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FOOD AND DRUG ADMINISTRATION
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P R O C E E D I N G S

Introductions

1
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3 DR. LEIN: I would like to have the committee, at
4 least the head table, introduce themselves. If we could
5 start with Dr. Fletcher, please.

6 DR. FLETCHER: I am Oscar Fletcher, College of
7 Veterinary Medicine at N.C. State University. I am
8 representing avian medicine.

9 DR. KOONG: Calvin Koong, Associate Dean, Oregon
10 State University.

11 DR. CLELAND: I am Janis Cleland. I am a small-
12 animal practitioner in Georgia and I am the editor of the
13 Journal of the American Animal Hospital Association. I am
14 here as a consultant for small animal medicine.

15 DR. KEMP: I am Doug Kemp. I am Director of
16 Pharmaceutical Services, University of Georgia, College of
17 Veterinary Medicine. I am a consultant representing
18 pharmacy.

19 DR. WOLF: Alice Wolf, Professor of small-animal
20 medicine and surgery at Texas A&M University, representing
21 companion animal medicine.

22 DR. KORITZ: Gary Koritz, Professor of Veterinary
23 Pharmacology, University of Illinois, College of Veterinary
24 Medicine, representing pharmacology.

1 DR. GERKEN: Diane Gerken, College of Veterinary
2 Medicine, Ohio State University, representing veterinary
3 toxicology.

4 MR. GEYER: I am Dick Geyer. I am the Executive
5 Secretary for VMAC.

6 DR. LEIN: Don Lein, Director of the Diagnostic
7 Lab, Cornell University, representing micro and Chair of the
8 Committee.

9 MS. HUDSON-DURAN: I am Sue Duran, a large animal
10 clinic pharmacist from Auburn University, and I am the
11 consumer affairs representative.

12 DR. LANGSTON: Corey Langston, Mississippi State
13 University, a consultant in veterinary clinical
14 pharmacology.

15 DR. RAVIS: William Ravis, Professor and Head,
16 Department of Pharmaceutical Sciences, Auburn University. I
17 am a consultant.

18 DR. FRANCIS-FLOYD: I am Ruth Francis-Floyd,
19 University of Florida, and I am a consultant representing
20 aquatic sciences.

21 DR. BARKER: Steven Barker, Professor in
22 Toxicology, Louisiana State University School of Veterinary
23 Medicine representing analytical chemistry.

24 DR. STERNER: I am Keith Sterner, professional

1 meeting attender and occasional dairy practitioner from
2 Ionia, Michigan, and in private practice.

3 DR. LEIN: If we could start on my right. Bert?

4 DR. MITCHELL: I am Bert Mitchell, Center for
5 Veterinary Medicine, Policy and Regulations.

6 DR. SUNDLOF: I am Steve Sundlof, Director, Center
7 for Veterinary Medicine, representing government
8 bureaucracy.

9 DR. TOLLEFSON: I am Linda Tollefson. I am
10 Director of the Office of Surveillance and Compliance at
11 CVM.

12 DR. VAUGHN: I am Steve Vaughn. I am the Director
13 of the Division of Therapeutic Drugs for Food Animals in the
14 Office of New Animal Drug Evaluation.

15 DR. LARKINS: I am Marcia Larkins. I am here
16 representing the Division of Drugs for Non-Food animals.

17 DR. KELLER: Bill Keller, Director of the Division
18 of Epidemiology and Surveillance at CVM.

19 DR. LEIN: Thank you very much. Welcome all of
20 you to the meeting.

21 At this time, our first speaker is an introduction
22 by Dr. Steven Sundlof.

23 **Introduction**

24 DR. SUNDLOF: Thank you. Welcome back. It was a

1 very long day yesterday and I think we had a very productive
2 day, and I want to personally extend my appreciation to the
3 committee for enduring the extremely lengthy presentation --
4 the number of presentations. The presentations themselves
5 weren't all that lengthy. But it was a productive day and I
6 thank you for all your hard work.

7 Today, we are switching subjects and we are going
8 to be talking about what constitutes clinical
9 ineffectiveness in drugs that are approved by the Food and
10 Drug Administration.

11 Now, the importance of this issue has been brought
12 up during the negotiations and the discussions, and the
13 regulations writing on AMDUCA, the Animal Medicinal Drug Use
14 Clarification Act.

15 Originally, when we had originally proposed the
16 regulations under AMDUCA, we did not include clinical
17 ineffectiveness as a criterion for allowing veterinarians to
18 use drugs in an extra label manner.

19 This was counter to our previous Compliance Policy
20 Guide in which we clearly recognized that there was a need
21 when the drug was determined to be clinically ineffective,
22 that veterinarians would have the authority to use another
23 drug that may not be approved for that purpose.

24 The reason that we didn't include it in the

1 original draft or rule, final rule on AMDUCA was because it
2 was really difficult to find in the language, the actual
3 language that was passed into the law. The actual legal
4 AMDUCA language does not anywhere in there specifically
5 mention clinical ineffectiveness as a criteria.

6 We were able, through the numerous comments that
7 we did receive, to interpret the Act in such a manner that
8 we felt that it was important to include clinical
9 ineffectiveness as a criterion for allowing extra label drug
10 use.

11 But now we are in a position where we need to put
12 some more meat on that skeleton, and we need to define in a
13 little bit better terms, broader terms, what is meant by
14 clinical ineffectiveness and how would a veterinarian know
15 it when they see it.

16 I think that this issue was brought out in the
17 teleconference that we held in February, on February 12th,
18 1997, in which we received a lot of calls from veterinarians
19 wondering what is it that constitutes clinical
20 ineffectiveness.

21 So there is a concern out there within the
22 profession, and we think that this will give the profession
23 better guidance.

24 We are going to have Dr. Tollefson talk a little

1 bit about what is involved in AMDUCA in a few seconds, but
2 one of the issues that we have to deal with is what does
3 this mean in terms of FDA's regulatory efforts, and the
4 answer is that we do not require veterinarians to keep
5 records of the reasoning behind determining that a drug is
6 ineffective, so this is not compulsory, veterinarians do not
7 have to list in their records the criteria that they use to
8 determine that a drug is ineffective, we don't require that,
9 but we do want to have some assurance that once that
10 determination is made, that it is made for legitimate
11 reasons, and that means that we don't want veterinarians out
12 there declaring drugs to be clinically ineffectiveness when,
13 indeed, they may be effective, for the purpose of using some
14 other drug.

15 You can't use this as an excuse just to use some
16 other drug that may be less expensive or that you may have
17 on the shelf. So, we need to make some fairly solid
18 guidelines on what does constitute clinical ineffectiveness.

19 There are really two questions that we are going
20 to be asking you to address today, and those questions are:
21 how should the term "clinically ineffective" be defined for
22 purposes of the Animal Medicinal Drug Use Clarification Act?
23 That is Number 1. Number 2: How should a veterinarian go
24 about determining whether a drug is clinically ineffective

1 for a labeled indication, what steps should he or she take
2 in making that determination?

