

1 We have an aging population susceptible to
2 respiratory infections. Clearly, we will see more
3 antibiotic use there. We have a larger growing
4 immunocompromised population, not just age, but also from
5 transplants which are becoming much more routine.

6 So, clearly, in the human field, you are going to
7 see much more use of antibiotics driven by those kind of
8 factors, and those are the factors which we really ought to
9 be focusing on that will drive human antibiotic use and the
10 animal use, quite frankly, is peripheral as far as they can
11 see in this whole issue, to say nothing, of course, of
12 international travel and spread, and so forth.

13 According to the U.S. Centers or Disease Control,
14 there are 88,000 deaths annually from nosocomial infections.
15 Of those, we have been advised that about a third or 30,000
16 deaths involve infections resistant to antimicrobial
17 treatment. These deaths are not from food-borne pathogens,
18 but from hospital-acquired pathogens, such as Staph aureus
19 and Pseudomonas aeruginosa.

20 While the number of deaths in the U.S. from food-
21 borne pathogens we are currently estimating is somewhere
22 between 2,000 and 9,000 annually, we are unaware of any
23 documented case of a treatment failure resulting from --
24 this much lower number -- of resistant food-borne pathogen
25 disease caused by an animal drug.

1 So, up to this point we don't have any failures
2 that we are aware of, so this perspective of what is
3 happening on the human side, but the animal side, I think is
4 a very important one that seems to be missing from the
5 document and the discussions.

6 Now, clearly, resistant bacterial infections are a
7 serious human health problem. There are extensive efforts
8 underway in human medicine to address the resistance
9 problem, from educating parents on the appropriate and
10 inappropriate antibiotic therapy for their children,
11 encouraging doctors and hospitals to use antibiotics
12 judiciously, but I do not believe that FDA's Center for Drug
13 Evaluation and Research, CDER, is proposing to impose
14 drastic new approval requirements on antibiotics for human
15 use as CVM is proposing to do for animal use here.

16 While I do not suggest that the issues are exactly
17 parallel, this tremendous disparity in the public health
18 impact of antimicrobial resistance caused by human drug use
19 compared to animal uses raises serious questions as to why
20 FDA is proposing an excessively restrictive and
21 disproportionate kind of a regulatory approach for
22 veterinary medicine, while relying still on largely
23 educational and monitoring-based approach with respect to
24 human medicine where the problem truly resides.

25 Now, make no mistake. This is significant change

1 in terms as proposed in the regulatory document, the
2 framework document. The regulatory approach in the
3 framework document would have serious negative consequences
4 for animal agriculture.

5 It is difficult to imagine any new antimicrobial
6 that has a use in human medicine, now or in the future,
7 being approved for food use animals under this proposal, and
8 this is the proposal as it exists in the framework document.

9 If we try and think, then, about how it will be
10 applied in practice, reducing this to practice, to something
11 of a debate between reviewers and companies trying to
12 interpret this, to set out new guidelines, and set on, is a
13 fiercely complex process. So, it is a very complex
14 bureaucratic process we are proposing here to deal with this
15 situation. Quite frankly, to us it seems unworkable in
16 practice.

17 The research and development costs and the time
18 involved in bringing new animal drugs even through the
19 current approval process already make it very difficult for
20 companies to justify the expenses involved.

21 The extensive new requirements envisioned in the
22 framework proposal, as I say, when they are reduced to
23 practice, would, in our view, effectively prohibit companies
24 from committing the resources necessary to develop new
25 products.

1 We are all aware of FDA's workload. We have
2 passed the Animal Drug Availability Act. We still don't
3 have guidelines out in certain of the cases. There is a
4 tremendous amount of work generated by each of these changes
5 in regulations, and this one again would just add another
6 layer of complexity and uncertainty about interpretation
7 between reviewers within the agency, and so on.

8 It would also impose a very fixed framework, and
9 as we all know, science continues to develop, and this could
10 rapidly be outdated by progress in science, so we need
11 something a lot more flexible to approach the real issues
12 here.

13 Additionally, the concepts outlined in the
14 framework clearly could be used to seek removal of existing
15 approvals of many safe and effective animal antimicrobials.

16 Now, there is a need for new products and new
17 entities for use in food animals. Enabling veterinarians to
18 help to provide a healthy and safe supply of meat which the
19 consumer requires, we should all keep in mind that the
20 current drug approval process is extremely rigorous with the
21 approval of very few new antibacterials. For example, we
22 are estimating there is about only one new therapeutic
23 product which has been approved for use in swine over the
24 last 12 years.

25 A similar situation exists on antimicrobials for

1 beef, dairy, and poultry, with a total of only eight new
2 antimicrobial entities being approved for all food producing
3 animals since 1986, so less than one new antimicrobial a
4 year, and now a burdensome new process here being proposed.

5 Taken together, this question of an end of new
6 animal drug approvals and removals of existing approvals,
7 these developments would seriously harm the health of farm
8 animals and would result in significantly higher costs to
9 farmers to meet market demand, and these added costs would
10 be passed on to consumers in the form of higher food costs.

11 And to what end? It is highly unlikely that the
12 framework concepts would have any significant impact on
13 reducing the problem of antimicrobial resistance in human
14 medicine because the major resistance problem we are dealing
15 with here is the result of antibiotic use in humans.

16 I must say we are also disturbed by some details
17 of some more specific points. I won't go into too much
18 detail, but it does talk about E. coli 0157 in the document,
19 and it goes on to say, "The link between antimicrobial
20 resistance in food-borne pathogenic bacteria and the use of
21 antimicrobials in food producing animals has been
22 demonstrated in a number of studies."

23 There are several things wrong with that, but more
24 specifically, there are no studies regarding a link between
25 antimicrobial resistance in E. coli 0157 and the use of

1 antimicrobials in food producing animals.

2 Another disturbing argument is a discussion of
3 vancomycin resistant enterococci and citing the European
4 epidemiological evidence, the document says, "VRE in humans
5 may have been related in part to the induction of cross
6 resistance to vancomycin due to food animal use of the
7 related glycopeptide avoparcin."

8 But VRE is a problem in hospitals here in the
9 U.S., as well, and, of course, avoparcin has never been
10 approved in the U.S. So, a major fault in logic there.

11 The fact that VRE is a problem both in the U.S.,
12 where avoparcin isn't used, and in Europe, where it has been
13 approved and used, would seem to argue against not for the
14 proposition that VRE is related to use of the glycopeptide
15 in food animals, and the only common denominator between the
16 U.S. and Europe on this issue is the widespread use of
17 vancomycin in human medicine.

18 As an aside, my scientific colleagues in Lilly
19 have produced a paper which showed that the kilos of
20 vancomycin used in human therapy, both in the U.S. and in
21 Europe, increased very significantly over the 1980s and into
22 the 1990s. It increased, the original parenteral form
23 increased very, very significantly, and an oral form was
24 introduced into the marketplace with, of course, direct
25 exposure to the gut flora.

1 So, clearly, here was a major increase in
2 vancomycin usage both in the U.S., both in Europe, but
3 completely ignored, and somehow this relationship to a very
4 peripheral issue is sort of justified as being the major
5 cause of some of the problems. So, again, the logic does
6 not seem to be there.

7 Finally, before I turn to Dr. Carnevale, let me
8 say what I find perhaps most troubling about the framework
9 proposal is that FDA has looked at the same evidence as
10 numerous other bodies, this is not the only body which has
11 examined this issue, but it has arrived at sharply different
12 conclusions.

13 The proposal is based on the assumption that we
14 know antibiotic resistant pathogens can and do pass from
15 animals to humans, that means there is a public health
16 threat that requires extensive new, and to our mind
17 scientifically questionable, regulations.

18 But many others have looked at this problem,
19 affirmed the existence of resistance transfer, but found the
20 evidence to suggest major changes was not there.

21 Specifically, last summer, the National Research
22 Council examined the resistance issues in its report
23 entitled, "The Use of Drugs in Food Animals: Benefits and
24 Risks." This report, which was requested by USDA and FDA's
25 CVM, does not recommend the regulatory changes proposed in

1 the framework document.

2 On the contrary, the NRC called for an oversight
3 commission to advise FDA on both human and animal antibiotic
4 resistance issues and for the establishment of an integrated
5 national database to support sound scientific decision-
6 making processes for regulatory approval and use of
7 antibiotics.

8 According to NRC, "Until more accurate data on
9 animal antibiotic use, patterns and rates of resistance
10 transfer to humans, and occurrences of actual disease
11 emerge, and mechanisms of resistance are available, actions
12 aimed at regulating antibiotics cannot be implemented
13 through a science-driven, well-validated, and justified
14 process."

15 The report also contained the following comments
16 which seem especially relevant to the issues under
17 discussion by VMAC, as follows:

18 "Substantial information gaps contribute to the
19 difficulty of assessing the effect of antibiotic use in food
20 animals on human health. First, it is uncertain that the
21 observed or perceived increases in transference of
22 antibiotic resistance to humans is associated with the use
23 of antibiotics in the food-animal industry."

24 The report does go on to cite several other
25 information gaps which I won't quote in the interests of

1 time.

2 Finally, it does say, "Finally, although
3 conservative measures in the food-animal drug approval
4 process might be prudent until these questions are answered
5 definitely, the quest for new antibiotics for use in food
6 animals must continue. Mechanisms must be instituted to
7 increase research funding to discover new mechanisms of
8 antibiotic-drug action; to increase and expedite FDA
9 approvals of new drugs; to provide base funding for aspects
10 of long-term experimental resistance-emergence research and
11 surveillance research, which are not likely to be funded by
12 short-term competitive grants; and to develop much more
13 precise and accurate and quick tests of microbial, pathogen,
14 and antibiotic-resistant organisms for monitoring purposes.

15 Also, in 1998, the Institute of Medicine issues
16 its report on "Antimicrobial Resistance: Issues and
17 Options," and it looked again at a whole bunch of issues on
18 both human and animal medicine, and the IOM report, like the
19 NRC report, did not recommend regulatory changes along the
20 lines proposed in the framework document.

21 On the contrary, the report called for increased
22 research, more and better surveillance, collaboration
23 between government, industry and agricultural producers on
24 the development of educational materials and strategies.

25 Finally, at a World Health Organization meeting, a

1 panel of international experts examined the issue of
2 quinolones, et cetera, and I think we have already referred
3 to that, the use of fluoroquinolones in food animals has led
4 to the emergence of fluoroquinolone-resistant Campylobacter
5 and Salmonella with reduced susceptibility, but the report
6 goes on to say, "There has been little documented impact of
7 this resistance on human health" -- this has been referred
8 to earlier here -- "but there is a concern about potential
9 human health consequences if it were to increase. Again,
10 further research and data gathering are essential to
11 quantify this." And it goes on to specify a certain number
12 of things, but nothing like the very bureaucratically
13 complex restrictions and regulations we are talking about in
14 this document.

15 Let me close my comments by saying simply that we,
16 along with many others, have examined the issue of
17 antimicrobial resistance, concur with FDA's goal, which is
18 reducing the rate and development of resistance to protect
19 the viability of antimicrobial drugs, but we don't believe
20 the concepts outlined in this particular document provide a
21 workable basis from which to address this issue.

22 So, for a more detailed analysis and the proposals
23 that we think are more realistic, I will now pass on to my
24 colleagues, Dr. Carnevale and Mr. Mathews.

25 Thank you.

1 **Dr. Richard Carnevale**

2 DR. CARNEVALE: Thank you, Dr. Fox. Good
3 afternoon. I am Rich Carnevale, vice president of
4 scientific and regulatory and international affairs for the
5 Animal Health Institute.

6 Dr. Fox has provided you with an overview of the
7 animal drug industry's concerns regarding the issue of
8 antimicrobial resistance. At this time, I would like to
9 comment on some of the more specific aspects of the
10 framework.

11 In the introduction to the document, the CVM
12 claims that new reports, particularly from Europe, have
13 renewed concerns for the contribution of animal
14 antimicrobial use to the development of resistance in food-
15 borne bacteria.

16 Several literature references have been cited to
17 support their conclusions, and some of those have been
18 commented on today. Their conclusions are that immediate
19 action is necessary to change the regulatory approach and
20 the approval of antimicrobials in food producing animals.

21 AHI believes that the citations provided do not in
22 all cases represent new information, and moreover, do not
23 provide the compelling scientific justification for such a
24 significant change in animal drug approval requirements.

25 We would like to briefly comment on some of these

1 publications as it builds our foundation for further
2 comments on the specific framework proposals.

3 One of the key reports that is referenced in the
4 document is that of Threlfall et al., from the Central
5 Public Health Laboratory in Great Britain published in 1996.
6 In a series of articles, the authors suggest that temporal
7 increases in "resistance" levels of Salmonella typhimurium,
8 Determinant Type 104, are directly tied to veterinary use of
9 fluoroquinolones.

10 This and other reports from this laboratory were
11 what the industry viewed as the trigger which set CVM on
12 their current path to propose sweeping changes to the
13 regulatory process.

14 While we viewed this information as important
15 regarding an emerging a food-borne threat, we did not
16 believe that the information was sufficient to cause such a
17 significant disruption to the current approval process for
18 veterinary drugs.

19 First, the use of the term "resistant" has been
20 used by the authors not to describe clinical resistance, but
21 rather a shift in susceptibility. They have chosen lower
22 breakpoints than the standards set by the National Committee
23 for Clinical Laboratory Standards (NCCLS) and the British
24 Society for Antimicrobial Chemotherapy. What have been
25 reported as "resistant" isolates are in reality clinically

1 susceptible according to the NCCLS and BSAC guidelines.

2 Second, as far as we know, there has not been a
3 documented case of a human fluoroquinolone treatment failure
4 in the UK because of DT104 as a result of the treatment of
5 animals.

