,
14 these are the methods that I felt that they were going to
15 use to implement these goals. One was to quantitate the
16 antimicrobial drug resistant enteric bacteria formed in the
17 animal's intestinal tract following exposure to the
18 antimicrobial new animal drug, which this was their
19 definition of resistance.

20 [Slide.]

21 The second is determine changes in the number of
22 enteric bacteria in the animal's intestinal tract that
23 causes human illness. This is the pathogen load. They go
24 on to say that enteric bacteria in animals represent a
25 special risk for causing human illness and for including

1 resistance in bacteria in humans because they are the
2 bacteria most likely to contaminate a food product and then
3 be ingested.

4 I would like to address the second issue first,
5 which is determine the changes in the number of enteric
6 bacteria in the animal's intestinal tract that causes human
7 illness.

8 Determine the changes in the number of enteric
9 bacteria in the animal's intestinal tract that causes human
10 illness. Wow. As a microbiologist, how would I do that?
11 If you go to the next overhead.

12 [Slide.]

13 If you look at the work done by Herdt and his
14 graduate students, the mean concentration of total viable
15 bacteria, aerobes and anaerobes per 5 cm segment of
16 intestinal tract in healthy calves, you can see that 10^6 ,
17 10^6 , about 10^6 , clear up here at 10^9 , this is a very
18 conservative estimate, and this aerobes and anaerobes.

19 Are anaerobes involved in human health? I don't
20 think that we have an answer to that question yet because we
21 really haven't looked into it.

22 [Slide.]

23 If we look at just the coliforms, 10^5 , we are
24 going to see how the use of antibiotics changes this. To
25 give you an idea of the complexity of this question, go to

1 the next one, please.

2 [Slide.]

3 This is some work done by Moore and Holdeman back
4 in 1976, and what I have listed here are the rankings of the
5 bacteria found in the gastrointestinal tract of humans, this
6 work has not been in animals for logical reasons, we don't
7 have the money to do it, but if you look at the ranking and
8 the percent of isolation, and these are all of the bacteria
9 that they have isolated.

10 I am not going to read them to you for the lack of
11 time. If you could go to the next one.

12 [Slide.]

13 You get clear down here to 56 or somewhere, 52, or
14 72, somewhere in this area, and this is where E. coli ranks.
15 So, E. coli is not very prominent in terms of the
16 gastrointestinal tract, at least in humans, and so where is
17 it in animals? We don't know.

18 If we are looking at enteric pathogens or
19 pathogens that could be transmitted by food, do anaerobes
20 play a role in this? Again, this is an issue we don't know.
21 This is just something that the FDA has proposed to include
22 in their database.

23 [Slide.]

24 Say we are going to look just a E. coli or
25 pathogens. This slide is a very complex slide, and I wanted

1 it to be this way, just to emphasize a point. What we have
2 here are 52 different canine or different dogs, fecal
3 samples from 52 different dogs, all raised in the same
4 environment, and what we did was we looked at five E. coli,
5 we streaked the plates for isolation, picked five individual
6 colonies from each one of those dogs, and looked at it for
7 virulence factors where there was attaching interfacing gene
8 or shiga-like toxin gene, hemolysins, and also the somatic
9 antigens, and you can see from looking at this that there is
10 a tremendous complex environment here.

11 Now, are these organisms potentially human
12 pathogens? Well, they have the attaching interfacing gene,
13 they produce a shigatoxin, at least some of them do, so they
14 are potentially human pathogens, although this is a canine,
15 and we don't ingest canine feces, not even in the home
16 environment, so this is a kind of a moot issue.

17 [Slide.]

18 This is some work done by Dr. Holland where he
19 looked at the distribution of the attaching interfacing gene
20 and the shigatoxin and E. coli among serogroups in
21 relationship with attaching interfacing lesions in calves,
22 and you can see the different serotypes that are present
23 here. Here is 0157. It is only one of the many that was
24 there, and it didn't have an attaching interfacing lesion,
25 but you can see the complexity of this, and are these

1 potential human pathogens that haven't manifested themselves
2 yet?