3 Those are the questions that you are going to be
4 asked. We are going to hear from Dr. Steve Vaughn and also
5 Marcia Larkins is here to assist in answering questions
6 about clinical effectiveness, and how we determine clinical
7 effectiveness, the efficacy requirements, why drugs aren't
8 always effective.

9 We will on occasion approve drugs that we know are
10 not going to be effective in all cases. This is much more
11 common on the human side than it is for veterinary medicine,
12 but for instance, let me give you a human example where the
13 Agency has recently approved drugs for amyotrophic lateral
14 sclerosis, Lou Gehrig's disease, that they know are not
15 going to be effective in the majority of the patients, but
16 for a small number of patients, the drugs will be effective,
17 and for that reason, the Agency does approve drugs that in
18 some cases it knows will not effective in all cases.

19 There are other conditions - drugs may lose
20 efficacy over time, for instance, antibiotics may become
21 less effective of the bacteria developed a level of
22 resistance. This also occurs for parasitic drugs. Over
23 times the conditions of the disease may change.

24 We require companies to test drugs under field

1 conditions, but on occasion -- well, we can never test under
2 all conditions, and sometimes those conditions may change,
3 so there is a number of reasons why a drug may be clinically
4 ineffective, but we want the profession, the veterinary
5 profession, to make the determination of what are the
6 criteria that can be used for that.

7 In addition to the people I have mentioned, Dr.
8 Tollefson, Dr. Larkins, Dr. Vaughn, we will also have a
9 post-approval perspective about what happens when the Agency
10 receives information that indicates the drugs are no longer
11 effective for their intended purpose or at the label dose
12 are no longer effective, and how the Agency deals with that.

13 You have less material to go through today and it
14 should be a little bit more relaxed than it was yesterday,
15 and I am looking forward again to a very productive meeting.

16 Thank you.

17 DR. LEIN: Thank you, Dr. Sundlof.

18 The committee has heard the questions. I think
19 there is copies, if you don't have one, out in the front
20 yet. I think we are out, we will try to get some more off
21 the table, and give those to the committee basically.

22 The next presentation will be by Dr. Linda
23 Tollefson on AMDUCA Overview.

24

AMDUCA Overview

1 DR. TOLLEFSON: Good morning. I am going to be
2 providing you some background information to help you better
3 address Dr. Sundlof's questions, and I will be followed by
4 Steve Vaughn for a preapproval aspect, and then Dr. Bill
5 Keller for postapproval.

6 Very briefly, I am going to go over the relevant
7 points in the AMDUCA regulation that is required for you to
8 better understand the clinical ineffectiveness provision.

9 [Slide.]

10 What I am going to be talking about is actually
11 FDA's final implementing regulations to the AMDUCA Act.

12 [Slide.]

13 The statute actually became a law in October of
14 1994, and it was effective late in 1996, after the adoption
15 of the final regulations.

16 AMDUCA really does legitimize extra label use in
17 animals of both approved animal and human drugs. This is
18 always either by the veterinarian or under the supervision
19 of a veterinarian, and always in accordance with the
20 regulations that we adopted.

21 [Slide.]

22 Extra label use here means any use of a drug in an
23 animal in a manner not in accordance with the labeled
24 indication, but meaning species indications, dosage levels,

1 frequencies, routes of administration, anything other than
2 that stated in the labeling.

3 Also, it includes deviations from the labeled
4 withdrawal time if there is one based on those different
5 uses.

6 Now, extra label use is only permitted under a
7 valid veterinarian-client-patient relationship. The
8 criteria for this is that a veterinarian must have
9 sufficient knowledge of the animal or animals to make at
10 least a preliminary diagnosis and also the owner of the
11 animal is willing to follow through on the instructions that
12 the veterinarian leaves.

13 Also, the veterinarian needs to be available for
14 follow-up evaluation in the event of any adverse reactions
15 or failure of the treatment regimen.

16 [Slide.]

17 The veterinarian has a responsibility for making
18 the clinical judgment, the client agrees to follow the
19 veterinarian's instructions.

20 [Slide.]

21 The veterinarian knows these animals to at least
22 make some kind of a general diagnosis, and then he or she is
23 readily available.

24 [Slide.]

1 Under the conditions of a valid VCPR, then, extra
2 label drug use, when is it permitted? This is a real good
3 overview slide. It is maybe simplified, but I think it is
4 really all you need to know.

5 First of all, when there is no animal drug
6 approved for the intended use or when there is an animal
7 drug approved for the intended use, but the approved drug is
8 not in the require dosage form or concentration, it has been
9 found to be clinically ineffective when used as labeled --
10 and we will get into that a little bit more -- or if the
11 intended use is in non-food animals and an approved human
12 drug can be used.

13 [Slide.]

14 Now, in the final implementing regulations, we
15 went forward with some special priority rules. The reason
16 we did this is to protect as much as possible the approved
17 drugs, such that in food animals, we are asking for the
18 first resort for extra label use to use an approved animal
19 drug rather than a human drug than one that doesn't require
20 compounding is preferred over one that does, and when
21 compounding is appropriate, if you have gotten down to that
22 level, then, an approved animal drug should be used first
23 before a human drug. Also, all the other requirements of
24 the regulations must be met.

1 [Slide.]

2 In food animals, in summary, there are a couple of
3 extra conditions when you can't use the drug in an extra
4 label manner regardless of all of the previous conditions.
5 That is when its use has actually been prohibited because it
6 presents a risk to the public health and there is a process
7 to do that, or when the extra label use results in residues
8 above an established an established safe level of
9 concentration or tolerance and when the intended use is in
10 feed. Those are conditions under which you can never use
11 them.

12 [Slide.]

13 To get into the clinical ineffectiveness provision
14 in a little bit more detail, Dr. Sundlof mentioned that the
15 clinical ineffectiveness provision was not in the statute or
16 the proposed regulations, however, it was in a Compliance
17 Policy Guide on extra label use that CVM had been using for
18 a number of years.

19 So in the response to comments, in the final
20 regulation, we determined that allowing extra label drug use
21 when an approved new animal drug is clinically ineffective
22 is actually supported under AMDUCA, and the wording that is
23 in the regulation is shown on the bottom of that overhead.

24 It is permitted when an approved drug is found by

1 the veterinarian to be clinically ineffective for its
2 intended use in the animal or animals involved.

3 Note that the veterinarian must have a basis for
4 determining that the use of the approved new animal drug is
5 clinically ineffective. The provision applies to both food
6 animals and non-food animals. I didn't want to be confused
7 on that issue.

8 We did define those circumstances, we meant to
9 define them narrowly, because we don't want to undermine the
10 animal drug approval process or jeopardize the approved
11 products that are out there.

12 [Slide.]

13 These are your questions that CVM is asking you to
14 address.

15 [Slide.]

16 In doing this and considering these questions,
17 there are a number of relevant issues that we thought of
18 that I think may be helpful to you. For example, do you
19 feel that it is necessary for actual clinical experience to
20 determine that a drug is clinically ineffective.