6 Third, reports from that same laboratory over the
7 last two years demonstrate a marked decline in the incidence
8 of Salmonella typhimurium DT104 and no clinical resistance
9 to the fluoroquinolones has yet emerged. At the same time,
10 the incidence of DT104 with increased MICs to
11 fluoroquinolones has really not changed.

12 Another study concerns fluoroquinolone resistance
13 levels in Campylobacter species in poultry in the
14 Netherlands published in 1991. This information was
15 considered by the 1994 FDA Joint Advisory Committee prior to
16 it recommending that the fluoroquinolones were approvable
17 for therapeutic use in food animals with certain
18 restrictions.

19 The Advisory Committee did not consider the
20 Netherlands experience adequate evidence establishing a
21 public health risk to preclude the approval of quinolone
22 animal drugs in poultry. For one thing, a high level of
23 resistance was already present in Campylobacter prior to the
24 introduction of fluoroquinolones for use in poultry.

25 The study from Spain was mentioned earlier, where

1 increases in resistant strains of Campylobacter species
2 were, in fact, observed, however, Spain is a country where
3 manufacturing, distribution, and sales of relatively low
4 quality generics do abound, and other veterinary and human
5 pharmaceuticals are generally less controlled.

6 In particular, these products tend to be more
7 readily available, as was mentioned, for human and animal
8 use without prescription, in contrast to the limited and
9 veterinary controlled uses in the United States. It is
10 important that we make that difference.

11 This report also failed to demonstrate that there
12 was a direct link between the use of fluoroquinolone in
13 animals and the actual development of resistance that was
14 determined in people.

15 Another reference from the Minnesota Department of
16 Health has also been referred to here today. That data is
17 yet to be published, so we really don't know exactly what it
18 says, but we have heard at various meetings pieces of it.

19 From the information we know about, only a very
20 small percentage of human clinical cases were associated
21 with the fluoroquinolone-resistant Campylobacter, and the
22 majority of these were attributed to foreign travel.

23 The same author has reported that fluoroquinolone-
24 resistant Campylobacter has been increasing in human
25 isolates since 1991 in Minnesota, and that is four years

1 prior to the approval of any fluoroquinolone in food
2 producing animals.

3 Now, the document also points out concern for
4 development of antibiotic resistance in non-pathogenic
5 enteric bacteria, which may under certain circumstances be
6 pathogenic. References are appended from several studies in
7 Europe suggesting a link between vancomycin resistant
8 enterococci and glycopeptide use in animal feeds. We have
9 heard a discussion about that this afternoon.

10 These references represent a significant research
11 effort in Europe to incriminate the use of antimicrobial
12 growth promoters as being responsible for transferring
13 resistance to humans.

14 I would comment that these and other studies have
15 been considered by the Scientific Committee on Animal
16 Nutrition, an advisory body to the European Union
17 Commission.

18 They have reviewed the situation with several
19 drugs, avoparcin, virginiamycin, tylosin, and spiramycin,
20 all the drugs that the European Union has decided to ban.
21 In every case, their conclusions have been that the data
22 falls short of being able to conclude that the use of these
23 drugs in animal feed represent a significant public health
24 risk. However, as we know, the European Union moved ahead
25 with their ban.

1 Now, there is no question that common resistant
2 isolates or resistance determinants can be found in humans
3 and animals as a result of antibiotic use. Clearly, animals
4 and humans can exchange bacteria carrying these properties.
5 I think we have seen evidence for that. However, the cited
6 evidence in the framework document, in our view, simply does
7 not rise to a level which justifies the extreme measures
8 being proposed here by CVM. This does not mean that we
9 shouldn't take safeguards, and we will try to discuss what
10 we think is our approach to the problem later in this
11 presentation.

12 Now, let me talk a few minutes about some of the
13 specifics on the proposal, so you can get our views of it.

14 With regard to categorization, the agency is
15 proposing that the human health impact will be evaluated on
16 two factors: one, the importance to human medicine; and
17 two, the potential human exposure. That was discussed
18 earlier by Dr. Sundlof.

19 Based on this evaluation, FDA proposes placing the
20 antimicrobials into three categories based on their value to
21 human medicine and their exposure.

22 Now, AHI shares the concern for preserving the
23 usefulness of antimicrobial drugs for treatment of human
24 infections, while at the same time balancing the need to
25 assure the availability of needed antimicrobials in food

1 animals.

2 However, we believe the plan proposed by CVM will
3 likely assure that development of important new
4 antimicrobials for food producing animals may not even be
5 attempted, as Dr. Fox alluded to.

6 A significant problem with establishing pre-
7 approval and post-approval requirements based on the
8 categorization is a dynamic new process by which pathogens
9 emerge and new antimicrobials are discovered and developed.

10 Because new drugs in discovery require 10 or more
11 years to develop, it won't be possible at the time of
12 discovery to really project the importance of a new
13 antimicrobial to human medicine.

14 That, of course, will be dependent on diseases of
15 importance to humans and availability of other effective
16 drugs at the time of expected commercialization of the new
17 antimicrobial.

18 Because virtually any class of antimicrobial that
19 has the potential benefit for animals will have similar
20 benefits for human medicine, it is really difficult to
21 imagine that any innovative antimicrobial would be developed
22 for animal use without really having to meet the criteria of
23 Category I, and we recognize there are several categories,
24 but to us it appears that most drugs are going to fall into
25 Category I, and this is obviously going to lead to a

1 reluctance by companies to invest in their development.

2 The result, of course, will be more reliance on
3 the older products, and hence, more resistance selection for
4 those older products.

5 Now, some might suggest that animal health
6 companies should just develop drugs for animal use, and
7 avoid anything related to human medicine. Well, as I said
8 before, this is rather difficult because any drugs that have
9 a potential for treating human disease will probably have
10 applications in veterinary medicine, and, in fact, most
11 animal health companies share their discovery research with
12 their human counterparts.

13 The economics of trying to do discovery research
14 for animal drugs only simply doesn't make sense and
15 certainly can't be justified economically.

16 Further, what might not be important today for
17 medical uses might become important in the future. So, it
18 is a very difficult balancing act - how do you determine
19 what is important to human medicine today, so that you have
20 that vision for the future.

21 CMV also talks about exposure scenarios, and AHI
22 certainly agrees that potential exposure of humans to
23 resistant organisms is important to consider. In fact, we
24 believe it is the primary factor to consider.

25 FDA states, and AHI concurs, that antimicrobial

1 resistance transfer is determined by a complex chain of
2 events. The proposal lists many factors that should be
3 considered when classifying potential exposure.

4 These include attributes, product use, and
5 potential human contact. Although food processing is
6 mentioned, the emphasis is clearly on the attributes of the
7 drug and how the product is used on the farm.

8 The industry sees a problem with this. The number
9 of animals treated, for example, has little relationship to
10 actual human exposure to food-borne bacteria.

11 Clearly, the most critical factors in determining
12 potential exposure take place after the animal or food
13 products, in the case of milk, leaves the farm. For
14 example, consider the use of antimicrobials in dairy calves.
15 Exposure to pathogens, whether they be susceptibility or
16 resistant, is eliminated with pasteurization. The risk
17 essentially is zero assuming there are no failures in the
18 pasteurization process.

19 So, drug attributes, product use, potential human
20 contact, manure management practices, a lot of these factors
21 are essentially non-factors.

22 Of course, we have a different situation with meat
23 and eggs. These products are not pathogen-free. However,
24 we are all aware of steps that are being taken, such as
25 HACCP, steam sterilization, irradiation, that should have a

1 major effect on reducing food-borne pathogens from a number
2 of animal sources.

3 AHI doesn't believe that this important aspect
4 relating to exposure has really been given adequate
5 consideration by CVM in the development of their proposal.

6 Let me comment a moment on pre-approval studies.
7 The framework proposes that pre-approval studies would be
8 necessary for all Category I and II to assess the rate and
9 extent of resistance development in enteric bacteria.

10 The document also talks about resistance
11 thresholds and monitoring thresholds. For Category I, the
12 agency says it may be possible to establish a level of
13 resistance that will not cause a significant transfer to
14 human pathogens.

15 However, lacking that data, the agency would
16 consider any level of resistance change to be a cause for
17 the drug not being shown to be safe. In other words, the
18 drug sponsors must demonstrate by pre-approval studies what
19 level of resistance is safe prior to approval.

20 We believe the concept here proposes a standard
21 that simply can't be met. Aside from the fact that the
22 document is unclear as to whether these thresholds are based
23 on susceptibility shifts or clinical resistance, the Center
24 is acknowledging that in many cases it won't even be
25 possible to define a safe level of resistance.

1 Since there is very little correlation between in
2 vitro susceptibility of enteric bacteria from food animals
3 and impacts on human health, there is little likelihood that
4 you could ever set a safe level of resistance. Therefore,
5 the agency, we believe, is proposing a rather prohibitive
6 standard given the fact that resistance development is a
7 natural response by bacteria.

8 Furthermore, it appears that CVM may be using a
9 similar concept -- and I think others have commented on this
10 -- to the way animal drug residues are handled, but there
11 are important differences which make that an unworkable
12 approach. I think Lyle Vogel commented on that.

13 At least with drug residues, we have assays, we
14 have safety factors, statistics can be applied. The
15 scientific basis and protocols for establishing resistance
16 standards that are similar to drug residue tolerances simply
17 haven't been developed. There isn't a long history of
18 toxicological research that has gone into antibiotic
19 resistance. It simply doesn't work to really quantify
20 resistance by the methods used to establish residue
21 tolerances.

22 Pathogen load. We have some concerns about
23 pathogen load. FDA suggests that this is necessary to
24 determine the time required for the pathogen load to
25 decrease following treatment. We question the basis for

1 this requirement.

2 Implicit in the requirement for pathogen load
3 studies is the assumption that quantitative viable counts of
4 pathogens, above a baseline normal, will present a greater
5 risk to public health.

6 We are not really aware of evidence that
7 correlates increased on-farm gut concentration or prevalence
8 of food-borne pathogens to increased human disease from
9 those pathogens, nor are we aware of data which indicate
10 that shedding of gram-negative bacteria, which are sensitive
11 to a drug under test conditions -- and that would be the
12 case with any new products -- should even be of concern with
13 broad spectrum antimicrobials.

14 I think we heard this morning the use of a
15 resistant strain. Well, that seems to be imprudent to
16 develop resistant strains just to do studies.

17 There are a number of inherent difficulties that
18 can be pointed out if one attempts to acquire the
19 information, and I think it was already mentioned that there
20 are some studies in swine, I won't go into that, but these
21 on-farm studies that USDA has collected have shown a
22 multitude of factors that contribute to pathogen shedding,
23 and transportation is certainly one of those.

24 Establishing a relationship, a clear relationship
25 between pathogen load and the use of the drug, we think is a

1 very difficult thing to do, confounded by many factors.

2 Let me move to post-approval studies. It is clear
3 that FDA believes that on-farm studies to monitor
4 antimicrobial resistance development will be necessary for
5 all Category I and Category II drugs, again, to ensure that
6 thresholds are not exceeded.

7 The proposal would have drug companies collect
8 such data on a drug-by-drug basis to establish and monitor
9 these farms to meet the established monitoring and
10 resistance thresholds, so that intervention and mitigation
11 strategies could be investigated and initiated in a timely
12 fashion.

13 AHI has serious concerns with this concept. We
14 don't believe that on-farm isolation and susceptibility
15 testing of food-borne bacteria, in particular pathogenic
16 organisms, represents the best or most efficient location
17 for assessing exposure.

18 Because of the relatively low prevalence of
19 pathogens, numerous animals would need to be sampled in
20 order to gather meaningful statistically valid data upon
21 which to determine changes in susceptibility.

22 Now, in order to get around these problems, CVM
23 has suggested that surrogate organisms might be used as
24 sentinels for pathogen changes. We are concerned that the
25 use of a surrogate removes the relevance of the results even

1 further from what we are trying to accomplish, that is, to
2 assure food safety.

3 The framework lays out FDA's belief that it would
4 be appropriate to evaluate mitigation measures. Now, we are
5 certainly interested in determining mitigation measures that
6 could be used to decrease the rate and extent of resistance
7 development. The information would be helpful to our
8 companies in prolonging the effectiveness of antimicrobials.
9 However, we don't see how such studies can really be
10 justified as part of the approval process.

11 Information from these studies should be used in
12 the judicious use initiative, and this is an area where
13 industry, the veterinary profession, and government should
14 work together, but we don't think it belongs in the drug
15 approval process.

16 Now, as you will hear in a few minutes, we believe
17 the best early warning system to monitor for changes is not
18 on the farm, but in the slaughterhouse and closer to the
19 consumer of meat and poultry. Further, we view testing for
20 food safety purposes to a federal government responsibility
21 as it is with other food-borne hazards, such as animal drug
22 residues and pesticides.

23 The costs of on-farm testing should not be
24 underestimated, or the logistics of even trying to collect
25 representative data to determine if a pre-determined

1 quantitative threshold has been exceeded. Estimates run
2 more than a million dollars per drug per year even if
3 studies could be adequately designed and conducted, and that
4 is probably an underestimate.

5 The scope of testing that CVM has in mind, we
6 believe might be beyond even what the federal government is
7 capable of doing in the surveys that FSIS and APHIS have
8 conducted over the years.

9 Thresholds. It is not clear in the document what
10 is meant by a "threshold," whether it's a resistant or
11 monitoring threshold and how the two may differ. We are
12 assuming a resistance threshold might be a higher value than
13 established for monitoring. If that is the case, then, we
14 have complicated an already difficult process and added yet
15 another set of assumptions to the approach. We have not
16 only one threshold, but multiple thresholds. It is getting
17 very difficult.