3 Go back 15 years. Take a mindset back 15 years,
4 and tell me all you know about E. coli 0157:H7. Very, very
5 little, and so next year maybe it's going to be one of these
6 other attaching interfacing E. coli that becomes a pathogen,
7 but we are not looking at it, because we are only looking at
8 0157:H7.

9 [Slide.]

10 Evaluate the quantity of antimicrobial drug
11 resistant enteric bacteria formed in the animals' intestinal
12 tract following exposure to the new animal drug.

13 [Slide.]

14 This is a slide where we looked at a fecal sample
15 from a cow, streaked it for isolation, picked 25 colonies,
16 assayed each one of them individually for their
17 susceptibility to ampicillin, enterofloxacin, or gentamicin,
18 and you can see that there is quite a bit of flexibility or
19 diversity in terms of their susceptibility to these drugs,
20 and these are E. coli isolated from the same animal at the
21 same time.

22 [Slide.]

23 This is again a study by Dr. Holland where he
24 looked at those attaching interfacing resistance patterns,
25 and again you go back and you look at these serogroups that

1 have these different numbers and their susceptibility
2 profiles. What are we going to use for the baseline?

3 [Slide.]

4 So, I think what we need to do, we need to look at
5 a fairly extensive national monitoring system, I think,
6 where maybe we involve the farm, the laboratory, and the
7 abattoirs, the different food animals that are involved.

8 [Slide.]

9 We need to look at, like Dr. Thornsberry said,
10 from a variety of samples, enteric, respiratory, milk
11 samples.

12 [Slide.]

13 We need to look at a variety of organisms, E.
14 coli, not just E. coli 0157:H7, but let's look at E. coli as
15 a whole and see what it is looking like. Salmonella, there
16 is not going to be very many of those, so it is not going to
17 be an extensive database. Campylobacter, it could be
18 extensive. Proteus, one of the things that we found is that
19 Proteus is a very sensitive indicator of susceptibility to
20 fluoroquinolones.

21 [Slide.]

22 What we found when we looked at E. coli, in 1991
23 to 1996, there really wasn't much of a change in their
24 susceptibility to the fluorinated quinolones, but the
25 Proteus mirabilis, there was a tremendous change. Here, the

1 MIC nidi is equal to or less than 0.08 -- this is 1991 data
2 -- in 1996, 98 percent of them are right at the breakpoint.
3 They are still classified as susceptible, but they are right
4 at the breakpoint. I think an extensive monitoring system
5 would have picked these up long ago saying that this trend
6 is occurring.

7 [Slide.]

8 If you look at trends, this is a trend from
9 Lorian's, when we are looking at setting these threshold,
10 Ciprofloxacin, where do we sound the alarm here in this
11 decrease in susceptibility? You can look at any one of
12 these drugs and see that there is really not a dramatic
13 change in them, so where do you call it, where do you sound
14 the alarm? Has FDA really identified that point?

15 Look at the next one. Perhaps the thing to do --
16 this is the last one --

17 [Slide.]

18 I think what we need to do is we need to look at
19 looking at MICs and changes in MICs in relation to time, not
20 resistance or susceptibility, but changes in the MIC, and
21 just to emphasize that example, here we have Ciprofloxacin,
22 tested in '98. There should be '98 there, that's a typo
23 error. But if we look at Proteus, we can see that they are
24 beginning to creep up.

25 This should be an indication that there is

1 something going on here, and this is where I think education
2 can come in.

3 So, from my perspective, I would encourage the
4 committee to think very, very carefully about the decision
5 that you are about to make, very, very carefully about the
6 path that you are about to go down, because it can adversely
7 affect the use of anti-infectives in veterinary medicine.

8 Thank you.

9 DR. STERNER: Thank you, Dr. Walker.

10 Next, we have Larry Glickman from Purdue
11 University on the agenda, and, Larry, your title is not
12 there, but I assume you will explain that to us in short
13 order.