21 That implies within either an individual animal or
22 herd, or maybe within a practice area versus the
23 alternative, which is relying on external sources, such as
24 published literature or possibly professional meetings where

1 this type of information is generated and disseminated.

2 [Slide.]

3 Also, how frequently should a finding of
4 ineffectiveness be considered or actually reconsidered? For
5 example, if the approved drug is found ineffective one
6 particular time, should it be tried again after a certain
7 amount of time before reverting to extra label drug use?

8 That is a question that we were struggling with
9 for a while.

10 [Slide.]

11 We also didn't know if maybe that latter question
12 couldn't be placed in perspective by changing the guidelines
13 due to different classes of drugs. The obvious case with
14 antimicrobial agents is that they can become resistant and
15 then lose their resistance after time if they are not being
16 used again or at least some of them may. So, in that case,
17 you might want to recheck more frequently than in the case
18 of some other class of drug.

19 Finally, we may want to consider the status of the
20 specific intended use, such that there are a number of
21 labeled indications, the drug may work for one, it might not
22 for another. There are other things we can do, such as
23 removing that particular indication from the label to make
24 it clearer for the veterinarians.

1 That is all I have. If you have any questions or
2 if you want to go further with the more specific preapproval
3 and postapproval issues.

4 DR. LEIN: Any question for Dr. Tollefson from the
5 committee? Yes, Ruth.

6 DR. FRANCIS-FLOYD: I certainly don't want to open
7 up a can of worms, but did I understand you to say that the
8 restriction on using drugs extralabely in feed applies only
9 to food animals?

10 DR. TOLLEFSON: No.

11 DR. FRANCIS-FLOYD: Okay.

12 DR. TOLLEFSON: It is not approved at all.

13 DR. LEIN: Other questions? Thank you.

14 The next presentation is on preapproval
15 perspective. Dr. Steven Vaughn.

16 **Preapproval Perspective**

17 DR. VAUGHN: Good morning. What I wanted to do
18 for the next 10 or 15 minutes, hopefully not longer than
19 that, was to give you a little bit of perspective of what we
20 go through when we determine that a drug is effective and
21 where those boundaries are at and where there is some room
22 for comparing and contrasting how a drug may be considered
23 clinically effective or clinically ineffective.

24 [Slide.]

1 Let's start with the legalese, always have to
2 start there. Under the Animal Drug Availability Act, the
3 term that has been used to set the standard, if you will,
4 for what constitutes drug effectiveness is "substantial
5 evidence," and through the Animal Drug Availability Act,
6 Congress has asked us to redefine that definition.

7 They have provided us some language to guide us in
8 that redefinition and this is the language that appears in
9 the Act. "The term substantial evidence means evidence
10 consisting of one or more adequate and well-controlled
11 investigations, such as a study in a target species. The
12 target species would be a species for which a product will
13 ultimately be labeled, a study in laboratory animals, any
14 field investigation that may be required," and there are
15 some provisions that are built into it when we ask for more
16 than one field trial, which is the language that flows
17 there.

18 Below that there is a bioequivalence study or an
19 in vitro study.

20 [Slide.]

21 Now, these investigations need to be conducted by
22 experts that are qualified by scientific training and
23 experience to evaluate the effectiveness of the drug on the
24 basis of which it could fairly and reasonably -- and those

1 are important words -- be concluded by such experts that the
2 drug will have the effect it purports or is represented to
3 have under the conditions of use prescribed, recommended, or
4 suggested in the labeling.

5 [Slide.]

6 So from that definition of substantial evidence,
7 there needs to be -- or as we are driven by that -- there
8 needs to be a certain quality and quantity of scientific
9 evidence that provides a basis, a weight of evidence if you
10 will, upon which experts could reasonably and fairly, or
11 fairly and reasonably, conclude that a product will have its
12 intended effect.

13 So when we look at that, there are some principles
14 that -- and these are by no means cast in stone -- we
15 intentionally or unintentionally go through these thought
16 processes and followed some of these principles to a greater
17 or lesser extent depending on the type of application.

18 I wanted to throw these out for you as you are
19 thinking about trying to define clinically ineffective. You
20 need to understand where we are coming from when we say a
21 drug is effective.

22 [Slide.]

23 The first one on that list would be that the
24 product would have to have a reasonable claim, and this is

1 the first thing we do. Everything from the start to the end
2 is driven by what the label says, so a reasonable claim
3 would be a claim that we can study, that would have meaning
4 both biologically and to a clinician in the field, but they
5 do have quite a bit of variation.

6 For example, you could have a label indication or
7 a label claim for decreasing mortality in poultry or you
8 could have a claim for the treatment of endotoxemia, which
9 would be fairly broad clinical syndrome, or we could have
10 the treatment of a specific disease, say, bovine respiratory
11 disease, and in each of those we would approach the data
12 package from a different perspective.

13 One point I want to make about that is we have to
14 be very acute in looking at what the label claim actually
15 says for determining whether the drug is intended for that
16 use or not, and part of that, let me explain, give you an
17 example. Drugs could be labeled, like an antimicrobial, for
18 example, for the prevention of a disease where we would
19 actually be studying the drug from the standpoint of putting
20 the drug in the animal or group of animals prior to the
21 introduction of the disease, it could be for control of
22 disease, which could be to decrease symptoms in an
23 individual animal or to mitigate an early outbreak in a
24 group of animals, or it could be for the treatment of

1 disease where we are actually treating the full-blown
2 disease in an individual or we are the peak of the disease
3 cycle in a group of animals.

4 So, when we say whether the drug is effective for
5 its intended use, we have to be very careful what the label
6 indication is.

7 The second would be that the response can be
8 reasonably measured, the endpoints that we decide are
9 reasonable. For some classes of drugs we have a standard.
10 For example, for anthelmintics, we require that they
11 demonstrate that they are able to kill 90 percent of the
12 parasites. Other diseases, it is not as clear.

13 For example, some of the diseases that we are most
14 familiar with are some of the most problematic to define
15 endpoints for. An example would be neonatal diarrhea. When
16 we look at endpoints like mortality, when we look at
17 clinical impressions for appetite or attitude to determine
18 that the drug was having a successful effect, but in any
19 event, those endpoints have to be correlated back to the
20 label claim.

21 The next point would be a dose-response
22 relationship. That is not necessarily a dose titration,
23 which has been the subject of a lot of prior discussion.
24 Dose titration would imply that we are optimizing a dose,

1 and that is not necessarily the case here.

2 We need to characterize the dose-response
3 relationship. We need to have a justification for why we
4 picked a particular dose, and we need to be able to provide
5 information on the label particularly for dose ranges to
6 individualize the dosing regimen for an individual animal or
7 group of animals in a particular clinical setting.

8 There is an assumption that more drug is better,
9 and I can assure you that in many cases that is not the
10 case, and so for a practitioner to be able to individualize
11 a dose when we have given a very broad dosing regimen from
12 which the practitioner can choose, there needs to be
13 information to allow that to occur.

14 The other thing is the assumption that there is
15 repeatable effect. When we look at the endpoints from the
16 response we would expect from the drug, we would want to
17 have a reasonable certainty that it was repeatable.