18 The use of in vitro susceptibility data as a
19 regulatory tool, I believe has many drawbacks. Now,
20 susceptibility testing is very valuable for evaluating
21 trends and useful as an indicator for selecting
22 therapeutics, but it is a measure of in vitro activity and
23 in no way assures therapeutic outcome. It's a laboratory
24 test. When in vitro susceptibility testing is used as a
25 monitoring tool, we have been told by experts in the field

1 that several years of data are really necessary to establish
2 trends before you could tell whether something is occurring,
3 and although shifts may be detected in the short term, more
4 time is needed to confirm these trends.

5 The Salmonella DT104 situation in the UK, that I
6 have mentioned earlier, is a good example of that, whereas,
7 shifts initially were seen, and they seem to be leveling
8 off.

9 With that, I think I will close and turn to my
10 partner, Mr. Mathews, but as you can see, FDA's proposed
11 framework for regulating antimicrobials, AHI does not
12 believe can be practically implemented.

13 In closing, I want to urge you in your role as
14 advisers to the Center for Veterinary Medicine to request
15 that the agency reconsider its proposal for a change in the
16 regulation of animal drugs as they have suggested.

17 Thank you.

18 **Alex Mathews**

19 MR. MATHEWS: Thank you, Rich.

20 Mr. Chairman, in closing -- when you are having
21 this much fun, time really flies. Dick, how much time do we
22 have left?

23 MR. GEYER: It has expired.

24 MR. MATHEWS: Thank you all.

25 MR. GEYER: You have time to finish your prepared

1 remarks. We have turned the clock off. You will stay on
2 green until you finish your script.

3 DR. STERNER: However, don't construe that as
4 license to carry on.

5 MR. MATHEWS: Okay, we won't run it up, but I
6 appreciate the indulgence of this committee very much. I do
7 think at this point you all deserve an award. You have been
8 very patient and tolerant with the number of speakers and
9 the amount of material that has been covered. I will be
10 very brief.

11 As Rich said, we would now like to present our
12 views, AHI's views on an effective strategy to deal with
13 this issue, given our industry's concerns with the overall
14 approach that CVM has proposed.

15 Antibiotic resistance is a problem that FDA and
16 the medical and veterinary communities have struggled with
17 for many years. Numerous studies have been conducted in an
18 attempt to better define the causes, the degree of potential
19 risk, and ways to manage it. The fact that we are here
20 today debating what to do about all of this indicates that
21 the problem is not easily solved, there is no magic formula
22 which, if followed, will assure regulators that they are
23 preventing a public health problem.

24 Every health concern that may present itself need
25 not be dealt with by an overly zealous regulatory approach

1 which simply adds additional burdens for both industry and
2 the government to deal with.

3 Absent a defined health crisis that can be clearly
4 prevented by specific risk management strategies, there are
5 usually other options that can be examined. We have
6 previously indicated that risk assessment is the first and
7 necessary component to judge how great a risk there may be
8 and whether a public health crisis exists.

9 Clearly, expert review of the issue, the current
10 literature, and documented instances of health problems has
11 led most scientists to conclude that there is a potential
12 risk, but that the evidence has not risen to a level which
13 indicates that there is an immediate health concern.

14 We refer to recent reports of the 1998 WHO meeting
15 on the medical impact of fluoroquinolones, as well as the
16 recently completed National Research Council report, "The
17 Use of Drugs in Food Animals: Benefits and Risks."

18 The fact is the long history of antibiotic use in
19 animals has generally failed to turn up compelling examples
20 of where antibiotic use has significantly impacted human
21 health that would justify the implementation of overly
22 stringent controls.

23 Moreover, there are a number of regulatory
24 safeguards currently in place for antimicrobials. All new
25 therapeutic antibiotics are now only permitted by or on the

1 order of a licensed veterinarian whether they be
2 prescription dosage form products or the new veterinary feed
3 directive drugs as recommended to FDA by this advisory
4 committee in 1994.

5 For certain drugs, such as the fluoroquinolones
6 and glycopeptides, FDA has established a policy prohibiting
7 extra-label use which has been widely publicized and
8 endorsed by veterinary and practitioner groups.

9 As you know, the approval process for veterinary
10 drugs is already extremely rigorous for all aspects of
11 animal safety, effectiveness, and human safety. FDA
12 establishes strict residue tolerances and withdrawal periods
13 for animal drugs.

14 USDA reports low level of residue violations in
15 the National Residue Program indicating that animal drugs
16 are, in the overwhelming majority of cases, being used
17 correctly. Producer and veterinary groups have had a major
18 impact through quality assurance programs by instilling the
19 principles of proper use. It has been said that veterinary
20 drugs may be among the most regulated consumer products in
21 the country.

22 The animal health industry supports strong
23 science-based regulation of its products, regulations which
24 thereby improve confidence in the safety of these products.
25 On the other hand, these policies must be based on an

1 objective risk assessment, the scientific validity and
2 practicality of the proposed measures, and a determination
3 of the economic impact on the affected parties.

4 We do not see these factors having been considered
5 by the agency in the development of the framework document,
6 nor do we see that FDA has considered the extensive efforts
7 of three prestigious groups of scientists - the National
8 Research Council, the Institute of Medicine, and the World
9 Health Organization - and the conclusions they reached after
10 their recent in-depth evaluations of the resistance issue.

11 Instead of building additional requirements of
12 dubious scientific value into the approval process, we
13 endorse building on what has already been learned and
14 recommended, and on approaches currently in place for
15 evaluating and controlling the spread of antibiotic
16 resistance. We believe the concerns that we all share can
17 best be addressed with a program encompassing the following
18 elements:

19 1. Risk Assessment. Dr. Fox has previously
20 emphasized the importance we place on objectively assessing
21 the potential for harm before any decisions can be made to
22 impose new regulations. Risk assessment has become a
23 fundamental principle in developing public policy.

24 Trade agreements negotiated within the World Trade
25 Organization have embodied this approach for resolving food

1 safety policy debates. In fact, I think it is worth
2 relating the recent comments of a high USDA official, Gus
3 Schumacher, as many of you know, the Under Secretary for
4 Farm and Foreign Agriculture, who, when speaking about U.S.
5 concerns over attempts to restrict foreign trade through
6 nonscientific-based sanitary and phytosanitary standards
7 said, and I quote, "We want to make sure that science, not
8 politics, is the guide when countries adopt measures
9 relating to health and safety. Belief in the scientific
10 method also must be the foundation of informed public
11 policy. A policy based on public perception, rather than
12 fact, will ultimately fail."

13 We believe that the risk and benefit assessment
14 methodology being developed by Georgetown University's
15 Center for Food and Nutrition Policy could serve as the
16 basis for this effort. A sound, science-based, risk and
17 benefit assessment approach is critical in assessing the
18 impacts on human health of using antibiotics in food
19 animals.

20 Monitoring and Surveillance. Strengthen and
21 expand the National Antimicrobial Susceptibility Monitoring
22 Program.

23 Subsequent to the hearings on fluoroquinolones in
24 1994, the FDA and USDA established an antibacterial
25 susceptibility monitoring program which focuses on carcass

1 sampling in slaughter facilities. AHI strongly supports
2 this program since in our opinion it is the optimum place to
3 assess potential exposure from resistant food-borne
4 pathogens.

5 However, the program is in need of additional and
6 continuing resources to maintain testing of all available
7 isolates coming from governmental food safety testing
8 programs, and the addition of new compounds to the program
9 as needed.

10 This will improve the sentinel value of the data
11 in detecting changing trends in susceptibility with
12 important antibacterials. Current HACCP sampling provides
13 isolates of Salmonella obtained from short term focused
14 testing by FSIS to determine a plant's compliance with
15 pathogen reduction standards.

16 Testing of these isolates is useful and should be
17 continued. However, it should be supplemented by
18 susceptibility testing of isolates obtained from more
19 routine national baseline surveys that FSIS plans to
20 reconduct on a species-by-species basis in the future.
21 Improving the national monitoring program to be a better
22 indicator of what is occurring nationally is important in
23 addressing the potential human exposure to resistant food-
24 borne bacteria.

25 Appoint an expert blue ribbon panel of scientists

1 to evaluate data from the national monitoring program,
2 examine current research and the need for new studies, and
3 make recommendations to FDA on resistance issues.

4 The FDA should form this blue ribbon panel
5 composed of, as we envision it, microbiologists,
6 epidemiologists, public health experts, and other
7 appropriate experts to regularly review data from the
8 susceptibility testing of animal isolates, and report to the
9 agency their findings regarding whether or not any patterns
10 or resistance or decreased susceptibility are appearing.

11 This group could work with CDC on findings from
12 the human sentinel site testing program in order to compare
13 results with the animal data. The panel of experts should
14 also analyze and critique the scientific knowledge of
15 predictive studies for assessing antibiotic resistance,
16 examine current model studies, and make recommendations to
17 the agency.

18 Based on analysis of the national monitoring
19 program, government agencies should then conduct focused
20 epidemiological investigations to determine location and
21 causes of susceptibility changes.

22 This is currently listed as one of the objectives
23 of the national monitoring program as stated in its 1998
24 report. We support this approach in using the monitoring
25 program data as it uses resources appropriately and where

1 necessary when problem are encountered. Under the
2 President's Food Safety initiative, follow-up investigations
3 could be conducted through the auspices of APHIS and ARS to
4 determine the source and possible causes of susceptibility
5 shifts.

6 Establish an action team composed of veterinary,
7 producer, industry, government representatives and other
8 scientists to propose specific mitigation steps to control
9 problems identified in epidemiologic investigations.

10 These steps could range from efforts to
11 communicate and educate producers and veterinarians on
12 changing the pattern of use of an antibiotic, to more
13 stringent measures such as labeling changes or temporary or
14 permanent suspension of use.

15 The key concept here is that by involving and
16 seeking the commitment of all stakeholders in addressing a
17 potential problem, we can achieve a swift, focused solution.
18 It was mentioned earlier the efforts that are underway in
19 human medicine the control the development of antibiotic
20 resistance through the efforts of public health agencies,
21 industry, health care facilities, and practitioners. There
22 are strong parallels with those activities and what we are
23 proposing here.

24 Education. Encourage, promote, and help to fund
25 efforts to develop and integrate judicious use principles

1 and guidelines as standard operating procedures for all
2 veterinarians and produces.

3 AVMA has undertaken to develop judicious use
4 principles for antibacterial use in animals and is currently
5 supporting efforts to develop more detailed species
6 guidelines. These efforts have involved not only practicing
7 veterinarians, but also producer groups, FDA, and Centers
8 for Disease Control and Prevention.

9 AHI is also encouraging development of judicious
10 use principles and guidelines for antibacterials used in
11 animal production. Through these efforts we believe the
12 principles of judicious use will become more deeply
13 integrated and embedded in the practice of food animal
14 medicine and animal production.

15 In closing, I would like to reiterate that we in
16 the animal health industry share the concern over the
17 development of antibiotic resistant bacteria, and we support
18 comprehensive efforts to assure that the use of antibiotics
19 in animal agriculture does not harm public health.

20 We believe the programs we have outlined here -
21 establishing a risk assessment methodology to quantify
22 potential impacts of antibiotic use, educational efforts to
23 promote judicious use, strengthening the government's
24 national monitoring and surveillance efforts to assess
25 potential human exposure, increased epidemiological

1 investigations, and appointment of a blue ribbon panel to
2 advise FDA on resistance development - are the appropriate
3 measures to address this issue.

4 We are committed to helping find effective means
5 for monitoring and controlling antibiotic resistance that
6 may arise from animal use while still making sure we
7 maintain the availability of needed therapeutic and
8 production tools.

9 For the past 58 years, a key part of our mission
10 has been to help America's farmers produce the safest, most
11 nutritious, high quality food supply possible. The steps we
12 have outlined will continue that important mission while
13 assuring that the health of the American people are not
14 compromised in any way.

15 Thank you, Mr. Chairman.

16 DR. STERNER: We will now entertain questions from
17 the panel of the three speakers that we heard, and I will
18 exercise the Chair's prerogative by asking about the
19 Georgetown report and when will it be due out.

20 MR. MATHEWS: We understand that we don't have
21 control over the timing of that, Mr. Chairman, but we
22 understand it's a matter of months before it's out. There
23 may be a preliminary report out within the next month or so,
24 but I think that Dr. Crawford is slated to be a speaker
25 tomorrow, and may be able to provide more specific

1 information about that, though it should be a matter of
2 months.

3 DR. STERNER: Dr. Bell.

4 DR. BELL: Our three colleagues have raised a long
5 list of issues, some technical, that could probably be
6 addressed, some more philosophical, that we basically don't
7 agree with.

8 I guess my question, though, is as I tried to
9 indicate in my talk this morning, the real challenge is how
10 are we going to get off the dime and move forward, and I
11 would like to ask Rich and your two colleagues, your
12 proposals to do a more comprehensive risk assessment and
13 appoint a blue ribbon panel, well, first, how would this
14 blue ribbon panel manage to do what multiple blue ribbon
15 panels in the past have never been able to do, which has
16 been produce something that both the human and animal health
17 people could agree on, and second, the risk assessment, you
18 know, I mean it really sounds good, but the problem we have
19 is that risk assessments are dependent on assumptions, on
20 modeling, on methodologies, and I perceive this notion that
21 if, oh, we just waited for the risk assessment, then, the
22 clouds overhead would part, the light would shine through
23 from the heavens, and the way would then be clear, and we
24 would all agree, and I guess, it seems pretty clear to me
25 that whatever the risk assessment's conclusions were, the

1 people in either human or animal health who disagreed would
2 challenge the assumptions and the methodology and everything
3 else, so I am at a loss to see how we move forward based on
4 the admittedly laudable principle of waiting for scholarly
5 risk assessments.

6 You know, we at CDC, we like surveillance because
7 we feel like surveillance measures, what is going on in the
8 real world, and it enables us to leapfrog ahead of some of
9 these debates as to what would happen if we did this or
10 that.