14 DR. GLICKMAN: My title is not what?

15 DR. STERNER: It is not titled. It says you are
16 from Purdue, that's it.

17 DR. GLICKMAN: That's enough.

18 **Dr. Larry Glickman**

19 DR. GLICKMAN: I am on the faculty at Purdue
20 University. I have no financial interest in the
21 pharmaceutical industry. My travel expenses to this meeting
22 have been paid by the Animal Health Institute, however, the
23 comments I am about to make have not been reviewed or even
24 shared with the Animal Health Institute.

25 I appreciate the opportunity to comment on the

1 proposed framework document that sets out a conceptual risk-
2 based framework for evaluating the microbial safety of
3 antimicrobial drugs.

4 One question asked by the FDA at this time is
5 whether the concepts set out in the document, if
6 implemented, will accomplish the agency's goal of protecting
7 the public health by ensuring that significant human
8 antimicrobial therapies are not lost due to use of
9 antimicrobials in food producing animals, while still
10 providing for the safe use of antimicrobials in the food
11 producing animals.

12 The agency also requested input on important areas
13 of scientific complexity identified in this document. This,
14 in fact, is indeed a very complex issue that has been
15 recognized and debated for some time by the regulatory and
16 scientific communities.

17 It sort of reminded me as I was sitting back there
18 of a quote about complexity from H.L. Mencken, who said,
19 "For every complex problem, there is a solution that is
20 simple, direct, and wrong." I hope the framework document
21 is not that solution.

22 Now, no one individual possesses all the expertise
23 to address the questions raised in their entirety. As an
24 epidemiologist, I would like to comment on six key points or
25 principles put forth in this framework document, which I

1 admit is not simple.

2 The first and perhaps most important point I want
3 to make is that insufficient information and knowledge
4 currently exist to establish definitively scientifically-
5 based protocols for monitoring and regulating the impact
6 that veterinary antimicrobials have on human health when
7 used in food producing animals.

8 I fully agree with the recent report, The Use of
9 Drugs in Food Animals: Benefits and Risks, that was
10 published by the National Research Council, Institute of
11 Medicine, and I know it has been said several times, but I
12 think their quote from that document is well worth
13 repeating.

14 It says, "Until more accurate data on animal
15 antibiotic use, patterns and rates of resistance transfer to
16 humans, and occurrences of actual disease emerge, and
17 mechanisms of resistance are available, actions aimed at
18 regulating antibiotics cannot be implemented through a
19 science-driven, well-validated, and justified process."

20 This indicates to me that the highest priority now
21 for regulatory agencies should be to establish and
22 strengthen programs, to collect the scientific facts that
23 are needed for adequate risk assessments, that is, establish
24 the scientific knowledge base which will lay the foundation
25 for future regulations regarding use of antibiotics in food

1 producing animals.

2 In addition, a greater effort should be placed on
3 educational programs directed at veterinarians and food
4 producers to promote judicious therapeutic antimicrobial use
5 in food producing animals. I think this should be a
6 tremendous effort.

7 Point 2. The FDA in its framework document
8 developed concepts for evaluating, "complex issues related
9 to the use of antimicrobial drugs in food producing
10 animals."

11 Given the complexity of these issues and the lack
12 of a scientific database for drafting regulations at this
13 time, an interdisciplinary task force representing the
14 disciplines of veterinary medicine, human medicine,
15 epidemiology, biostatistics, economics, and microbiology
16 should be established for several purposes, and this could
17 be referred to this blue ribbon committee which another
18 speaker mentioned.

19 The purpose would be (a) to define the multiple
20 endpoints that should be used to determine safety of
21 antimicrobial use in animals.

22 Two. Conceptualize the appropriate monitoring
23 systems to measure these endpoints in a cost effective
24 manner.

25 Three. Once regulations are enacted, this

1 committee could serve to constantly evaluate their impact on
2 the endpoints selected, and recommend changes to the
3 monitoring systems. In effect, the regulatory and
4 scientific process concerning the safety of antimicrobials
5 should be a dynamic one until such time as the measures of
6 safety can be validated using human health as the gold
7 standard.