18 [Slide.]

19 In some cases, the only way to get there is to do
20 a multilocation field trial.

21 [Slide.]

22 In other cases, particularly when we use model
23 studies, we have validated the model through prior tests and
24 we have confidence that that model would represent or give

1 us a degree of certainty that the response would be
2 repeatable.

3 [Slide.]

4 Again, this comes out of the statute itself, the
5 qualification of investigators. The study needs to be
6 conducted in such a way that the people who are actually
7 doing the observations and the measurements are capable of
8 doing those measurements. I don't think we need to go much
9 farther on that.

10 [Slide.]

11 The form of the drug. Right now we require
12 sponsors to use a GMP-like clinical supply of the drug for
13 doing these studies. In that way, we have the relationship
14 between the drug that was used in these studies to the drug
15 that is commercially marketed.

16 We do have provisions where as drugs are being
17 developed and they are evolving as they are being studied
18 for sponsors to be able to conduct bridging studies from a
19 prototype formulation, if you will, to the final
20 commercially marketed formulation.

21 Then, lastly, the inferential value of the data,
22 from the data package we have, would it be for the whole
23 population, would it be for the majority of animals. An
24 example would be an ivermectin treatment for heartworms and

1 ultimately, we know we have a breed of animals, collies,
2 that may be more sensitive. That is an example of where it
3 would be to the majority of the population rather than the
4 whole population.

5 We also put label restrictions to define that
6 inferential value, for example, age restrictions, class of
7 animal restrictions, physiologic class restrictions, for
8 example, we may label a product that is not intended for use
9 in reproducing animals. We may not have studied all of the
10 effects that may be associated with that.

11 [Slide.]

12 We give you an example of how study packages can
13 vary, for example, production drugs versus therapeutic
14 drugs. We look at production drugs almost in a risk-benefit
15 -- I don't say we will -- but almost in a risk-benefit
16 fashion where the production effect has to obviously be
17 beneficial, but at a level where there is minimal risk.

18 Certainly, it is not prudent for us to jeopardize
19 human, environmental, or animal safety in a situation where
20 we are using a drug for production and arguably an economic
21 benefit. But on the other hand, for a therapeutic drug, we
22 can accept some level of potential for adverse side effects
23 if the therapeutic value of the drug is deemed to be
24 greater.

1 If we have a treatment for a very serious disease
2 situation, for example, your oncology drugs, we certainly
3 have side effects and they are acceptable considering the
4 alternative of not treating.

5 Another difference would be prescription versus
6 over-the-counter. For example, a prescription antimicrobial
7 may have a dosing range or dosing regimen that gives the
8 practitioner some latitude to choose or individually titrate
9 the dose for a particular animal or group of animals as
10 opposed to an over-the-counter drug which would have a very
11 finite dose.

12 The data that would be necessary to support those
13 ranges will be different for a prescription drug than the
14 data that will be necessary to support an over-the-counter
15 product, where essentially for a prescription drug,
16 combining the knowledge and experience of a practicing
17 veterinarian with the label information we provide to come
18 to a sum total of adequate directions for use for a
19 particular product.

20 The class of drug certainly will have a bearing on
21 the type of studies that we would require. For example, for
22 an anthelmintic, we traditionally use a battery of studies
23 that include a dose titration, a dose confirmation and field
24 trials.

1 In field trials, we are usually measuring fecal
2 egg counts which are highly variable, but in the dose
3 confirmation trials we are actually counting parasites. In
4 those cases, then certainly the most critical study would be
5 the dose confirmation trials.

6 On the other hand, for a systemically absorbed
7 antimicrobial, we may use a battery of pharmacokinetic or
8 MIC information that relates back to clinical effectiveness
9 information or data from prior trials.

10 Another example would be a drug in which we were
11 treating congestive heart failure in a dog where the dose
12 actually must be provided as a loading dose followed by an
13 individualized titration of the dose to the animal depending
14 on the stage and severity of the congestive heart failure
15 and the refractoriness to treatment.

16 [Slide.]

17 Dosage form. Certainly those will require
18 different kinds of trials, and I think that is important
19 from the standpoint of when we look at those trials in order
20 to be able to determine when we have clinical effectiveness,
21 there are different considerations.

22 For example, if we used an implant or sustained
23 release product, we would have to study that over several
24 months to make a determination of effectiveness as opposed

1 to a short-acting injectable therapeutic drug that may only
2 require a trial lasting for a few days or we may use a
3 validated model study.

4 Another example in the dosage form arena would be
5 if you have a drug that acts locally, such as a drug that
6 would be injected for treatment of a joint disease, that
7 would be injected intra-articularly, it would be studied in
8 one way as opposed to a drug that would be administered for
9 the same disease systemically.

10 The species of animal. Obviously, we are going to
11 have different types of trials that would be necessary to
12 demonstrate drug effectiveness. Certainly, studying disease
13 in individual animals, dogs, cats, or horses, would be
14 markedly different than studies to be used to demonstrate
15 drug effectiveness in a flock of turkeys or broilers or a
16 fish pond.

17 In companion animals, the endpoints for
18 determining effectiveness are based more on the animal's
19 quality of life, if you will, much more like human medicine
20 than in a food animal where economic profitability of the
21 animals are a factor in determining the endpoints.

22 [Slide.]

23 Let me just summarize then the label implications,
24 which brings it up to what the practitioner would actually

1 see, and that is that the indications and dosage and the
2 conditions of use are supported by the label, and then the
3 information that is in that label has been supported by the
4 data package with all the thoughts and considerations that I
5 just went through, and that data is summarized in the
6 Freedom on Information Act summary.

7 The last point would be at the time of approval,
8 we are fairly confident that the drug is effective for those
9 conditions of use that are in the label in the majority of
10 clinical situations.

11 That is all I have.

12 DR. LEIN: Questions for Steve? Yes, Dr. Wolf.

13 DR. WOLF: When a drug then changes status from
14 prescription to OTC, what sort of process does the
15 manufacturer need to go through to change that drug status?

16 DR. VAUGHN: Basically, they would have to submit
17 a supplemental application, and then we would have to
18 consider the basis upon which we designated that product to
19 be prescription in the first place, and depending on what
20 those conditions are, if they are no longer concerns, we can
21 convert it to an over-the-counter drug.

22 On the other hand, a lot of the prescription drugs
23 nowadays we have started down the clinical development path
24 where we have made that designation early in the course of

1 the drug development, and it would be very difficult in
2 those cases for a sponsor to come back and convert from a
3 prescription to an over-the-counter drug.

4 DR. LEIN: So that will be made upfront basically
5 in the preapproval usually if it is going to be over-the-
6 counter?

7 DR. VAUGHN: Correct. That is a designation that
8 we do in the preapproval review process.

9 DR. WOLF: I guess my question was one thing. A
10 couple of the antiparasite products for small animals came
11 out as prescription drugs, and then within a fairly short
12 time, like two years, they are now converting to OTC, so
13 clearly it is not a matter of licensure and running out on
14 the patent, and all that, which is often the case in those
15 instances.