11 So, my question is how are the blue ribbon
12 commission and the risk assessment that you proposed really
13 going to help us move forward now, whereas, this kind of
14 thing really hasn't helped in the past, in my opinion?

15 MR. MATHEWS: Richard, you may want to respond, as
16 well, but let me take a stab at that.

17 I think with respect to the risk assessment, let
18 me address that first. I think the need to have that can't
19 be overstated. What we don't have, what we lack is a
20 quantifiable risk assessment from farm to table, what is the
21 risk to public health.

22 What we are proposing here, what is being proposed
23 in the framework is an extraordinary shift in terms of how
24 animal drugs are approved, and what Dr. Fox talked about is
25 absolutely spot on it. It will squelch R & D, it will

1 squelch production, it will cause a shift in husbandry
2 practices, it will have far reaching residual impact.

3 To get to that point, to reach those kinds of
4 judgments and decision that that has to be done, first, a
5 risk assessment has got to be conducted. Now, how it is
6 done, I think it requires, as I indicated in my remarks, it
7 requires the commitment from all the stakeholders involved
8 focused on this issue.

9 I think that leads me into the blue ribbon panel.
10 The blue ribbon panel needs to be focused exclusively on
11 this issue, but I think again with science driving it, and I
12 think that there may have been other panels, some termed
13 blue ribbon and others, but they haven't specifically
14 focused on this issue in terms of how it can go forward.

15 DR. STERNER: Any other comments from the
16 panelists? Okay. Dr. Norden.

17 DR. NORDEN: I think I would like to follow up a
18 little bit on Dr. Bell, but I have a couple of comments. I
19 mean what I keep hearing in a sense is what I call a smoking
20 gun hypothesis - show us a case in a human organism that was
21 acquired from an animal with resistant flora, and I think
22 everyone who knows about epidemiology and surveillance knows
23 that that is virtually impossible. It is almost impossible
24 with a nosocomial infection in the hospital to find out
25 exactly where it came from.

1 Maybe a risk assessment will give you great value,
2 I am not sure. I am like Dr. Bell on that.

3 The other is simply to say that I think that in
4 terms of regulation of drugs for human use and resistance,
5 speaking as a member of the FDA Anti-infective Advisory
6 Committee, not as an FDA member, that CDER is struggling
7 with exactly the same issues that, in our evaluation of a
8 drug like Synercid, one of the major questions is how do you
9 achieve regulation, how do you approve a drug with a major
10 emphasis on resistant organisms, and I think that my
11 impression is that FDA is moving toward more stringent
12 regulatory involvement with drugs for human medicine that
13 are going to involve resistance.

14 There are requirements for postmarketing
15 surveillance that don't exist presently that have been
16 proposed. So, I don't think there is quite the discrepancy
17 between "human" and "animal" medicine that was cited by our
18 colleagues.

19 DR. STERNER: Dr. Angulo.

20 DR. ANGULO: My concern is that certainly the
21 negative tone of your presentation, first, you discount much
22 of the background material that is provided in the framework
23 document, which although not extensive, we could point you
24 towards extensive evidence, and please be assured that the
25 Centers for Disease conclusion clearly is that there is an

1 increasing trend of antimicrobial resistance in food-borne
2 pathogens, and the use of antimicrobials in food animals is
3 the driving force behind this increasing antimicrobial
4 resistance.

5 Yes, it is true that we do not yet have human
6 treatment failures because of completely resistant in food-
7 borne pathogens, but we are rapidly approaching that arena
8 or that situation, and we believe strongly at the Centers
9 for Disease Control that we need to mitigate this problem
10 now, not in 20 years.

11 That being said, and I would be happy to discuss
12 with the panel, the critiques made of the background
13 documents, I would be happy to offer a different impression
14 of the background documents, but my first comment is about
15 the negative nature of the critiques of the framework is
16 because I just am wrestling with what is the alternative.

17 Although you can say many negative things about
18 the framework, I just don't see an alternative, and no
19 alternative was offered. The Animal Health Institute did
20 provide an outline of a risk assessment, increased
21 epidemiological investigations, increased monitoring, a blue
22 ribbon panel, where is the public health safeguard? There
23 is no safeguard there. Is there a public health safeguard if
24 we increase monitoring? No.

25 If we do more investigations, where is the

1 safeguard? Where is the consumer of the United States
2 protected by any of those actions?

3 Now, if we do increased monitoring, and if we
4 respond to certain things we see on increased monitoring,
5 then, we begin to have a safeguard, and now we begin to
6 start sounding like the framework document.

7 So, rather than throwing the baby out with the
8 bath water, rather than throwing the whole framework out,
9 your comments and critiques about the framework are well
10 taken, and the framework needs to be fine-tuned and the
11 details have to be worked out, but the framework of the
12 framework document provides for the first time light at the
13 end of the tunnel that we can begin to assure the consumers
14 of the United States that the public health is being
15 protected, the public's health is being protected.

16 DR. STERNER: Respondents?

17 MR. MATHEWS: If I can make just an initial
18 reaction to that. The point is well taken. I am glad I
19 have a chance to respond to it.

20 I think in the question, what you are saying is
21 how do we protect the public health, and I come back I think
22 to our original fundamental point, which is what is the risk
23 to the public, what is the risk to public health, and circle
24 then back to an examination of understanding what that risk
25 is from beginning to end, complete with intervention steps

1 along the way, what is the risk that we need to address here
2 and how best to address it in an effective means.

3 DR. ANGULO: A 30-second response is that is why
4 the framework document is so visionary because if, as you
5 present, there is no risk, then, you shouldn't be afraid of
6 the framework document because when we put thresholds in, we
7 will find no effect, and there will be no effect upon the
8 industry.

9 If you are so certain that there is no effect,
10 then, why are you so concerned about threshold and
11 corrective actions? In public health, it allows us to go
12 forward confidently with new approvals and assure the public
13 that they are being protected because there is going to be
14 corrective actions later on if it should emerge.

15 I don't understand why you can be so vehemently
16 opposed to the framework document if you are so insistent
17 that there is no risk. If there is no risk, this framework
18 document is not going to influence you.

19 DR. STERNER: Dr. Angulo, we have other panel
20 members who want to ask questions also, with due respect.

21 Richard, I believe you were next.

22 MR. WOOD: I also am concerned about the global
23 perspectives, the point you are raising, but I want to look
24 at a specific item that was in your comments, but not
25 referred to, and that has to do with reporting.

1 You are, in this one section, identifying that you
2 are not supportive of reporting sales information, and I
3 wish you could address that, particularly in light of you do
4 in steps that you would like to take, you want to increase
5 monitoring and surveillance, and the NARMS, you know,
6 susceptibility and monitoring program, and in the framework
7 document it identifies the value of having the sales data to
8 be able to identify more strongly mitigating steps.

9 So, to me, it's a disconnect if you don't have
10 those two together.

11 DR. STERNER: Respondents?

12 DR. CARNEVALE: We didn't comment on that, and I
13 think it is because, you know, taken together with
14 everything else, that was just another overwhelming piece of
15 the whole puzzle.

16 Sales data right now is collected by companies,
17 and certain information is reported to FDA on units
18 distributed. There is really no system set up at the moment
19 that most companies have that can track the kind of
20 information that seems to be envisioned in this document,
21 but we are not entirely clear what FDA has in mind.

22 The fact is that to implement such a monitoring
23 system that they have in mind would be enormously expensive
24 if it could be done, and then the question arises of what
25 real value is it, and I think it is just another piece that

1 has to be taken within the whole framework.

2 So, we have concerns about it, not from the
3 standpoint of the request itself, but really in context with
4 what is its value, and then what is the economic cost to the
5 industry of having to try to develop a reporting scheme like
6 this, which they may not be able to practically do, but I
7 don't know all the details of the problems with that.

8 We put it in there as a concern we had, but we
9 didn't elaborate on it in the talk.

10 DR. STERNER: Dr. McEwen.

11 DR. McEWEN: I just wanted to emphasize that I
12 think that you should bear in mind that there are different
13 types of risk assessment, and I think the question out there
14 is whether we have to wait until the absolute ultimate
15 quantitative risk assessment is done before any action is
16 taken. That is one extreme, I guess.

17 The other one would be to do a qualitative risk
18 assessment based on the information that is available and
19 then make a decision on actions. I think there are
20 gradients of assessing risk, and it is not entirely an all
21 or nothing thing the options that the committee is facing.

22 DR. STERNER: Dr. Galbraith, you had a question?

23 DR. GALBRAITH: Yes. I would just like to add a
24 comment about risk assessment. I think it's laudable that
25 you are supporting the development of risk assessment, but I

1 wonder what in the history of risk assessment and regulatory
2 affairs makes you optimistic that this will help be a
3 resolution?

4 DR. FOX: Let's just say, for example, it is now
5 mandatory in WTO actions, GATT actions, I think there is a
6 lot more now, it is becoming a lot more sophisticated, and
7 clearly, there are different models, and so on.

8 It is used in a fair number of regulatory
9 decisions on toxicology, and so on, and even more recently,
10 I think in the UK, at some of the BSE decisions, when it
11 came down to the beef on the bone, and the 1 in a billion
12 kind of thing, that was something that began to get talked
13 about much more publicly, so I think we are on a journey
14 here, but I do think the whole question of the involvement
15 of risk assessments, the sophistication, the understanding
16 is steadily building.

17 DR. STERNER: Dr. Barker.

18 DR. BARKER: One man's vision can be another man's
19 nightmare. It is obvious that there is a big of difference
20 between the perceived vision of one and the hallucination
21 that it appears to be to another. We are better to deal
22 with the issues than with personalities.

23 I would like you to respond to this issue. Now,
24 the FDA has already established a fair amount of
25 requirements for approval of antibiotics that include

1 determination of safe levels, determination of an ADI,
2 flexible labeling, which would permit lower and higher dose
3 administrations, there were a range of concentrations that
4 often exceed proven effectiveness, and that the role of the
5 FDA is to provide safe and effective products and to assure
6 the health of the American public in the use of these
7 compounds.

8 When we look at antibiotics, we start to see
9 shifts in effectiveness. We start to see susceptibility
10 changes. It is still an effective drug, and under
11 effectiveness, it would still meet the requirements.

12 We seem to be starting to bump up against the
13 other requirement that FDA make, that it also be safe.

14 When do changes in susceptibility become perceived
15 or actual differences that define resistance, and then can
16 be interpreted as being unsafe because of the perception
17 that it could somehow be passed on to the American public?

18 DR. CARNEVALE: I think the question is how do you
19 establish thresholds?

20 DR. BARKER: Pretty much.

21 DR. CARNEVALE: I don't know that I can answer
22 that. That is exactly the question we are asking. The
23 threshold concept, you know, I understand how CVM came to
24 that, how the thinking got them to that point, because it is
25 a very nice tool to use.

1 The problem is you are raising a very essential
2 point - when does susceptibility change or resistance change
3 in a certain number of pathogens in a certain study mean
4 that you have got a problem, and I don't know how to make
5 that determination, and it is one of the problems that we
6 have in this document.

7 It has to be recognized that it is a diagnostic
8 tool. MIC changes are affected by how you do the test.
9 MICs are only an approximate measure of whether a drug will
10 work or not work. There is some correlation with a number
11 of antibiotics. I recognize NCCLS has set clinical
12 breakpoints, and related that to clinical effectiveness, but
13 the bottom line still is an approximation.

14 It doesn't mean that the patient won't respond.
15 It means there is a likelihood the patient might not
16 respond. There are a lot of other factors in the patient
17 that dictate whether they are going to respond to the
18 disease or not, and you can look in the literature and see
19 where drugs that have been fully effective, supposedly fully
20 effective by in vitro tests have not worked. Why? Because
21 they were treating a patient that had an underlying immune
22 compromised state.

23 So, the problem we are having is, yes, where do
24 you set those threshold values, because the correlations
25 simply haven't been developed that show that you reach a

1 certain point, and that means you have a human health
2 impact.

3 Now, one could argue that, you know, you don't
4 need that to regulate products, and getting back to what
5 Fred was saying, we are not discounting the literature, we
6 are not suggesting the literature doesn't show that there
7 have been resistance transfer and there has been development
8 of resistance. We are simply saying that the literature
9 doesn't rise to a level at this time to change what we are
10 currently doing. We think there are other ways to control
11 antibiotic resistance because we don't envision that the
12 literature says that there is a crisis occurring at the
13 moment.

14 Now, that is a point that obviously certain people
15 are disagreeing with us on. Some people are saying there is
16 a crisis. We don't think there is a crisis that would
17 dictate massive changes to the regulatory approach. Do we
18 think there should be things done? Absolutely. There are
19 things being done now. We just think they ought to be
20 strengthened. We think we ought to look for alternative
21 approaches other than always looking to the drug approval
22 process to try to correct a perceived problem.

23 DR. STERNER: In fairness to our next speakers, I
24 will give Dr. Barker his last opportunity to comment or a
25 question.

1 DR. BARKER: Thank you.

2 Just to kind of follow up on that, is it clear to
3 industry based on the framework document exactly how they
4 are to proceed in trying to get an approval at this point?
5 Was that too obvious?

6 DR. FOX: How long have we got here? No, I think
7 as I said in my comments, seriously, there is a very big
8 concern because I think it is one thing to talk about a
9 framework document here, and speaking as one of the other
10 drug sponsors, who has been through this process many, many
11 times, it is very difficult right now to get drugs cleared.
12 Taking a framework document and putting it into something in
13 practice, how reviewers are going to interpret it, how the
14 lawyers are going to get involved, how you get a reviewer to
15 review variations, how is FDA going to write guidelines?

16 It is truly a nightmare, and this is a very big
17 shift. I can only close with one comment, which was from
18 one of our very senior corporate research people, and it
19 was, "It seems to me that in veterinary medicine, the more
20 innovative the drug, the less likely it is to be approved."
21 That, I think has serious consequences for veterinary
22 medicine in the U.S.