8 Point 3. The multiple and complex human health
9 and safety issues raised by FDA, the CDC, and other federal
10 agencies concerning the use of antimicrobials in food
11 producing animals cannot and should not be addressed by
12 imposing post-approval monitoring requirements at this time
13 on a product-specific basis. This would be neither cost
14 effective nor in the best interests of public health.

15 Rather, systematic and uniform monitoring systems
16 should be designed that assess appropriate safety endpoints
17 in such a manner that any antimicrobial on the market can be
18 identified if it significantly increases the pathogen load
19 or the resistance threshold, two outcomes suggested in the
20 framework document.

21 Furthermore, if changes in pathogen load or
22 resistant thresholds are used to assess safety of
23 antimicrobials, a significant change should be based not
24 only on statistical principles, but also use measures of
25 biological significance that have been validated.

1 For example, even a very small increase in
2 pathogen load or resistance threshold can achieve
3 statistical significance with a large enough sample size,
4 however, such a small increase may have little or not
5 biological relevance to public health.

6 Point 4. Existing programs, such as NARMS,
7 established in 1996 as a joint effort by FDA, USDA, and CDC,
8 should form the basis for monitoring fluxes in antimicrobial
9 resistance associated with antibiotic use in food producing
10 animals rather than establishing new and costly systems for
11 this purpose.

12 However, monitoring systems, such as NARMS, are
13 designed primarily to detect changes in antimicrobial
14 resistance of pathogens or indicator microorganisms over
15 time rather than to identify the specific reasons for these
16 changes.

17 Even if the increased use of a specific antibiotic
18 in food producing animals is associated temporally with
19 increased antimicrobial resistance of potential human
20 pathogens, there is no scientific way to prove that the two
21 phenomena are related using only NARMS data.

22 Therefore, additional investigation is required to
23 not only this specific question, but also to identify other
24 risk factors related to farm management, inappropriate
25 antibiotic use, et cetera, that contribute to increased

1 antibiotic resistance over time.

2 One mechanism to do this is to use NARMS data to
3 identify changing antibiotic resistance patterns that merit
4 further investigation. For example, farms that were the
5 source of antibiotic resistant microorganisms of concern --
6 we call these case farms -- could be compared with farms
7 that were the source of the same type of microorganisms, but
8 that showed no increased antibiotic resistance, which I call
9 control farms, using standard case control epidemiologic
10 methods.

11 This can involve farm business by individuals who
12 are blinded to the case control status of the farms to
13 collect management information, as well as blood or
14 microbial samples from animals in the environment.

15 This approach would measure the risk of antibiotic
16 resistance occurring in animals associated with the use of
17 specific antibiotics on the farm. However, it would also
18 identify other farm level management factors that contribute
19 to this resistance, including inappropriate use of
20 antibiotics.

21 Such findings would be extremely useful in
22 determining the relative importance of these factors in the
23 development of antimicrobial resistance, and would be
24 valuable to the regulatory process and in establishing
25 educational programs of farmers and veterinarians to prevent

1 resistance.

2 In fact, FDA alludes to such studies in the
3 framework document on page 20 by stating that if NARMS data
4 indicated that unacceptable resistance was emerging, FDA
5 could reevaluate ongoing post-approval studies, order other
6 studies to be conducted, or institute other appropriate
7 actions.

8 Point 5. The framework document, on page 17,
9 states, "FDA believes that on-farm studies to monitor
10 antimicrobial resistance prevalence by the sponsor would be
11 necessary to ensure that resistance thresholds are not
12 exceeded after approval." Furthermore, data generated
13 through these studies in addition to other scientific data
14 would provide an early critical warning system for detecting
15 and evaluating the emergence of resistance under field
16 conditions.

17 For the reasons stated above, it does not seem
18 reasonable or cost effective for reach manufacturer to
19 monitor a geographically representative sample of swine,
20 poultry, and cattle farms in the U.S. to determine the
21 prevalence of antimicrobial resistance.

22 This is better achieved by using or expanding the
23 existing NARMS system coupled with the follow-up studies I
24 described. It is not in the public's best interests to
25 establish a broad national on-farm program in a drug-

1 specific manner as FDA believes or at least as they state on
2 page 17 of the framework document.