16 DR. VAUGHN: Did you want to comment to that, Dr.
17 Larkins?

18 DR. LARKINS: Yes. In those cases that you just
19 mentioned, the company or sponsor will try to get some
20 marketing experience at the Rx level, and after a while if
21 they deem that they would like to change to an over-the-
22 counter, they will come back to the Center, apply for a
23 supplement and change, and as long as they can write a label
24 that is understandable to the average lay person, and

1 requires a minimal amount of veterinarian intervention,
2 then, we will grant OTC status.

3 DR. WOLF: So, that is kind of based on experience
4 with adverse reactions, and things like that, that would ask
5 for that information?

6 DR. LARKINS: To convert to OTC status?

7 DR. WOLF: Yes.

8 DR. LARKINS: No, that generally is not based on
9 adverse reactions. It is based on marketing experience and
10 whether or not you can write a label for the average lay
11 person. Dr. Tollefson just mentioned that is the choice of
12 the sponsor to do that.

13 DR. LEIN: Other questions? Yes, Steve.

14 DR. BARKER: Dr. Vaughn, you gave a list of all
15 the things that are done to determine clinical effectiveness
16 and, of course, there is no expectation that those types of
17 studies will actually be done to determine clinical
18 ineffectiveness in the field.

19 We are going to have to rely for a large part on
20 the observations, intuition of the veterinarians actually
21 using the drugs, is that correct?

22 DR. VAUGHN: Yes. In fact, in prescription drugs,
23 as I mentioned at one point, we are building in very wide
24 indications for labels where we are actually setting the

1 outer boundaries rather than the specific indication like we
2 would for an over-the-counter product, and we do rely in
3 those cases on the knowledge and experience of the
4 veterinarian to make those clinical judgments.

5 DR. BARKER: The approvals, of course, though, are
6 usually based on limited observations in a given species,
7 the drug approval being what it is and how expensive it
8 would be to look at all these.

9 DR. VAUGHN: Correct.

10 DR. BARKER: But now that is in light of AMDUCA,
11 which gives veterinarians a great deal of flexibility in
12 selecting drugs to use in different species by different
13 doses or routes, not really determined to be clinically
14 effective necessarily.

15 What prevents a veterinarian from taking a term
16 that is kind of in the middle of all this, clinically more
17 effective?

18 DR. VAUGHN: I am not sure if I am the person to
19 answer that question.

20 DR. BARKER: Well, clinically ineffective doesn't
21 work at all, the drug doesn't work at all, in my observation
22 for its labeled purpose, it is not working anymore.

23 This drug over here is not determined to be for
24 that, and I could switch to that. Now, that would be the

1 determination I think we are trying to make, something that
2 is clinically ineffective and trying to pick another drug
3 that is more clinically effective that you could substitute,
4 but if something is -- well, it works fairly well on this
5 animal, but I think their drug works better, it is more
6 clinically effective. Is there a process to deal with that,
7 as well?

8 DR. VAUGHN: I think if you can hold that
9 question, Dr. Keller in his presentation is planning to
10 cover that. It is a postapproval issue.

11 DR. KELLER: I got stuck with that question.

12 DR. BARKER: That is what I am trying to
13 understand here. Something that is determined in the field
14 by veterinarians who have plenty of experience in making
15 observations, but will not have the support of actual data
16 like is required for determining effectiveness, is there
17 really a need for a determination of clinical
18 ineffectiveness, still permit the same flexibility that is
19 going to happen anyway?

20 DR. LEIN: Maybe we should wait on that until the
21 next presentation, and none of this is subjective, of
22 course.

23 DR. BARKER: I would also request copies of the
24 overheads and slide from the last presenters, if possible.

1 DR. LEIN: Fine.

2 The next presentation will be on Postapproval
3 Perspectives by Dr. Bill Keller.

4 **Postapproval Perspectives**

5 DR. KELLER: Good morning.

6 Just to perhaps further address Dr. Wolf's
7 question from a postapproval perspective, I think the
8 situation that you were addressing, switching a prescription
9 product to over-the-counter, there is actually a nuance in
10 the law which treats over-the-counter products differently
11 than prescription products for advertising purposes

12 One of the major considerations for companion
13 animal products, which you were talking about, is the
14 ability to advertise direct to consumers, and a manufacturer
15 can do that with over-the-counter products, but not with
16 prescription products, so that was a consideration there.

17 First of all, let me apologize for my voice. It
18 seems that every spring and fall I get this. Some people
19 might think it is spring and fall, but I think it is VMAC.

20 [Slide.]

21 I would like to acknowledge Dr. Mike Talley and
22 Dr. Ed Spencer for their contributions to the material that
23 I am going to present. The good stuff is theirs, the bad
24 stuff is mine.

1 Following good presentation practices, being the
2 last speaker this morning, I am going to tell you what you
3 have been told, so a lot of what I will present you have
4 heard a little bit before.

5 These are the two questions. As I said, the
6 background on this issue has been explored by other
7 speakers.

8 [Slide.]

9 For completeness sake, I will note again that the
10 AMDUCA did not contain specific language allowing extra
11 label use of animal or human drugs based on the rationale
12 that the approved animal drug for a particular indication
13 was judged to be ineffective, nor did the proposed AMDUCA
14 regulation published last spring.

15 The AMDUCA did, however, include language stating,
16 "The Secretary may prohibit particular uses of an animal
17 drug and shall not permit such different uses of an animal
18 drug if the labeling of another animal drug that contains
19 the same active ingredient and which is in the same dosage
20 form and concentration provides for such different use." I
21 will return to the concepts in this paragraph shortly.

22 [Slide.]

23 Language allowing extra label use of animal or
24 human drugs based on the rationale that the approved animal

1 drug for a particular indication was judged to be
2 ineffective, as Dr. Sundlof said, was specifically
3 articulated in the Compliance Policy Guide, which is
4 directions to our field staff.

5 The title is "Extra Label Use of New Animal Drugs
6 in Food-Producing Animals." So that language was there in
7 what we call the CPG.

8 [Slide.]

9 Again, as Dr. Sundlof has said, we received
10 numerous comments last year in response to the proposed reg
11 that we include in the final regulation verbiage that
12 provides for a latitude similar to that, that was in the
13 CPG.

14 These comments contended that veterinarians
15 frequently encounter clinical situations in which an
16 approved drug is ineffective. In considering this issue,
17 the Center determined that to allow extra label use when
18 there was no product labeled for treating a condition, while
19 denying extra label use when there was a product labeled for
20 the condition, but it had been found to be clinically
21 ineffective would produce in essence an absurd result.

22 The two situations are essentially identical in
23 that no effective product is available and therefore the
24 outcome should also be essentially identical. Consequently,

1 the Center published the final regulation with language that
2 provided for extra label use when a veterinarian finds,
3 within the context of a valid CPG, that the approved new
4 animal drug is clinically ineffective for its intended use.