23 Thank you.

24 DR. STERNER: Thank you, Dr. Fox.

25 That concludes remarks from AHI at this time.

1 There will be perhaps an opportunity tomorrow morning to
2 further address questions to them.

3 We are going to take a 10-minute break, at which
4 time we will open with some housekeeping announcements from
5 Dick Geyer, and then we will begin our public commentary and
6 try and keep people on task.

7 Thank you.

8 [Recess.]

9 DR. STERNER: If I could have the attention of the
10 audience, the floor is now Richard Geyer's.

11 MR. GEYER: If you all would take your seats, we
12 need to run through just a few procedures for the public
13 session.

14 For the public speakers, for the benefit of the
15 committee, we would like for you before you start with your
16 remarks to answer two questions. First of all, do you have
17 any financial interest in or financial support from any
18 manufacturers of animal drugs, and number two, have your
19 expenses to attend this meeting been paid entirely or in
20 part by animal drug manufacturers.

21 So, if you would respond to those questions, we
22 would appreciate it. I might run real quickly through the
23 list. If you have the list of public participants in front
24 of you, we are going to make just a few changes in it.

25 Dr. Rebecca Goldberg, who is now No. 13, we are

1 moving up to No. 2. These few changes that we are making
2 are to accommodate people's schedules.

3 Tom Burkgren, who was No. 2, his time will be 12
4 minutes instead of 10 minutes for the benefit of those who
5 are setting the clock.

6 No. 12, Jim Jarrett, will be speaking tomorrow.
7 No. 14, Dr. Robert Walker, his time allocation is 10
8 minutes.

9 No. 17, Ran Smith, will be speaking tomorrow.

10 We have added to the end of the list Dr. Barbara
11 Glen with 10 minutes, and she will be speaking this
12 afternoon.

13 So, our present plan is to have just two speakers
14 tomorrow, but I think that depends upon how rapidly we move,
15 and I am going to turn it over to our Chair to talk about
16 that.

17 DR. STERNER: In fairness to the committee and
18 given the workload that we expect and the discussions to go
19 tomorrow, we will ask you to adhere strictly to the time
20 allotted, and I will be very unceremonious in saying time is
21 up when that right light comes on. That is just a common
22 courtesy to the other speakers who have all tried to prepare
23 their remarks and fall within the time frame.

24 So, with that, we have our first speaker from the
25 public sector, Margaret Mellon from the Union of Concerned

1 Scientists with 10 minutes, Margaret.

2 **Public Speakers**

3 **Margaret Mellon**

4 MS. MELLON: Well, I will start by saying that I
5 am receiving no money from any animal drug manufacturer, nor
6 have my expenses been paid by anyone other than my own
7 organization, the Union of Concerned Scientists. I also
8 congratulate the committee for asking the question. I think
9 eliciting the interests of speakers is a very important part
10 of taking testimony from the public.

11 My organization, as I said, is the Union of
12 Concerned Scientists. We are a Boston-based,
13 nongovernmental organization with an interest in the
14 interface between technology and society. I am here as the
15 director of our agriculture and biotechnology program.

16 We are very pleased to be here today to comment on
17 CVM's proposed framework for the use of antibiotic in food
18 producing animals. The emergence of antibiotic-resistant
19 pathogens is a looming health issue of major proportions.
20 Scientists, physicians, and public health agencies around
21 the world are raising the alarm and, in some cases, taking
22 action. It is certainly time for the U.S. to step up to the
23 bar.

24 We applaud the FDA for taking the initiative in
25 addressing the issue both in the medical and the animal

1 settings, but particularly for this, the neglected area of
2 the animal uses of antibiotics.

3 We do not in any way underestimate the problems of
4 dealing with the antibiotic resistance. Dealing with this
5 problem runs counter to the most human of predispositions,
6 dispositions to favor benefits today over problems tomorrow
7 that may never emerge, but nevertheless, this is an
8 important problem and will require strong leadership if we
9 are to stave off the resurgence of untreatable infectious
10 disease.

11 As a national sort of aside, I hope that the U.S.
12 is in the forefront of addressing that problem, and that it
13 is not only those in Europe that are going to take it
14 seriously.

15 Since time is short, I will make brief comments.
16 First, is that the FDA's policy should encompass existing
17 drug use, and should start with sub-therapeutic uses of
18 antibiotics. The policy with a few footnotes aside seems to
19 focus on new therapeutic drugs for use in animals.

20 Well, it leaves completely untouched the existing
21 use of antibiotics and particularly those that are used for
22 growth promotion. In our view, a risk-based policy ought to
23 be like bank robbers, the they ought to go where the money
24 is, and in this case, the money is with the existing annual
25 use of antimicrobials.

1 From our perspective, a prospective use-only
2 policy is something like two decades too late. It might
3 have made sense before there were multi-drug resistant
4 pathogens, before resistance had been shown to emerge on the
5 heels of initiating use in animal systems, perhaps when
6 people still believed that resistant strains of
7 microorganisms were not going to be virulent or that they
8 were carrying such an energy cost as a result of carrying
9 antibiotic resistance that they would revert to
10 susceptibility.

11 We now know that that is not true. We believe the
12 U.S., we believe the CDC when it says that use of
13 antimicrobials in animals is the dominant cause of
14 antibiotic resistance in food-borne organisms.

15 We know that resistant strains are virulent and we
16 know that they are not likely to revert to susceptibility on
17 discontinuing the use of the antimicrobial. So, in our
18 mind, this puts us in a situation where we need to act and
19 where the burden of proof has been shifted from those who
20 say that there is no problem to those of us who ask, you
21 know, not to be told that there is no proof that there is a
22 problem, we now want proof that there is no problem.

23 I think there is enough scientific evidence on
24 record for that to be the responsible public response. Now,
25 we do understand that there are lots of places where we need

1 more data, that there are lots of holes, there is a lot of
2 uncertainty, but as we said, I don't think that that is
3 enough anymore.

4 That was enough 20 years ago, that is not enough
5 now. We also understand that medical settings are primarily
6 responsible for the overall problem of antibiotic
7 resistance, but again, that doesn't get us very far. It
8 doesn't mean that agricultural use is not a problem. It
9 seems to us that it is.

10 I mean with all of the data that have been brought
11 forth, I have seen no scientific explanation for why
12 prolonged exposure to antimicrobials in animal settings
13 would not lead to an antibiotic resistance problem.

14 So, pointing out that animal use isn't as
15 responsible in medical use doesn't mean that animals aren't
16 a problem.

17 Third, we are really troubled by this notion that
18 we ought to wait for therapeutic breakthrough before we act.
19 I mean we don't want to wait until there are dead bodies in
20 clinics before we act. If we can see antibiotic and
21 antimicrobial resistance rising in pathogen populations,
22 that ought to be enough. We need not wait until we have
23 gone through all the antibiotics and people are actually
24 dying in clinical situations. I think that is an
25 irresponsible position for us to take.

1 We suggest that we need a new antimicrobial
2 policy, one that would basically eliminate nonessential uses
3 of antimicrobials and one that would shift the burden of
4 proof to those who want to use antibiotics to prove that
5 their uses are essential, are required.

6 We think that we need to save all of our
7 antimicrobials, our crown jewels, for use in human medicine,
8 that we can't afford to compromise their efficacy unless
9 there is a compelling public benefit.

10 Turning to the framework specifically, we would
11 like to -- well, first of all, we would like to say that if
12 resources are limited at the FDA, we think that the better
13 focus is on reviewing and eliminating existing uses of
14 antimicrobials rather than doing a lot of work with review
15 applications for new ones.

16 Second, we certainly recommend that the FDA adopt
17 the CDC recommendation that antimicrobials used in humans or
18 those that select for cross-resistance in humans be banned.
19 We have a number of reasons for that.

20 The first is that it is the easiest way of
21 accomplishing major public health benefit. It is the
22 easiest way, much easier than controlling medical settings
23 to limit our use of antibiotics.

24 The second is that the economic benefits are
25 completely tenuous and, in fact, may not exist at all, but

1 even if the National Research Council's estimate, probably a
2 high one, of 5- or \$10 per year per person is the cost of
3 eliminating sub-therapeutic antibiotics, I suggest that it
4 is a cost that most people are willing to pay.

5 Finally, I would say that the handwriting is on
6 the wall in Europe, that the public will begin here and
7 there to demand a livestock industry that is not dependent
8 on antimicrobials, and that it is time to get started with
9 the new animal management research that will make that
10 possible.

11 We would like to recommend, in addition, that the
12 aquaculture, that the committee recommend that FDA take up
13 aquaculture specifically and not let it be wrapped into the
14 other parts of its livestock program, and that it consider
15 all the uses in aquaculture as sub-therapeutic because all
16 of them are going to be or most all of them, it seems to me,
17 are going to be broad in duration, and they are going to
18 have very wide environmental exposure.

19 In conclusion, I want to say that the landscape,
20 the policy landscape under which the FDA is undertaking this
21 inquiry is changing. The public wants antibiotics for
22 themselves, for their children, for the communities, and
23 they do believe that they are at risk.

24 They are no longer going to tolerate a compromise
25 in the efficacy of those drugs for any but the essential

1 uses. Now, some of those essential uses will certainly --

2 DR. STERNER: Ms. Mellon, unfortunately, time.

3 MS. MELLON: Half a sentence. We will include
4 treating animals in pain and animals who are diseased. They
5 are not going to, however, include an overly productive
6 export industry.

7 Thank you.

8 DR. STERNER: Thank you.

9 Next, from the Environmental Defense Fund, we have
10 Dr. Rebecca Goldberg, and she has 10 minutes.

11 **Dr. Rebecca Goldberg**

12 DR. GOLDBERG: Thank you. I will begin by saying
13 that I have no funding from the pharmaceutical industry. I
14 came here with money from my own organization.

15 I would also like to say that I am trained as a
16 biologist and that I work as a senior scientist at the
17 Environmental Defense Fund, sometimes known as EDF, which is
18 a large, nonprofit organization that does research and
19 advocacy on a variety of environmental issues.

20 I am here today to comment on FDA's draft
21 framework because the Environmental Defense Fund has become
22 extremely concerned about the threat to public health from
23 antimicrobial resistance bacteria. The heavy use of
24 antimicrobials in animal agriculture is clearly an important
25 component of this health problem.

1 I want to begin by saying that the Environmental
2 Defense Fund applauds the Food and Drug Administration for
3 beginning to consider the role, the issues of antimicrobial
4 resistance should play in evaluations of new antimicrobials
5 used in food animal production.

6 We agree with FDA that new uses of antimicrobials
7 should be evaluated and, as appropriate, restrict it to
8 ensure that they do not pose a threat to human health via
9 the development of bacterial resistance.

10 In addition, EDF is extremely pleased that the
11 Food and Drug Administration has proposed that detailed drug
12 sales information be submitted as part of drug experience
13 reports. Such information, which has been heretofore
14 unavailable in the United States is essential to more fully
15 understanding relationships between drug use and the
16 evolution of resistant bacteria.

17 We urge that the FDA make such information
18 publicly available to the fullest extent allowed under the
19 law, so that researchers have access to it.

20 These points made, EDF has some significant
21 criticisms of the framework, and in the interests of time, I
22 would like to limit myself to articulating concerns about
23 three items.

24 The first item that EDF would like to take issue
25 with is FDA's assertion that the framework is risk based.

1 Within the narrow confines of new uses of antimicrobials in
2 animal agriculture, an argument can be made that the
3 framework has a risk basis in that FDA's proposed actions
4 are at least related to the likelihood and threat to human
5 health from particular new uses of antimicrobials.

6 However, if one looks broadly at the problem of
7 antimicrobial resistance, it is apparent that at least in
8 the near term, the greatest risk to human health from
9 agricultural uses of antibiotics comes from the very
10 considerable existing uses of antimicrobials in animal
11 agriculture, not future uses.

12 Yet, these existing uses are ignored by the
13 framework and, as a result, it makes it extremely hard for
14 EDF to view FDA's proposed framework as truly risk based.

15 The second point I want to make is that EDF
16 disagrees with FDA's priorities as expressed in part in the
17 new framework. In other words, where there are tradeoffs
18 between allowing antimicrobial use in food animal production
19 and protecting public health, we believe that FDA gives too
20 much priority to food animal production. EDF would give
21 much more priority to protecting the bacterial
22 susceptibility and therefore protecting the public health.

23 In our view, the most troubling example of this
24 difference in priorities concerns FDA's proposed
25 categorization of antimicrobials. FDA's proposed Category I

1 includes those drugs whose efficacy is immediately critical
2 to human health. This category includes drugs that are --
3 and I quote -- "essential for treatment of a serious or
4 life-threatening disease in humans for which there is no
5 satisfactory alternative therapy.

6 In other words, Category I includes drugs for
7 which the loss of bacterial susceptibility would likely
8 result in human deaths. Yet, FDA proposes to allow Category
9 I drugs to be used in food animal production albeit with
10 some evaluation and often, I assume, with considerable
11 limitation to prevent the spread of resistance, but even
12 limited use of Category I drugs carries some use and will
13 likely increase the risk that bacteria will evolve
14 resistance to these antimicrobials.

15 Thus, FDA's proposed framework potentially
16 jeopardizes human lives, and we are frankly appalled that
17 FDA would propose to allow such uses of Category I
18 antimicrobials in animal agriculture.

19 We believe that few members of the public would
20 make such a tradeoff between animal production and
21 protecting human health if given the choice, and we urge
22 that FDA take a similar perspective.

23 Our third point concerns some of the science
24 underlying the policy. In particular, FDA distinguishes
25 between enteric and non-enteric human pathogens in its

1 categorization scheme, suggesting that it would not be
2 expected or biologically plausible for resistance to be
3 transferred from animal enteric pathogens to non-enteric
4 pathogens.