3 Such programs would significantly increase the
4 cost associated with drug development and potentially
5 diminish the availability of new antimicrobials for
6 therapeutic use by veterinarians.

7 Finally, the last point. At a recent national
8 conference on emerging food-borne pathogens, entitled
9 "Implications and Control," sponsored in part by combined
10 FDA, USDA, and CDC, it was noted that, and I quote,
11 "Infectious diseases transmitted by foods have become a
12 major public health concern in recent years. Response by
13 both the food industry and public health and food safety
14 regulatory agencies to new microbiologic health threats and
15 reemerging pathogens in food have been primarily reactive.
16 The multiplicity of factors and complex interactions
17 involved in the emergence and reemergence of microbial food-
18 borne hazards, and the need for multifaceted integrated
19 approach to protecting the population prompted this national
20 conference."

21 In the closing address to the conference, it was
22 concluded -- and I quote -- "Concerted controlled efforts by
23 public and private sectors are needed."

24 The FDA framework document should be viewed as the
25 first step in this process. A coordinated team effort

1 involving both the public and private sectors is now needed
2 to develop a strategy to bridge the human and animal health
3 issues related to the use of antimicrobials in food
4 producing animals.

5 Such an effort will required considerable time
6 since an adequate knowledge base for a scientific risk
7 assessment does not currently exist. It must not be
8 approached in an adversarial manner since too much is at
9 stake.

10 Premature promulgation of regulations without a
11 sufficient knowledge base at this time might only serve to
12 retard development of long-range solutions that best serve
13 the public's health and farm animal welfare.

14 Thank you.

15 DR. STERNER: Panel members, questions of Dr.
16 Glickman?

17 [No response.]

18 DR. STERNER: Thank you.

19 Dr. Jim Cullor from the University of California,
20 who is the director of the University of California at Davis
21 Veterinary Medical Teaching and Research Center, is our next
22 speaker, running rapidly to the lectern.

23 **Dr. James S. Cullor**

24 DR. CULLOR: I appreciate being here. My travel
25 expenses are being paid by the Animal Health Institute. I

1 am the director of the VMTRC. From time to time our faculty
2 and our Center, through the contract and grant process,
3 receives money from private industry including my
4 laboratory, although it is mainly vaccines and not
5 pharmaceuticals.

6 [Slide.]

7 I am here today to talk about the framework
8 document as a representative of and the director of the
9 Dairy Food Safety Laboratory.

10 [Slide.]

11 What we are being asked by all these discussion we
12 have talked here today is really how do we do daily
13 management of the production unit for animal health and
14 well-being, public health, environmental health, and medical
15 ecology, and still manage the financial well-being of the
16 dairy. That, in fact, is what we are doing at the VMTRC
17 with our students through programs like Dr. [Sisco's], TQM,
18 breakthrough management, and infectious disease control, and
19 so on, and so forth.

20 [Slide.]

21 We have had several reviews today, and this one I
22 think we need to go back and look at. The probability of
23 disease transmission from animals to man is really
24 influenced by the length of incubation period in the animal,
25 the length of time the animal is infective, the pathogen

1 load contained in the animal product or placed into the
2 environment, the stability of the agent in the environment,
3 the population density of animals and man, animal husbandry
4 practices, maintenance, production, and control of wild
5 rodents and insects, virulence of the microbe, and the route
6 of transmission.

7 [Slide.]

8 In all of this, the compounds we are talking
9 about, these anti-infective or antimicrobial agents, really
10 have a positive impact in two main areas. By shortening the
11 length of time the animal is infective and reducing the
12 pathogen load contained in the animal product, or placed
13 into the environment.

14 At the American Academy of Veterinary
15 Pharmacologists and Toxicologists last year, we presented a
16 model where we looked at, on one end of the spectrum,
17 absolute, unrestricted use of all antibiotics where you
18 could violate any orifice you wanted to, with any antibiotic
19 you wanted to, and given enough time you would get enough
20 drug resistance that the pathogens would overwhelm the
21 pasteurization and our meat processing, and we would have an
22 increased risk to the human population.