5 Since the AMDUCA language does not specifically
6 provide for extra label use when an approved product is
7 determined to be clinically ineffective, but does provide
8 for extra label use when the approved product does not
9 contain the same active ingredient, in the same dosage form
10 and the same concentration as needed, we should ask from a
11 practical standpoint: Is there a frequent and significant
12 difference in the outcome of these determinations, and if
13 not, should not consideration of these concepts, clearly
14 stated by AMDUCA, be part of the process for determining
15 that an approved product is clinically ineffective?

16 In other words, establishing the active
17 ingredient, dosage form and concentration needed to provide
18 successful treatment, it seems fundamental to a
19 determination that the available approved product would be
20 clinically ineffective. It should be noted, however, that
21 the opposite approach is typically followed by busy
22 practitioners.

23 Following a diagnosis, a treatment is selected
24 based on information on therapeutic products provided to the

1 veterinarian by a wide range of sources including local
2 colleagues, textbooks, academia, and industry. This
3 information may identify agents which are thought to be
4 clinically ineffective or identify alternative agents which
5 are thought to be clinical superior.

6 In either case the result is the same: selection
7 of an alternate product for extra label use. At this point
8 one must ask the question, "When does clinically superior
9 become of sufficient weight to relegate the clinically
10 inferior product to clinically ineffective status?"

11 If we are dealing with two approved products,
12 policies and regulations would provide a road map for this
13 issue, largely through regulating competitive product
14 promotion practices.

15 On the other hand, a clinically superior product
16 that must be used extra-labely, may not be promoted for that
17 extra label use. So how would clinical superiority be
18 established? The approach usually taken is a peer-reviewed
19 journal publication, but that type of information may only
20 be disseminated in response to an unsolicited request from a
21 veterinarian to the sponsor.

22 Clearly there are limitations on industry's
23 ability to provide information on clinical effectiveness to
24 veterinarians for extra label uses. That should have a

1 dampening effect on the amount of extra label use that
2 results under the clinical ineffectiveness concept. Thus,
3 the Agency's regulation of promotional activity,
4 particularly what we term preapproval promotion, may impact
5 on this issue. Preapproval promotion has to do with
6 promoting a product that is under investigation.

7 [Slide.]

8 Let me shift from the clinical to the regulatory
9 for the next issue. I would like to contrast two
10 fundamental underlying concepts in the Act as they relate to
11 AMDUCA - the lack of substantial evidence provision and the
12 clinically ineffective determination requirement.

13 The lack of substantial evidence provision of the
14 regulations is found in the subsection titled "Withdrawal of
15 approval of applications."

16 In deference to my voice, I am going to pause here
17 and let you read that. It is in your package also.

18 Simply stated, this paragraph is the basis for
19 withdrawal of an application for lack of effectiveness.

20 These are our tools. The term used is lack of substantial
21 evidence.

22 [Slide.]

23 On the other hand, the term you have been asked to
24 provide advice in defining is found in Section 530.20 of the

1 regulations, conditions for permitted extra label animal and
2 human drug use in food-producing animals.

3 Now it does apply to both food and non-food
4 animals. This section in non-food animals simply refers
5 back to this paragraph.

6 Again, I will allow you to read that. The concept
7 in question is at the bottom in italics, "*clinically*
8 *ineffective.*"

9 Let me pose the potential dilemma arising from
10 these two sections of the Act and hopefully resolve it over
11 the next few minutes. If the Agency were presented with a
12 product which has a significant volume of determinations
13 that it is clinically ineffective under AMDUCA, what should
14 our response be under the "lack of substantial evidence"
15 that such drug will have the effect it purports or is
16 represented to have under the conditions of use prescribed
17 section of the regulations?

18 While there is nothing in AMDUCA to suggest
19 Congress intended to link these issues, scientifically they
20 lie on the same continuum and ultimately must be
21 rationalized.

22 [Slide.]

23 As background for this issue I would like to
24 provide some information on the typical dynamics of

1 withdrawal of approval activity over the last few years. I
2 have also included approval information to emphasize the
3 product life-cycle character of our discussion.

4 As you can see, during the years '92 through '96,
5 the Center has withdrawn over 100 NADAs. Invariably, these
6 withdrawals were voluntary. While there may have been
7 questions about efficacy of some products, ultimately
8 withdrawal involved mostly marketing and economic factors
9 rather than substantial questions of safety or efficacy.
10 Let's look more closely at the question of why a product
11 might be voluntarily withdrawn due to economic or marketing
12 decisions.

13 I have a series of three slides here and I will
14 run through all three and then back up.

15 The first two have to do with Bayer products.
16 There is roughly two dozen. These are all products that
17 were withdrawn voluntarily. We are not picking on Bayer by
18 any means. It is not unusual to have -- this is an unusual
19 situation at least in the five years that I have been
20 involved with this -- but it is not unusual to have five or
21 six or eight products from one sponsor.

22 The fact is a new director of marketing comes in,
23 companies are consolidated, et cetera, and inventory is
24 updated.

1 It is instructive to see the character of these
2 withdrawn products. Because of the large number of
3 withdrawals -- as I said, I presented this information in
4 three overheads, two for Bayer and one for the other firm --
5 again, in virtually no instance were any of the products
6 removed from the market based solely on the lack of
7 substantial evidence provision. In fact, all were
8 voluntarily withdrawn although, to be fair, it is true that
9 in some instances the Agency may have inquired about the
10 safety or efficacy of a product based upon new information.

11 Thus, in these limited -- and they are limited --
12 situations, one might have to include the need to respond to
13 the Center's inquiry as one of the considerations in
14 determining future marketing status of a product.

15 A far more common reason for withdrawing a product
16 on this list is an uncomplicated marketing decision by the
17 firm. Given this information, one must ask why are these
18 products being withdrawn if they are safe and effective.

19 Surely, a safe, effective, and reasonably priced
20 product would continue to be in demand and profitable. But
21 in fact, as we all are aware, therapeutics and the
22 pharmaceutical industry are not static but dynamic entities.

23 Drugs and families of drugs are developed,
24 marketed, and then fall into disuse, displaced from their

1 niche by some other product or products that are either more
2 effective, safer, or both, or perhaps even less expensive.

3 If you look on the left side under NADA, these are
4 the products numbers. They tell you a little bit about the
5 character of the list. The NADAs with single digits are
6 from the '40 and '50s. There is one up there. I think
7 there were a couple of Bayer products also. That is 1940s.
8 I don't see a 30 up there, but there is a 12, and there were
9 some on the Bayer side. There they are, the teens and 30s
10 from the 1960s.

11 The NADAs that are in the hundreds to 120 are from
12 the late '70s to early '80s. Obviously, most of these
13 products are old.

14 In addition, in looking at the marketing status of
15 these products, only one product was being actively marketed
16 when it was withdrawn, and that was very small in terms of
17 volume. So in almost every case the products withdrawn
18 during 1996 were old and inactive. So that is the temporal
19 relationship that we are dealing with them in product
20 withdrawals.

21 [Slide.]

22 Let me illustrate the concept of clinical
23 ineffectiveness geometrically with acknowledgment to Dr.
24 Bond. It was his idea. I hope that I have expressed it

1 reasonably well.