5 This is hogwash, if you will excuse the pun. The
6 more that scientists learn about patterns of bacterial gene
7 transfer, the more it becomes abundantly clear that
8 bacterial genomes are extremely plastic and that bacteria
9 exchange genetic material frequently and across substantial
10 taxonomic distances.

11 There is no reason to expect that genes from
12 enteric bacteria will not be transferred to non-enteric
13 bacteria. As someone with at least a little background in
14 microbial ecology, I can tell you that antimicrobial
15 resistance genes are extremely common among all sorts of
16 bacteria in the environment including those in soil, those
17 in water, and those on the surfaces of leaves of plants.

18 In other words, it is abundantly clear that non-
19 enteric bacteria frequently acquire antimicrobial resistance
20 genes. There are probably a variety of reasons for this.
21 These include linkage of antimicrobial resistance genes with
22 heavy metal resistance genes, and perhaps selection pressure
23 from some antimicrobials that are persistent in the
24 environment.

25 But what it all boils down to is that FDA's

1 argument that non-enteric pathogens will, for practical
2 purposes, not acquire resistance genes from enteric
3 pathogens doesn't stand scientific scrutiny.

4 In short, FDA should concern itself with the
5 effect of antimicrobial use in animal agriculture on the
6 development of resistance in non-enteric, as well as enteric
7 pathogens.

8 Finally, because I think I probably have a minute
9 or two more, I would like to make a comment on a point made
10 by the previous commenter, Margaret Mellon, concerning
11 aquaculture and uses of antibiotics or antimicrobials in
12 aquaculture as fish farming is actually something I have
13 some personal expertise in.

14 Unlike most forms of livestock production, one
15 cannot directly administer antimicrobials to fish that are
16 being farmed. You can't dive into the water and inject a
17 particular salmon or a catfish with an antimicrobial drug,
18 and therefore, outside of hatcheries of fish antimicrobials
19 are almost invariably given to fish through feed, which is
20 put directly into the water.

21 Since most aquaculture facilities in this country
22 have no effluent treatment of any sort, that means that low
23 sub-therapeutic doses of antimicrobials from uneaten feed
24 and that have survived a fish intestinal tract, which is
25 rather different than that of higher organisms, are probably

1 in the water and present at sub-therapeutic level providing
2 selection pressure for spread of antimicrobial resistance
3 genes. We, therefore, are very concerned about even
4 therapeutic uses of antimicrobials in aquaculture.

5 Finally, in closing, EDF would like to
6 congratulate the Food and Drug Administration for at long
7 last stepping forward to consider the threat to human health
8 from the use of antimicrobials in animal agriculture.

9 However, FDA's proposed framework falls short in a
10 number of critical ways, three of which I have elaborated.
11 We urge the agency to take an approach that is far more
12 protective of human health.

13 Thanks a lot.

14 DR. STERNER: Thank you. Actually, time has just
15 elapsed, so you have done well. You have set a good
16 template for the rest of the public speakers.

17 Next, from the American Association of Swine
18 Practitioners, is Dr. Tom Burkgren, and he has 12 minutes.

19 If you would state your associations.

20 **Dr. Tom Burkgren**

21 DR. BURKGREN: Yes. To the two questions, I have
22 no financial interest in pharmaceutical companies, and my
23 expenses to this meeting have been paid by my association.

24 I would first like to preface my remarks about our
25 association. We are a practitioner-based association of

1 veterinarians, and in our contact the past year with Dr.
2 Bell in our judicious use guidelines, I would have to say
3 that we appreciate his professionalism and his passion for
4 this issue.

5 We understand his frustration because my comments
6 today are as a result of deeply rooted frustrations on our
7 part as practitioners and not knowing if we will have a drug
8 approval process in the future, if we will have the
9 absolutely necessary tools, antimicrobial tools for us to do
10 our jobs on the farm.

11 The AASP recognizes and appreciates the efforts of
12 the FDA in keeping the nation's food supply safe. We
13 recognize the complexity of this issue. We are not naive in
14 thinking that this framework will not be instituted,
15 however, we do have severe and significant concerns about
16 this framework.

17 The framework proposed to manage a risk that has
18 not been adequately assessed. It fails to recognize the
19 need to separate hazard from risk. The FDA has identified a
20 hazard, but they have not addressed the issue of risk and
21 how likely the hazard is to occur, and what the magnitude
22 will be.

23 The AASP agrees with the FDA that the impact of
24 animal uses of antimicrobial drugs on human health should be
25 reexamined, however, we disagree that the proposed framework

1 is the appropriate approach. The evaluation of the issue
2 should be done within the scientific risk assessment whether
3 qualitative or quantitative. The risk assessment process
4 has value even if you do not meet your preordained measures
5 of success. It does help you fill data gaps and address
6 research agenda.

7 Risk assessment should not be implemented until
8 the risk has been laid in proportion. To undertake risk
9 management before risk assessment has no basis in logic, nor
10 within the accepted parameters or risk analysis in the
11 absence of a clearly identifiable severe risk.

12 In the worst case scenario, this framework could
13 appear to be a thinly disguised regulatory application of
14 the precautionary principle. Objective risk
15 characterization would enable this issue to be evaluated
16 within the broader context to which the hazard relates, that
17 is, the societal cost and the benefits of regulatory
18 restriction of antimicrobial use in all arenas.

19 The FDA states that its primary public health goal
20 must be to protect the public health by preserving the long-
21 term effectiveness of antimicrobial drugs for treating human
22 disease. By this statement, can one assume that the FDA is
23 acting in proportion to the relative magnitude of the
24 problem from the use of antimicrobials in the treatment of
25 humans?

1 At this publicly, it seems FDA's actions to
2 protect the public health with respect to antimicrobial use
3 in the human arena have been limited to education and non-
4 binding guidelines, and we have heard the opinion that these
5 are not successful. Why, in the absence of a credible risk
6 assessment should animal agriculture bear the brunt of FDA's
7 regulatory interventions?

8 As the document was examined for its scientific
9 merit, two immediate concerns were evident to our review
10 panel. The first eight references were anonymous, and did
11 not represent peer-reviewed science. Yet, we feel that if
12 there is something worth citing, then, it would be more
13 convincing to cite original peer-reviewed sources from those
14 documents.

15 Secondly, the examination of the document reveals
16 the words, "FDA believes" or some variant of this phrase
17 appears 47 times. The complexity of this issue requires
18 that belief be founded in science, and the document is less
19 than convincing on this matter.

20 The framework fails to adequately define many
21 scientific terms. This lack of clarity invites subjective
22 and misleading interpretation and raises further questions
23 of the scientific foundation.

24 Examples of the terms we would like to see defined
25 would be pathogen load, human health effects, induction of

1 resistance, significant baseline of colonization. This list
2 is not exhaustive, but we feel that a reference glossary of
3 scientific citations would be useful to further discern the
4 scientific basis of this framework.

5 There are examples given within the document which
6 tend to mislead and bias the reader. Other speakers have E.
7 coli 0157 as being included. Actually research has shown
8 this bacteria to be transient in individual animals, and not
9 a persistent colonizer of intestinal flora of various food
10 producing animals, and certainly not in swine, but E. coli
11 0157 has considerable emotive impact on the public, but its
12 pertinence to this discussion is questionable.

13 Vancomycin resistant enterococcus has been
14 mentioned in Europe, but in the United States we have no
15 glycopeptide use in animal agriculture. We fail to see the
16 relevance for this discussion other than, once again,
17 emotions are raised.

18 There are other instances where scientific
19 citations would be useful. The document often associates
20 pathogen level with duration of therapy. There are
21 statements in the document where the use of antimicrobials,
22 especially for long duration, is inferred to disturb the
23 normal intestinal ecosystem in the animal resulting in an
24 increase in the bacteria that could cause human infections
25 or prolong the duration of the carrier state.

1 In a cursory discussion of this point, our review
2 panel identified several papers on antimicrobial use in
3 swine that contradict the position of the FDA in the
4 document. Our minimal expectation is that the FDA would
5 conduct a credible review of the scientific literature
6 before proposing demanding expensive requirements for the
7 pre-approval testing based on a belief that appears to have
8 a very questionable and very narrow scientific basis.

9 We are troubled by the categorization of human
10 antimicrobials. We believe them to be plagued with
11 subjectivity and built-in bias.

12 In our review of the scheme for categorization and
13 in reference to the context of this discussion today from
14 several experts, it becomes clear to us that this
15 subjectivity allows a majority of significant antimicrobials
16 in swine medicine to be placed in Category I immediately or
17 in the near future. The subjectivity questions the
18 credibility, and, in fact, the clinical usefulness of this
19 categorization.

20 Other instances of bias comes through in terms of
21 all food-borne disease becoming elevated to the same status
22 as serious or life-threatening disease, when we know that
23 the vast majority of food-borne illnesses are not serious
24 nor life-threatening, and most do not require antibiotic
25 treatment, in fact, it is contraindicated.

1 In more general terms, the discussion of the
2 evaluation of potential exposure to humans centers more on
3 the exposure of the bacteria in the gut of the animal to the
4 antimicrobials than on the exposure of humans to resistant
5 human pathogens and the subsequent clinical human health
6 impact.

7 The examples that are given base potential
8 exposure of humans to resistant human pathogens on the
9 duration of treatment of the food animal. Once again, we
10 ask for scientific basis for this assumption. The use of
11 this type of surrogate measure for human exposure may be, in
12 fact, easy, but it has no potential for measuring true
13 clinical significance to public health.

14 The FDA has not revealed any valid model to link
15 exposure of bacteria in the animal gut to the human exposure
16 to the pathogens.

17 Now, we agree that the effects of antimicrobial
18 resistance transfer from animals to humans involves a
19 complex chain of events. The document lists only four parts
20 of this chain. We would add the following: the likelihood
21 the transfer will cause illness, the likelihood that the
22 illness will require antimicrobial treatment, and the
23 likelihood that the resistance will result in treatment
24 failure.

25 Other biases found within the discussion of the

1 example for the high potential human exposure, the label
2 claim of improved growth or feed efficiency is highlighted
3 in the example in the ensuing discussion. We question how
4 the label claim is relevant to this discussion for potential
5 human exposure to resistant pathogenic bacteria other than
6 the emotional value of placing that in the document.

7 Bias is also revealed within the evaluation of the
8 potential exposure of humans to resistant bacteria when they
9 state that drugs are -- and I quote -- "administered in feed
10 throughout the life of the animal on a flock or herdlike
11 basis."

12 This would mean, in a swine herd, that the entire
13 herd would be fed from birth to death antimicrobials, and
14 would be on a continuous basis. I know of no swine farm
15 today that could sustain that economic impact, nor clinical
16 science background to warrant that.

17 This statement is inflammatory and blatantly
18 misleading and has no place in this scientific document.

19 Monitoring and threshold levels and resistant
20 threshold levels must be tied to measurable public health
21 outcomes to be clinically important to the projection of
22 human health. We would cite the following questions needing
23 more data: how the FDA intends to measure the rate of
24 resistance transfer in vivo, what measure of resistance will
25 be used, if used, how MICs will be used to determine

1 clinical human health impact, and what constitutes
2 sufficiently sensitive tests.

3 Lastly, on farm post-approval monitoring programs,
4 we would ask that they carefully correlate measurable public
5 health outcomes to proposed thresholds from on-farm
6 monitoring before they come on our farms and disrupt our
7 production. We would ask that models that validate on-farm
8 monitoring be revealed.

9 In closing, we would propose the following to the
10 FDA: the scientific risk assessment before attempting risk
11 management, and we would offer our white paper that we have
12 jointly commissioned with NPPC, the National Pork Producers
13 Council, as helping to set the model and identify the
14 research needs; risk characterization of the issue,
15 strengthening of the NARMS program, continued and open
16 meaningful dialogue between the FDA experts and
17 stakeholders, and as part of this dialogue, identification,
18 prioritization, and funding of an aggressive research agenda
19 to help fill the data gaps.

20 Thank you.

21 DR. STERNER: Thank you. You probably have 30
22 seconds in which to field a question from the panel.

23 Any questions?

24 [No response.]

25 DR. STERNER: Thank you, Dr. Burkgren.

1 Next, from the Colorado Animal Research
2 Enterprises is Dr. Diane Fagerberg.

3 **Dr. Diane Fagerberg**

4 DR. FAGERBERG: First of all, I have not received
5 financial support from the animal drug industry with regard
6 to what I am going to present. In my presentation, I will
7 mention how I am, however, and otherwise involved with the
8 animal industry. As far as expenses, the Animal Health
9 Institute will defray my travel expenses.

10 [Slide.]

11 This who I am now. I am the president and
12 executive general manager of Colorado Animal Research
13 Enterprises in Fort Collins, Colorado. I am involved in
14 numerous types of FDA-required research for the approval
15 process of new animal drugs.

16 I have conducted numerous studies, in fact,
17 probably 99 percent of all of the feed additive antibiotic
18 studies that went through the 558.15 regs for pathogen loads
19 and microbial resistance.

20 [Slide.]

21 This is who I was 20 years ago. I sought and was
22 awarded an FDA contract that extended over a four-year
23 period. It was intended to be the baseline for comparison
24 to future years, the baseline for comparison to today, to
25 the 20 years later.

1 The contract number was 223-77-7032, and its title
2 was Database for Drug-Resistant Bacteria for Animals. It
3 was basically FDA's reaction to the European Swann
4 Committee.

5 [Slide.]

6 During the four-year period of 1978 to 1981, we
7 sampled on-the-farm broilers, beef, and swine, and we
8 sampled live swine at slaughter plants. We sampled 312
9 total units that represented 7- to 10,000 animals.

10 [Slide.]