23 That same model shows, on the other end of the
24 spectrum, if you completely remove antibiotics from the food
25 animal production system, the pathogen loads again will

1 reach critical mass where they will get past all of the
2 pasteurization and other types of procedures, and again
3 present a problem to the human population.

4 In that model, then, the middle ground is where
5 you combine management practices, antimicrobial therapy,
6 good methods of animal husbandry, and so on, and so forth.
7 That is where the human population is at the least risk of
8 being infected by these pathogens.

9 I submit to you that if you go to Vietnam today,
10 you can see one end of that spectrum. You can go see the
11 result of the human population for the lack of antibiotics,
12 and the model accurately predicts what happens.

13 I am afraid that if we continue this framework as
14 it is, that we will have that type of an environment and
15 really a problem for our food animal production industry.

16 We have talked about and heard a lot about
17 Salmonella, E. coli, and Campy, but I submit that the list
18 will grow and grow each year until we get these plus
19 Yersinia and others, and so that --

20 [Slide.]

21 We get often as veterinarians, we get the comment,
22 "Well, why don't you just go clean up the dairy" or "Why
23 don't you just go clean up the farm, and we wouldn't have
24 all this trouble."

25 I submit to you that every day in the hospitals

1 around this country, they have problems with cleaning them
2 up, and when we work in an environment where these are the
3 criteria for eradicating a pathogen, it has to be a single
4 host species with no external reservoir species. That is
5 not the case with Salmonella, E. coli, or any of the others.

6 In order to eradicate a pathogen, it has to be
7 identified to be present in only a small percent of the
8 farms, ranches, dairies, or feed lots, and we know that it
9 can be worldwide, not just in the U.S.

10 The pathogen of interest serves as a disease
11 marker for detecting endemic herds, and we know that
12 organisms like 0157 is not a marker for the endemic disease.

13 Appropriate assays are validated and can correctly
14 identify the carrier animals. In fact, they do not exist,
15 and not have been validated for such a purpose.

16 Effective means of intervening in the chain of
17 infection after the carrier animals have been removed from
18 the herd must be established, and that is where
19 antimicrobials and vaccines and management practices can
20 play a part.

21 We have to have substantial financing, many
22 billions of dollars to do this, and we don't see that
23 anywhere either in private industry or from the government,
24 and a long-term resolve by everybody involved to implement
25 all of the necessary measures for eradication, and we very

1 seldom see that long-term resolve exist.

2 [Slide.]

3 I know this is a little difficult to see and
4 almost impossible, but what I wanted to show is that we took
5 -- one of the issues is the surveillance system, how can we
6 track antimicrobial resistance and what is going to happen.

7 What we used was the USDA panel of organisms, and
8 what we did then is we took that panel and we looked at
9 heifers -- we call them springer heifers. They have been on
10 the dairy. This is a closed herd that milks about 5,000
11 cows a year. They have five dairies. They feed their
12 babies hospital milk, mastitis milk. It has been
13 pasteurized. It has antibiotics in it. They were raised on
14 that for at least 60 days in their early life.

15 Then, they are raised in the environment all the
16 way through out of the dairy until they are pregnant and
17 ready to calf. We go in and test those animals just before
18 they calf, and these are Staph aureus isolates.

19 What we saw was that on this dairy -- we did it
20 for 1995, 1996, and 1997, the same dairy where we know all
21 the antibiotics used -- and what this assay showed was that
22 in '95, 4 percent of the Staph aureus isolates were
23 resistant to chloramphenicol, in '96, 12 percent, and in
24 '97, zero percent.

25 We looked again at another one, streptomycin; in

1 '95, 4 percent were resistant; '96, 4 percent resistant, in
2 '97, none, and so on, and so forth. We had four different
3 antibiotics out of that panel that showed this resistance,
4 where, in fact, these animals weren't exposed to these
5 antibiotics any other way than at birth or in the
6 environment around.

7 We used this data as an early indicator. We are
8 going to do the 1998 data now. This surveillance system
9 can't be looked at, at any one year. It has to be looked at
10 over a period of time, and you have heard that several times
11 already today. Probably a minimum of three years is going
12 to be needed to take a look at some of this information.