2 In this figure on the left, the outer circle
3 represents the theoretical maximum limits of potential
4 clinical ineffectiveness, or the disease condition requiring
5 treatment, while the inner circle represents the clinical
6 effectiveness of a particular approved product.

7 As you can see, there are some circumstances where
8 a product will not be effective. The circles on the right
9 represent pharmaceutical progress in efficacy, for instance,
10 a broader spectrum antibiotic or antiparasitic or an
11 antiparasitic product that results in more complete removal
12 of a particular parasite.

13 As you can see, we have more area covered by the
14 efficacy, but there still is some area of ineffectiveness.
15 When this dynamic process is guided by indications on
16 approved labeling, we generally have a road map for making
17 therapeutic decisions, however, when minor species, minor
18 uses, and new chemical entities unapproved are involved, the
19 road map is less clear.

20 That is when we will mostly encounter situations
21 when an approved product may be judged to be clinically
22 ineffective, either because it is frankly ineffective,
23 substantially less effective, or perhaps even less safe.

24 The idea that I hope I have driven firmly home is

1 that this concept of clinically effective is a continuum,
2 with extremes on each end and various degrees of
3 effectiveness and ineffectiveness across the spectrum.

4 I also want to recognize that these determinations
5 are part of the normal activity involved in practicing
6 veterinary medicine and part of the normal process of
7 marketing veterinary pharmaceuticals. This is not a new
8 idea for veterinarians, the Agency, or industry.

9 I also want to emphasize at this point that a
10 determination of clinical ineffectiveness under AMDUCA does
11 not necessarily constitute grounds for withdrawal under the
12 lack substantial evidence provision of the law.

13 [Slide.]

14 One last comment in this abstract area of clinical
15 effectiveness is needed before I move on, and that has to do
16 with clinical indications themselves.

17 The set of approved clinical indications is also
18 not static, but dynamic. For instance, Micotil, as an
19 example, was originally approved for bovine respiratory
20 diseases associated with Pasteurella Hemolytica, but
21 recently was also approved for control of respiratory
22 disease in cattle at high risk of developing bovine
23 respiratory disease associated with Pasteurella Hemolytica.
24 The verbiage is a little bit different, the implications are

1 substantially different, and this is a new indication
2 previously unrecognized by the Center.

3 [Slide.]

4 Another example are the various combinations of
5 antiparasitic products that are beginning to be marketed,
6 for instance, combinations of heartworms and intestinal
7 parasites being treated by one monthly dose.

8 So this whole area, including the very clinical
9 indications themselves is very fluid, and regulatory
10 definitions and policies should take this into account.

11 [Slide.]

12 Finally, I would like to provide some examples
13 from our recent experience in the Center we thought would be
14 useful or illustrative to you in considering these
15 questions.

16 The first one there is a fairly unusual example,
17 but one that we actually encounter fairly routinely at CVM,
18 the use of potassium bromide for treating refractory
19 epilepsy in dogs versus the approved product primidone.

20 Over the last two years, the Division of
21 Compliance has issued over 100 letters to practitioners --
22 these letters are regulatory discretion letters --
23 practitioners who wish to dispense this product.

24 Interestingly, this product is not an approved drug, but a

1 grandfathered human drug widely used during the 19th and
2 early 20th centuries to control convulsions. It is
3 virtually always compounded.

4 [Slide.]

5 A second example is one of extra label use of
6 antimicrobials. Someone pointed out that amoxicillin and
7 Clavamox is essentially the same example or acknowledged
8 that.

9 The point I want to make is that these are all
10 approved products, but in every example there are textbook
11 information, information in other publications that
12 indicates that these products are more effective when used
13 at a more frequent or higher dose than that on the label.

14 So, this is perhaps what we might call a good
15 example since these are exactly the same products, but we
16 are just increasing the dose or the frequency. So perhaps
17 this is something that is obviously covered by the phrase in
18 the implementing regulation.

19 [Slide.]

20 Moving on, here is a controversial issue.
21 Examples of economics driving a product selection decision
22 are common. The scope of veterinary medical treatment is
23 often tied very closely to the client's willingness to pay
24 for treatment. The more expensive the drug, the more

1 resistance there will be towards use of the product. Thus,
2 there is a force tending to push veterinary practice towards
3 selecting less expensive products, assuming the less
4 expensive product is effective, of course.

5 On the other hand, new drug development research
6 is expensive. In order to pay for bringing new products to
7 the market, a premium price is often charged for these new
8 products during the period of exclusivity.

9 Thus, we have opposing forces interacting to drive
10 product selection. It is perhaps an understatement to say
11 that balancing these two competing interests will be a key
12 to successful implementation of AMDUCA. Here are a few
13 examples.

14 4-methylpyrazol, a recently approved product for
15 treating antifreeze poisoning. According to the information
16 that we have received, following approval there was an
17 increase in the price of about \$100 per dose for the new
18 approved product versus the former compounded product.

19 We have also been told that clients won't pay the
20 increased price, and are electing to euthanize animals
21 instead. Is this clinically effective? It really doesn't
22 quite fit since there is not an approved human or animal
23 product that is an alternative. However, it is a good
24 example and a current one of the significant role that

1 economic factors play.

2 Next example. Human label cefazolin versus
3 Naxcel, approved veterinary product. In this case, the
4 decision seems to be based more on economics than clinical
5 effectiveness. Cefazolin is likely not as clinically
6 effective as ceftiofur. FDA is aware that some animal drug
7 vendors and/or distributors have promoted human cefazolin
8 for use in animals as an equivalent for ceftiofur.

9 It is a first-generation cephalosporin. Ceftiofur
10 is a third-generation cephalosporin. The two drugs have
11 different pharmacokinetics and are effective against
12 different bacteria. The two products are not equivalent.

13 Next example. Cyclosporin ointment. This is an
14 example from companion animal practice. We have been
15 informed that some ophthalmologists feel that the approved
16 form of cyclosporin ophthalmic ointment is not appropriate
17 for some patients due to the form and delivery system and
18 possibly other factors, and they continue to prescribe a
19 compounded liquid from time to time. The approved product
20 has been described as ineffective and also too expensive.

21 Another what we would call strictly economic-based
22 example of extra label use is the use of large animal
23 ivermectin to treat heartworms in dogs. That is also a very
24 unsafe practice.

1 [Slide.]

2 Combinations of products. They are used
3 extensively extralabely, but basically because practitioners
4 want to combine effects or they may perceive that a
5 combination will provide benefits not attained from the
6 single product. We are all familiar with that, but it is
7 seen very commonly.

8 [Slide.]

9 These are some of the questions. Most of those
10 you have seen before this morning - the need for
11 documentation, as Dr. Sundlof has said. The answer to that
12 is essentially no for this particular part of AMDUCA.

13 Need for actual personal experience versus
14 external information. How frequently does the decision need
15 to be reconsidered? What is the minimum level of evidence,
16 clinical tests versus clinical impression versus literature?
17 How does economics fit into the clinical effectiveness
18 picture, is it a legitimate basis for an extra label use
19 decision?