11 From fecal samples of these animals we tried to
12 isolate any Salmonella that were there. We isolated out 10
13 coliforms primarily which were E. coli, and we isolated out
14 10 enterococci, calling them streptococci at that time.

15 We performed antimicrobial susceptibility testing
16 on all of those isolates, any of the Salmonella, all of the
17 coliforms and all of the enterococci. It represents over
18 3,000 coliforms and enterococci.

19 [Slide.]

20 Before proceeding to relate to you some of the
21 results of that work, I would like to relate to you -- and I
22 will relate it as best that I can -- that the trend of drug
23 usage in animals, food producing animals, during the most
24 recent 15 years has increased. Sulfonamide usage has
25 increased approximately 10 percent, streptomycin by

1 approximately 63 percent, tetracycline by approximately 18,
2 and penicillin type drug usage has increased approximately
3 150 percent. If of that 150 percent we eliminate the 70
4 percent that can probably be attributed to dogs, cats, and
5 intermammary cow infusions, we are down to about a 70
6 percent increase in penicillin type usage in food animals.

7 These figures are very generalized and do not
8 exclude companion animals. I am unable to tell you where
9 this information on usage came from because along with that
10 information, I was told it was confidential and that this
11 strict confidentiality is key to the continued data quality,
12 integrity, availability, and value.

13 [Slide.]

14 But the important thing, and I don't think anyone
15 will argue with me that the animal usage of antimicrobials
16 has increased over the last two decades.

17 [Slide.]

18 I am going to concentrate only on the Salmonella
19 portion of that survey that we did 20 years ago. I would
20 like to compare the past to the present. Basically, the
21 present is represented by the NARMS data that was generated
22 for 1997. Comparing all of our Salmonella to all of the
23 NARMS Salmonella, we see a decrease in resistance from the
24 then to now in most of the prevalent resistances, in
25 sulfonamide resistance, streptomycin, and tetracycline.

1 [Slide.]

2 Increases have occurred with ampicillin and
3 kanamycin. We saw no resistance to gentamicin,
4 chloramphenicol, trimethoprim sulfa, nalidixic acid, or
5 amikacin 20 years ago, whereas today, there is some
6 resistance to all of them except amikacin. Again, a
7 reminder, however, that decreases occurred in spite of
8 increased usage of the sulfonamide, streptomycin, and
9 tetracyclines.

10 [Slide.]

11 This is obviously difficult to read. I will tell
12 you that what it is trying to show is the number of
13 antimicrobials that were in a resistance pattern in the
14 past, Salmonella isolates versus the current isolates, as
15 well as what the patterns were.

16 There are 10 common antimicrobials between the
17 past data and the current data, and I have only compared
18 those. What has basically happened is we saw only 18
19 percent of the Salmonella isolates 20 years ago had no
20 resistance. Today, the majority of Salmonella from the
21 NARMS data have no resistance, 65 percent have no
22 resistance.

23 The greatest majority of resistance then and now
24 was either none or patterns that had just one or two
25 antimicrobials in them. The shift to no resistance today is

1 due to fewer Salmonella with resistance to one, two, three,
2 or four drugs. There has been a slight increase in the
3 number of isolates with five drug patterns. This is
4 primarily due to adding kanamycin or chloramphenicol into
5 the pattern, neither of which is used in food producing
6 animals.

7 Probably the best Salmonella data to compare
8 between the then and the now is that of slaughter swine,
9 because the numbers of Salmonella tested were fairly similar
10 between then and now. There were 128 tested back in the
11 late seventies, early eighties, and in 1997, there were 110
12 HACCP Salmonella isolates from swine. Thus, their source
13 was fairly similar also.

14 In neither case was amikacin or nalidixic acid
15 resistance found. Twenty years ago we found no resistance
16 to several of the drugs, gentamicin, trimethoprim sulfa,
17 chloramphenicol, and kanamycin, and very little resistance
18 to ampicillin, whereas, there are more with these
19 resistances today.

20 Tet resistance appears to have increased by about
21 20 percent, but sulfonamide and streptomycin resistances
22 have decreased by 25 to 30 percent. Despite the increased
23 usage of sulfonamide and streptomycin, there was this
24 decreased resistance. Despite that kanamycin,
25 chloramphenicol, and trimethoprim sulfa are not used in

1 livestock, their resistances have recently appeared.

2 Gentamicin is used in swine primarily in very
3 young pigs, and it was approved for such beginning in 1983,
4 but seeing that other resistances have appeared without
5 relationship to any drug usage in the animals makes one
6 wonder if gentamicin usage in pigs had anything to do with
7 finding gentamicin resistance in them now.

8 [Slide.]

9 These are just a few more comparisons of the types
10 that are possible between the historical data and the NARMS
11 data. This is cattle and swine on the farm, past and
12 present. Salmonella antibiotic resistance on the farm
13 cattle and swine show a major decrease in all of the major
14 resistances, sulfonamide, streptomycin, tetracycline,
15 ampicillin, but non-understandable increases in kanamycin,
16 gentamicin, and chloramphenicol.

17 [Slide.]

18 The same general pattern is seen when we compare
19 cattle and swine and chickens. This is comparing to the
20 NARMS data of the clinical and non-clinical isolates.

21 [Slide.]

22 When we talk about attributing animal
23 antimicrobial resistance to animal antibiotic usage, food
24 animals that is, we find that in the FDA survey, during
25 which we gathered information on antibiotic usage, there was

1 no correlation, and we tried all different ways, and could
2 find no correlation of antibiotic resistance to antibiotic
3 usage.

4 When we compare the past to the present, we find
5 that despite the increased usage of sulfonamide,
6 streptomycin, and tetracycline, there has been a decrease in
7 these resistances. Despite no usage of kanamycin,
8 chloramphenicol, and trimethoprim sulfa in food producing
9 animals, there has been an increase in these resistances.

10 Despite no change except increased usages or new
11 usages, there has been a major shift to finding that most of
12 the Salmonella have no antibiotic resistance.

13 [Slide.]

14 If we can't even make antibiotic usage in food
15 animals correlate to animal antibiotic resistance, how can
16 we make a far greater leap of animal antibiotic usage
17 affecting human antibiotic resistance?

18 [Slide.]

19 We gathered 20 years ago a wealth of baseline
20 resistance information. FDA ran out of money, so the data
21 was never summarized. If it is believed that surveys are
22 important, I think the E. coli and enterococci data would
23 provide even more, much more information than just the
24 Salmonella data because there were numerous isolates tested.
25 FDA has the data somewhere. They even should have the

1 actual isolates somewhere.

2 They were provided to them. I urge VMAC to insist
3 the data be found and be reviewed.

4 [Slide.]

5 I would like to interject my personal opinion
6 about the proposed framework document. Despite the fact
7 that I probably only have to gain from its implementation
8 because so much more research will be needed, I believe that
9 it will only be a costly adversity to food and food animal
10 well-being, and will be very ineffectual towards preserving
11 human health safety. In my opinion, it should not be
12 implemented.

13 DR. STERNER: Does that conclude your remarks, Dr.
14 Fagerberg?

15 DR. FAGERBERG: Yes, it does.

16 DR. STERNER: Dr. Angulo.

17 DR. ANGULO: So, if we don't implement this
18 framework, what would be your alternative suggestion, to
19 continue with the current approval process?

20 DR. FAGERBERG: Yes. I think it has been very
21 acceptable.

22 DR. ANGULO: And so the current state of the
23 approval process, which was most of us familiar with the
24 fluoroquinolone approval discussions, I think it is
25 interesting because other representatives have a very

1 different impression of the current approval process.

2 So, I would just comment perhaps that our
3 impression from the human data is very different than what
4 you have presented, and it is very clear there is an
5 increasing trend of antimicrobial resistance, and I think,
6 to remind the panel, that that wasn't a question for
7 discussion at this advisory committee, it is taken as a
8 background statement that where antimicrobial resistance in
9 food-borne pathogens come from.

10 DR. FAGERBERG: I think it does indicate that we
11 do not have all of the answers.

12 DR. ANGULO: We don't have all the answers, but we
13 certainly cannot stand still. We have to move forward if we
14 don't have all the answers, but we have to assure the public
15 health, and standing still and doing nothing is a statement
16 that is not -- that is, in fact, not a safeguard.

17 DR. STERNER: Further questions for Dr. Fagerberg?
18 Yes.

19 DR. SHELDON: Susceptibility test methods have
20 changed quite a bit in the last 20 years, and therefore data
21 derived from those methods may not be comparable.

22 What can you tell us about the susceptibility test
23 methods that were used 20 years ago and those that are being
24 used in the NARMS studies to assure comparability of the
25 interpretation of results and therefore that one can compare

1 them?

2 DR. FAGERBERG: I think that Paul and I would have
3 to sit down and do comparisons. We used NCCLS 1979
4 standards for breakpoints. For the last three years of the
5 study, we did MIC determinations. We used those
6 breakpoints. SensiTiter did not exist then, we prepared our
7 own MIC plates by the Anderson system.

8 They were manually read type plates for
9 breakpoints.

10 DR. SHELDON: As a member of the NCCLS Committee,
11 I can tell you that methods have changed quite a bit,
12 inoculum effects. We now have documents to assure the
13 quality of the media being used.

14 So, I think that before we can accept -- that one
15 can compare the information that you have here, we need to
16 have assurances that the methods are comparable.

17 DR. FAGERBERG: The procedural information is
18 available somewhere with FDA.

19 DR. STERNER: Thank you, Dr. Fagerberg.
20 Unfortunately, time moves on.

21 Our next speaker from NCCLS is Dr. Thomas R.
22 Shryock, Ph.D. He currently is employed by Elanco Animal
23 Health.

24 **Dr. Thomas R. Shryock**

25 DR. SHRYOCK: That's correct, as a microbiologist

1 with Elanco, obviously, my financial interests are obvious,
2 and my expenses have been paid by an animal health current
3 company.

4 [Slide.]

5 However, I am here today wearing as the hat as the
6 chairholder for the NCCLS Veterinary Antimicrobial
7 Susceptibility Testing Subcommittee. I needed 20 minutes
8 just to get that out, so if I can abbreviate, I promise the
9 presentation will that much shorter.

10 All day today we have heard the terms resistant,
11 susceptible, MIC used. My purpose in coming before you
12 today representing NCCLS is to provide some background on
13 the techniques as was just discussed here and set forth by
14 the NCCLS to help VMAC in addressing specifically Questions
15 3, 4, and 5.

16 [Slide.]

17 Just a real quick word about the NCCLS. More
18 information certainly is available on their web site, but
19 basically, it's an independent standards and guidelines
20 writing organization, primarily focused on the human,
21 clinical, laboratory and hospitals, and as you can see, one
22 of the chief areas of responsibility is with microbiology.

23 [Slide.]

24 This particular talk will deal just with
25 microbiology, terms of veterinary antimicrobial

1 susceptibility testing.

2 The process for the NCCLS is to have a tripartite
3 participation involving the professions or academia,
4 regulatory involvement, as well as industry, representing a
5 variety of type of industry. It is a consensus process
6 which means basically more than just simple agreement, but
7 all parties have an opportunity to review and comment on the
8 variety of documents which are elaborated, and there is
9 assurance that comments will be given serious competent
10 consideration.

11 [Slide.]

12 Now, the Subcommittee on V-AST, if I may
13 abbreviate as such, was first proposed in 1992, and has
14 since developed two approved level documents over the course
15 of the year.

16 The first document, the M31, deals with the
17 specific methodology to determine susceptibility test
18 methods, and we will talk a little bit more about those
19 momentarily.

20 The second is the M37, which is a guideline for
21 manufacturers of animal health antibiotics, to set the
22 quality control and breakpoint information. I should point
23 out that the AAVLD, the American Association of Veterinary
24 Laboratory Diagnosticians, has accepted this approved level
25 document for diagnostic laboratories as part of its

1 accreditation process.

2 [Slide.]

3 Just to give you a quick show of the members who
4 have voting privileges and the advisers who do not that
5 comprise the committee currently. There is also a third
6 category of observers which I have not listed.

7 [Slide.]

8 The M37, which is the document to guide
9 manufacturers of animal health products, contains, first of
10 all, guidelines for quality control development. The idea
11 here is to devise a valid reproducible methodology that can
12 ensure comparability of tests from time to time, and this is
13 done using ATCC, American Type Culture Collection strains
14 which are appropriate to the drug spectrum, and comprises
15 both disk and minimum inhibitory concentration, or MIC,
16 testing, and obviously, the value to doing this, to
17 establish the test validity.

18 I should point out that the concentration gradient
19 to strip test has not been included in NCCLS guideline
20 development.

21 [Slide.]

22 In terms of setting guidelines for MIC breakpoints
23 and zone interpretive criteria, three different aspects are
24 evaluated, and these include a pharmacological evaluation,
25 which attempts to take that information and establish a

1 tissue or serum concentration which is in excess of the MIC
2 on a population basis. That population basis is derived on
3 an epidemiologic ground where we are looking at a
4 scattergram which plots for the same isolate an MIC and a
5 zone or of an inhibition on the millimeter basis.

6 Finally, the third component is on the clinical
7 efficacy, which is derived from data during the NADA
8 process.

9 [Slide.]

10 So, those are the three key components that go
11 into the establishment of interpretive categories, and these
12 are the terms that have been used frequently today -
13 resistant, susceptible, and in your intermediate.

14 I should like to point out that resistant implies
15 that the organism would not respond to treatment with that
16 agent. It doesn't necessarily imply that there is a genetic
17 resistance determinant associated with it.

18 In the context of what the committee sets forth,
19 it reflects back on the achievable tissue concentrations
20 relative to the MIC, and would predict that those organisms
21 with that particular MIC or zone of inhibition size would
22 not respond to clinical treatment.

23 Susceptible obviously implies that there would be
24 a clinical success that would be favorable for the host, and
25 intermediate is kind of that category that's a bit gray to

1 account for day-to-day variations.