13 So, now we have been asked several times to
14 comment on the framework and what we might do.

15 Part 1, the categorization. It makes sense, but
16 it really needs to be better simplified, and you have heard
17 over and over again if you get in number 1 category, you
18 can't get out of there under this system.

19 So, I think we can reduce it maybe to three
20 categories, and then be objective and really make this
21 setting transparent; that an expert panel get together with
22 CDC and CVM and really relook at these categories and see if
23 we can't help them out a little bit.

24 Monitoring thresholds. It is a good idea, but we
25 really don't know where to set them, and you have heard that

1 over and over today.

2 For veterinary therapeutics, we have breakpoints
3 established for maybe three or four drugs, but none are set
4 for enterics, and we have got to look at that. Therefore,
5 it is not going to be very easy for these products and for
6 these zoonotics to be put together especially under a direct
7 regulatory action.

8 So, let's set some targets and then use them for
9 further study, let the NCCLS group sit in on this, and let
10 them be responsible for setting these targets and then
11 reviewing them, and not a government agency.

12 For therapeutic use in animals. Again, a full
13 risk assessment needs to be done, and we have heard that
14 over and over today, and we have heard it challenged over
15 and over, but I think we have heard from our colleague from
16 Canada of the fact this can be done, and if we don't know
17 how to do it, let's take him out to dinner tonight and get
18 some ideas.

19 We do support judicious use and education about
20 use of antibiotics, and we should continue to do that, and
21 this framework should reflect that position.

22 We need R & D on better slaughter, processing,
23 storage, and preparation of our food products, cold
24 sterilization with pulsed ultraviolet light, things like
25 that can be done, and we have seen over and over that the

1 HACCP program that is being implemented has been severely
2 underestimated by this document and by some of the early
3 speakers.

4 This is working. The statistics show it, and the
5 prevalence data shows it, and we need to keep supporting it,
6 and then build upon that. Resistance thresholds, really,
7 this is more appropriate as a research study, not that I am
8 from an academic environment or anything, but I think rather
9 than a regulatory document, we need to support more research
10 into this area, and really work from there and then set the
11 thresholds.

12 Regarding the pre-approval and post-approval
13 studies, basically, I support a good body of studies on the
14 pre-approval side, including the Salmonella shedding studies
15 and modifications that were proposed by Dr. Miller this
16 morning.

17 We should support other good descriptive studies
18 of treatment resistance, transfer of mechanisms, and so on,
19 and so forth. We should support and enhance slaughterhouse
20 under NARMS surveillance system. It is in its infancy right
21 now, we have heard that, and it has its strengths and
22 weaknesses and I think, as a group, we can together and
23 really pull it together and make it a better system, and
24 just like it was intended to be, and mature it as we go
25 along.

1 Really, I support research and not regulatory
2 studies for understanding on-farm animal epidemiology
3 through a competitive grant system. We have a wealth of
4 good university personnel, a lot of good scientists, a lot
5 of good veterinary students and animal science students, and
6 so on, and so forth, that can do a lot to improve this.

7 I think these suggestions represent really a
8 simple, solvable proactive way that is science driven, and
9 it does support public health. Remember, you are asking us
10 to, on a daily basis, manage these dairies for animal
11 health, public health, environmental health, medical
12 ecology, and the financial well-being.

13 This framework document, although a good start,
14 does not help us to do that, and we need to work on it, and
15 I support the idea that we can modify this and make it a
16 better document than it stands today.

17 Thank you.

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

19 Questions of panel members of Dr. Cullor?

20 [No response.]

21 DR. STERNER: We are at that stage, and I know you
22 have all been anxiously awaiting with relief to your
23 posterior, and that is our final speaker of the night.

24 Dr. Barbara Glenn, is that correct? I have no
25 affiliation for you, but I assume again that you will

1 explain that to us, and you have the final 10 minute period
2 of the night.