2 [Slide.]

3 Finally, to accommodate some of the newer
4 legislation, a flexible labeling category has been
5 established to account for that recent bit of activity.

6 [Slide.]

7 The M31 document, this is the one that the
8 laboratory would use, the actual technician at the bench, to
9 guide the conduct of the studies. The focus then is on that
10 diagnostic end user.

11 Now, originally, our scope was to limit the
12 document to therapeutic claims, but as some as these
13 products came before the committee and were approved for the
14 breakpoints, quality control, et cetera, the Working Group
15 on Non-therapeutic Claims was formed to address other uses
16 in animals of antibiotics, and fuller discussion of the
17 outcomes of these are included in the full M31 document, but
18 on the next slide, I can share with you how that was
19 basically delineated.

20 [Slide.]

21 The first item would be the control claims for a
22 group with therapeutic claims, primarily with the objective
23 that early treatment was viewed as therapeutic for those
24 member of a population with disease signs. So, if you had a
25 few animals showing disease in a flock or herd, that would

1 be acceptable for triggering a control claim.

2 Now, prevention and growth promotion claims, we
3 felt that susceptibility testing was not relevant. The
4 reason for this is that these are healthy animals, there is
5 no target pathogen which can be identified or recovered, so
6 it didn't make a whole lot of sense to try to predict a
7 clinical outcome.

8 You can't predict better growth or predict that
9 you will prevent disease from some unknown pathogen,
10 however, any epidemiologic studies could well use these M31
11 methods, but putting them into sensitive, intermediate, or
12 resistant categories does not appear to make a great deal of
13 sense.

14 [Slide.]

15 Finally, with the actual susceptibility testing
16 methodology, there really are two components, the
17 quantitative or MIC, and the qualitative, agar disc
18 diffusion test, and the purpose in this document is to
19 describe standardized procedures that all labs can adhere to
20 with strict quality control guidelines to validate the
21 testing in order to have inter- and intra-laboratory
22 reproducibility.

23 The second component would be the interpretative
24 criteria list, and this deals with specific host pathogen
25 drug-specific data. This would mean that, for example, for

1 swine, you might have swine actinobacillus pleuropneumoniae
2 and a specific antibiotic listed.

3 [Slide.]

4 I would like to share with the group that the
5 subcommittee is now expanding its scope and has decided that
6 Campylobacter species would be something that would be of
7 value to further explore for defined methodology.

8 Dr. Bob Walker from Michigan State University is
9 heading up this working group, and it is comprised of an
10 international collection of microbiologists. It also has
11 representatives from the Human Medical Microbiology
12 Committee, as well as regulatory and veterinary diagnostic
13 laboratories associated with it. So, this working group is
14 quite unique in its scope, not only on a national and
15 international basis, but also bridging the human, as the
16 veterinary groups.

17 The objective here simply is to standardize the
18 test methodology to define appropriate and quality control
19 strains, relevant antimicrobials, and appropriate tests and
20 incubation conditions. This all would seem relatively
21 boring except for the fact that it can be useful for
22 epidemiologic purposes. So far as one might read
23 literature, there are a variety of techniques that have been
24 conducted.

25 The last point that I kind of skipped over there,

1 but was the fact that no breakpoints will be set by the V-
2 AST to put antimicrobials into the category of susceptible,
3 intermediate, or resistant because there are no antibiotics
4 for Campylobacter claims. That would be a job the Human AST
5 group would need to conduct on its own initiative.

6 [Slide.]

7 As far as some future tasks that are before this
8 group, we do have a number of interpretive criteria for
9 which we have excerpted human data and incorporated those
10 for animal outcomes. This is recognized as a surrogate, and
11 we encourage the replacement of these with veterinary
12 specific guidelines as that information becomes available,
13 and there is a Working Group on Generic Antimicrobial Agents
14 to get this testing done or to scour the literature and come
15 up with an approximation for making these conversions.

16 Secondly, a future task here is looking at
17 specific test methods for other vet pathogens, you can see
18 which are listed there, and we certainly encourage, as the
19 final point, additional sponsors to present data on their
20 existing antimicrobial compounds. I hope that they will
21 come forward very soon.

22 [Slide.]

23 So, again, what is the value of the NCCLS V-AST
24 Subcommittee to the deliberations of the VMAC? It would be
25 for addressing Questions 3, 4, and 5, to provide an accepted

1 methodology which is available to ensure quality data
2 generation throughout the United States.

3 I should point out that some countries in the EU
4 are using these methods, as well. Obviously, this has
5 implications for clinical diagnostic laboratories in terms
6 of what they can provide to the practitioner in support of
7 judicious antibiotic selection, and it also implications on
8 surveillance application, assuring the quality of the
9 methodology.

10 That concludes my remarks, and I would be happy to
11 entertain any questions that the VMAC may have.

12 Thank you.

13 DR. STERNER: Thank you, Dr. Shryock.

14 Questions from VMAC or panel members, invited
15 speakers?

16 [No response.]

17 DR. STERNER: Hearing none, we will press on
18 regardless.

19 Our next speaker is Barb Determan from the
20 National Pork Producers Council, and she has been granted 20
21 minutes.

22 **Barb Determan**

23 MS. DETERMAN: I have no interests or income from
24 an animal health company, and my expenses are being paid by
25 my organization, which is producer funded. Every time a

1 producer sells a hog, they contribute to our organization.

2 Good afternoon. I am Barb Determan. I am a pork
3 producer from Early, Iowa. My husband Steve, myself, and
4 our three children have a family farming operation in
5 northwest Iowa. Our furrow to finish operation produces
6 about 2,000 head of pigs each year. As a volunteer on the
7 National Pork Producers Council, I donate my time to
8 represent producers from across the nation.

9 The policies and programs of the National Pork
10 Producers Council are overseen by a series of volunteer
11 producer committees. I am the chairperson for the Pork
12 Safety Committee.

13 NPPC is one of the largest commodity organizations
14 in the nation. Our headquarters are in Des Moines, Iowa,
15 and we also have an office in Washington, D.C. The council
16 works to build a strong and vital pork industry by solving
17 problems efficiently for the nation's pork producers.

18 There are approximately 85,000 producer members in
19 44 affiliated state associations, and the NPPC draws its
20 strength from the nation's grass-root pork producers.

21 Our members account for the overwhelming majority
22 of the nation's commercial pork production. The pork
23 industry is the fourth largest agricultural sector in the
24 country. We generate approximately \$11 billion in annual
25 farm gate sales, and while creating an estimated \$66 billion

1 in economic activity, employ 764,000 people.

2 As many of you and certainly the agency knows, we
3 have been very involved in this issue. We appreciate the
4 agency calling this meeting and the opportunity to make
5 comments on the proposed framework.

6 It is the hope and expectation of pork producers
7 that the agency will carefully consider all the comments
8 that are offered, and we are glad to hear that the program
9 and direction of the framework has not already been decided
10 on.

11 From the perspective of pork producers, we are
12 like any other animal agriculture sectors. We need timely,
13 economical availability and access to effective products.
14 We need this because we need to keep our animals healthy.
15 This is the right thing to do from the perspective of animal
16 welfare, environment, and doing all that we can do to
17 provide a product that is safe and wholesome.

18 We are very serious about food safety and public
19 health, and I can tell you personally, as a producer and a
20 mother of three children, I am very dedicated to producing a
21 safe food for my family at home, as well as families
22 throughout the world.

23 Another reason we need these products is because
24 they are a tool that we have to be able to use to raise our
25 animals efficiently and make a living to do so.

1 You probably have read about how difficult that
2 has been for the last six months. Well, it still isn't a
3 whole lot better today. Another reason we have been so
4 involved is because of the long-term effects the drug
5 approval process will have on our producers and their
6 animals.

7 We believe that the best process is an open one,
8 that is scientifically based. The proposed framework is a
9 thoughtful document that no doubt took a lot of hard work to
10 think through and what had to be very difficult to write,
11 but this is very important. We see it as an extension of a
12 lease and don't feel that it gives adequate scientific
13 justification to substantiate such a broad encompassing
14 program.

15 Because of this, there is a concern that it will
16 not result in an effective mechanism for protecting public
17 health. What we need is the assessment that will lead us to
18 what appropriately must be done to manage that risk.

19 The proposed framework is presented as ideas that
20 would be used to evaluate, but instead they are actually
21 ways to manage, not evaluate, risk. It is a risk management
22 document which, in numerous places, exposes the bias of the
23 authors with statements about the impact that antimicrobials
24 in our animals have on human health instead of the risk of
25 this happening.

1 If the agency believes the hazard is great enough
2 that it is compelled to develop new regulations, then, this
3 means that you must have already assessed how great that
4 hazard is, but we contend that the agency can't measure the
5 size of the hazard, because the hazard is either there or
6 it's not. It has to have measured the size of the risk to
7 be compelled to take that action.

8 Again, what the agency has given us is a risk
9 management program, one that is built on regulations. The
10 agency's risk assessment that compels it to propose this
11 framework is what most of us here are asking for, so we can
12 see if the framework is an appropriate response.

13 Understand, we do not deny that there is a hazard,
14 but what we need is a risk analysis, which includes risk
15 assessment before we have the regulatory risk assessment
16 program put into place.

17 I want to offer some comments on some of the
18 questions that the agency has asked about the framework. We
19 will be submitting written comments that will include our
20 views on the validity of some of the statements and
21 assumptions that are in the framework also.

22 The agency asks for public input in developing the
23 criteria for categorizing drugs as to their importance in
24 human medicine. The criteria and categorization that are
25 proposed are subjective. The Category I criteria talks

1 about drugs that are essential and important, and not having
2 satisfactory alternatives and limiting therapeutic options.

3 It also talks about resistance being rare among
4 human pathogens and the potential for long-term therapy.
5 How is propose to measure all of these? What is needed is
6 measurable objective criteria that can be objectively
7 applied. Without them, these would be black box decisions,
8 black box decisions that would ultimately come down to
9 belief.

10 We also see the framework as a clear indication
11 that despite attempt to rationalize criteria for Category II
12 and Category III, and given reasonable advances in
13 scientific ability to analyze resistance mechanisms, we
14 believe all present or future antimicrobials that are used
15 in pork production and animal agriculture will eventually be
16 classified as Category I.

17 This apparently is not what the agency intended,
18 but if you read the criteria very carefully, that is what
19 the outcome will be.

20 The agency asked for comments on the factors set
21 out with respect to evaluating human exposure. This begs
22 the question about a quantifiable link between enteric
23 pathogen levels and some measurable public health risk.
24 Without it, you have a regulatory program without purpose
25 because you don't know that it will have any effect on

1 public health, and we certainly don't know if it will have a
2 positive effect on public health.

3 The effect that the quantity of bacteria in the
4 animals intestine have on human health is a researchable
5 question, but it is also one that is so full of compounding
6 factors that realistically, it may not be able to be
7 answered.

8 Pathogen load, as presented, is a HACCP issue.
9 The USDA data shows that HACCP has been successful in
10 reducing pathogens on our carcasses. It is a program at the
11 USDA FSIS, not the FDA, and yet, it is not at its end point.
12 We, at the National Pork Producers Council, as producers,
13 are funding preharvest food safety research projects that
14 will help us answer the appropriate questions about pathogen
15 load, and if we can affect it on the farm, but at this time
16 we simply do not know enough to be able to make those
17 decisions.

18 Another very important point is that exposures may
19 also be dependent on advances in food processing
20 technologies, such as radiation. The framework correctly
21 mentions the ability of processing technologies to affect
22 human contact, but this is much more important to public
23 health than what the document gives it credit for.

24 Finally, the agency is proposing a system of post-
25 approval resistance monitoring that includes extensive on-

1 farm collection of samples. We question the agency's
2 authority to instruct companies to come onto our farms. The
3 proposal in effect holds the approval process hostage,
4 demanding the payment of an off-farm, post-approval
5 monitoring program, which the agency knows that in itself
6 does not have the authority to conduct.

7 I guess we question the agency's full
8 consideration of these actual costs and logistics needed to
9 gather this valid and usable data. Who would collect the
10 samples?

11 The health of our animals depends in part on the
12 biosecurity of our farms. Often, we even ask our
13 veterinarians not to come to our farms if they have had
14 recent contact with other pigs. Is the agency proposing to
15 ask a producer to take samples on the farm to show the FDA
16 that a product should be taken away from us as producers?

17 How would sample quality be assured? Who would
18 pay for the program? I believe we do know the answer to
19 that question. Animal agriculture would ultimately be
20 required to pay for a program which neither we, the agency,
21 or other public health agencies know whether or not it will
22 make a difference to all of animal health, to all of public
23 health.

24 I will say that we believe that the framework is a
25 good-faith effort, but as presented, it must be rejected in

1 favor of goals and objectives that are defensible and
2 attainable. The bottom line is that what has been laid out
3 cannot be accomplished for these reasons.

4 Categorization is subjective, and by the
5 document's own admission, will be changing according to
6 whoever the decisionmaker is. Research has to answer the
7 question of quantifying a link between the number and
8 characteristic of bacteria coming in to the packing plant
9 and then testing the animals and the bacteria leaving on the
10 meat.

11 There are strong concerns about logistics of post-
12 approval monitoring - what would it cost, who would do it,
13 and how would the health of our animals be protected.
14 Remember, HACCP is designed to prevent microbial
15 contamination, and it is working, and there are other
16 concerns that can't be presented because of the allowable
17 time for these comments.

18 Multiple scientific bodies have told us that the
19 hazard is there, but the risk is not quantified or is it
20 imminent. We need to answer these questions before
21 committing the massive resources that would be needed for
22 this.

23 We have the time to develop a comprehensive
24 program that will work, and we support that, forums, such as
25 this, that will start that process, and we committed to