3 **Dr. Barbara Glenn**

4 DR. GLENN: Mr. Chairman, it is my pleasure to be
5 the last speaker this evening. My name is Barbara Glenn,
6 and I am executive vice president for Scientific Liaison for
7 the Federation of Animal Science Societies.

8 I have not received any financial support
9 regarding my statement, and my expenses are paid by my
10 employer.

11 FASS, or the Federation of Animal Science
12 Societies, is a federation of three professional societies,
13 and has a membership of about 11,000 scientists who are in
14 academia, government, and industry. Our members do
15 research, teaching, and information exchange to students,
16 producers, consumers, and other members of the public.

17 Our three member societies are sponsors of three
18 major scientific journals that are respected around the
19 world in the animal, dairy, and poultry scientific
20 community.

21 We are familiar with the proposed framework that
22 you have released for review and comment. In general, we
23 request that you allow the science and the facts to guide
24 your deliberation and actions.

25 Some of the issues are old and have been raised

1 for 20 or more years. With new antibiotics and possible new
2 emerging strains of pathogens, some questions are new. We
3 should learn from past experiences and carefully look at new
4 situations while research should be directed to fill in the
5 information gaps that exist, so as to factualize the
6 decisionmaking process.

7 This is a topic of very serious concern and should
8 not be taken lightly. To not act if some of the concerns
9 turn out to be real is not ethical. Likewise, to take
10 actions that are not warranted also can be inappropriately
11 costly to both livestock producers and consumers.

12 Specifically, we believe the issue of implementing
13 a valid monitoring process to assess the development of
14 resistance in microbes to be much more complicated than
15 might be thought. There are a number of questions that seem
16 to be pertinent, and for which the answers are not obvious
17 from your framework.

18 Some of these that come to mind are the following.
19 First, how many samples are needed to provide assurance of
20 real changes due to antibiotics versus random changes that
21 occur over time? Are present baselines defined?

22 Secondly, what is the definition of resistance?
23 Is it just any increase in dose required to inhibit
24 organisms, or is it the total resistance to a previously
25 effective antibiotic?

1 Many new antibiotics have required an increased
2 dose after initial introduction, but remain effective at the
3 slightly higher dose levels on an indefinite basis. Would
4 such be considered evidence sufficient to remove an
5 antibiotic? If required dose increases, what level is
6 considered resistance, 2X, 100X, et cetera?

7 Thirdly, where would microbes be sampled? Is it
8 feasible to do adequate sampling on the farm? Who would do
9 this, and what level of funding would be needed to have
10 government employees doing this sampling? What does the
11 farm information do if it does not relate to the level on
12 the food? What are levels on farm or at the processing
13 level more important to human health considerations?

14 We hope that the VMAC and your professional staff
15 will discuss these and other related scientific issues, and
16 provide us with answers prior to taking any actions that
17 have a major impact on the health and well-being of animals.

18 Further, we would hope that your deliberations
19 would identify areas of critical information that are really
20 needed to shore up the basis for such decisions.

21 In addition, we would hope to have your support
22 for research funding to provide enough information to make
23 all of us more comfortable with the important questions that
24 are being raised.

25 Thank you very much.

1 DR. STERNER: Thank you, Dr. Glenn.

2 Questions from panel members?

3 [No response.]

4 DR. STERNER: You really drew the short straw when
5 it comes to how much we could stand.

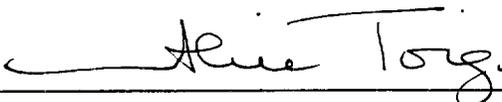
6 I want to personally thank you all for your kind
7 indulgence. I think we might have set an all-time record
8 for a continuous meeting. That is not my intent, but I
9 think you all see the importance of this issue and the
10 deliberations that will go on subsequent to our tomorrow
11 morning's two scheduled speakers.

12 With that, we stand adjourned until tomorrow
13 morning's reconvention.

14 [Whereupon, at 7:45 p.m., the proceedings were
15 recessed, to be resumed at 8:30 a.m., Tuesday, January 26,
16 1999.]

C E R T I F I C A T E

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script that reads "Alice Toigo". The signature is written in black ink and is positioned above a horizontal line.

ALICE TOIGO