20 [Slide.]

21 Conclusions. From a postapproval perspective,
22 decisions by veterinarians that approved products are
23 ineffective as labeled carry a responsibility to base the
24 decisions on supportable science. This science could range

1 from simple clinical tests such as culture and sensitivity
2 or other clinical pathology results to published scientific
3 information.

4 [Slide.]

5 FDA is unlikely to become involved in these types
6 of decisions by veterinarians. We do not intend to insert
7 ourselves into decisions that are based in the practice of
8 medicine. Cases where FDA might become involved include
9 violative tissue residues, use of prohibited drugs under
10 AMDUCA -- and there is a prohibited list -- animal safety
11 issues, public health issues or possibly cases of economic
12 fraud that are sufficiently egregious.

13 That concludes my comments and I will be happy to
14 take questions.

15 DR. LEIN: Any questions for Dr. Keller?

16 Audience? Joe Gloyde.

17 DR. GLOYDE: Dr. Keller, on your cyclosporin
18 example, it is my understanding that the people that were
19 involved in the development of that product had a patent on
20 the use of the chemical and that anybody that compounds that
21 product for use in clinical practice may be subject to some
22 civil action. Is that correct?

23 DR. KELLER: I have heard that same story. The
24 product is actually an approved human product. We have got

1 a couple of pharmacists here who may know more of the story
2 than that, but I have been told that, yes, there is a patent
3 involved. The product is an approved veterinary product and
4 an approved human product, and there are some questions of
5 economics involved, et cetera, et cetera.

6 DR. LEIN: Other questions? Yes, Dr. Kemp.

7 DR. KEMP: I could probably address that since I
8 was the first person to compound it in the United States for
9 veterinary use, I believe, and worked with Dr. Casline in
10 the development of the product for a limited time.

11 There is a use patent for the use of cyclosporin
12 as a chemical entity in animals, and yes, they do pursue
13 anyone who compounds this product quite actively, as I can
14 provide evidence that is on my desk, because they actually
15 came after me, but that is a separate issue from the FDA,
16 but if you are compounding, you are at risk of having
17 lawsuits, and they are quite aggressive with it.

18 DR. KELLER: The compounded product is different
19 than the formulation and we understand that some people, in
20 some specific instances, believe it is more effective than
21 the approved product.

22 DR. KEMP: Yes, I think that is definitely true.
23 We have seen clinical failures using the optimune product in
24 our hospital. It simply doesn't work, and some of these

1 animals had been successfully treated using the compounded
2 solution, which is usually the 2 percent solution. There
3 are efficacy concerns there, too, which I think are valid,
4 but I don't think that is going to get you around the
5 patent.

6 DR. LEIN: Other questions? Yes, Sue.

7 MS. HUDSON-DURAN: Yes. Would you please
8 elaborate on what you mean by economic fraud, does that
9 address using a less expensive item?

10 DR. KELLER: When we say economic fraud, we
11 generally refer to unapproved products. That is the bulk of
12 our economic fraud cases, things that are advertised for a
13 particular indication that they have done no work to show
14 that it is effective.

15 DR. LEIN: Could I follow up on that a little bit?
16 The slide that you had on economic factors as a reason for
17 extra label use, I could see that in the non-food animal.
18 In the food animal, that is not acceptable, is that right,
19 by AMDUCA, or am I wrong in that?

20 DR. KELLER: Well, I will give you my perspective
21 on it. Referring back to a presentation that you heard from
22 Dr. Bataller yesterday, the medically necessary veterinary
23 product policy, where he stated that economics can be a
24 factor.

1 The Agency is going through an evolution. I
2 remember 10 years ago when I got here, sitting in meetings
3 having industry tell us that it was going to be a hardship
4 to do certain studies, et cetera, et cetera, and having
5 people tell industry that there is nothing in the Food,
6 Drug, and Cosmetic Act to allow us to take economics into
7 account, but there has been a significant evolution in the
8 last few years.

9 To a large extent it is due to the HMOs. It is
10 due to the human side. It is beginning to dawn on people in
11 FDA that economics is important, so we tend to start out
12 trying to discount economics and put it down towards the low
13 end of the priorities, that sometimes we do have to consider
14 economics. That is my perspective on it, maybe someone else
15 wants to comment.

16 DR. LEIN: I know there was concern early on when
17 we sat and talked about this issue, that if that is allowed,
18 it is a situation that the pharmaceutical companies, why do
19 they want to license, then, a drug that is going to be
20 competitive with a cheaper, maybe human drug or another drug
21 that may be out there. It is a difficult one to answer.

22 DR. KELLER: I didn't answer it.

23 DR. LEIN: I understand that. You left the door
24 open anyway.

1 Any other questions? Steven.

2 DR. BARKER: Will the FDA question a
3 veterinarian's determination of clinical ineffectiveness?

4 DR. KELLER: 99.9 percent of the time the answer
5 will be no, and independently, I think 100 percent of the
6 time it would be no. Why I say that is that it would always
7 be associated with some other fairly egregious type thing,
8 for instance, economic fraud or being involved in
9 distribution of bulk drugs or some other type of violative
10 activity.

11 We just got this law and this regulation, so it is
12 just kind of --

13 DR. BARKER: So if their expert like will use
14 based on their determination of clinical ineffectiveness of
15 the product that is approved for that purpose leads to some
16 clear FDA violation, then, it will be prosecuted post-
17 incident, there is no way for the FDA to really make a
18 determination of whether or not the veterinarian is correct
19 in his assessment at the time because he wants to use
20 another drug to treat a patient.

21 DR. KELLER: There is no requirement for records.

22 DR. BARKER: And no requirement for records.

23 DR. KELLER: Now, there is another issue here,
24 liability totally unassociated with FDA, but when you get

1 into use of unapproved products for unapproved uses, et
2 cetera, there is a liability issue that veterinarians
3 obviously will be considering when they choose extra label
4 use, but that is separate.

5 DR. BARKER: So, veterinarians really have a very
6 great latitude in making the determination of clinical
7 ineffectiveness in their opinion.

8 DR. KELLER: From a practical standpoint, from my
9 perspective, yes.

10 DR. BARKER: And that will include economic
11 considerations?

12 DR. KELLER: I can't answer that. From my
13 perspective it has.

14 DR. BARKER: Yes, and there is some evidence that
15 that is occurring already.

16 DR. KELLER: We certainly don't want to put that
17 up at the top of the list by any means, but there are
18 situations where it is difficult to argue against it.

19 DR. BARKER: A determination of clinical
20 ineffectiveness based on something that is available that is
21 considered to be more clinically effective?

22 DR. KELLER: As I said, it is a continuum.

23 DR. BARKER: That was the earlier question. You
24 know, it is a sliding scale, and it is a continuum. If I

1 have a product that is clinically effective, but it is just
2 not as clinically effective as another product that it is
3 not actually intended for that purpose, not labeled for that
4 purpose, can I not determine, as a veterinarian, that this
5 product is clinically ineffective and I choose to use the
6 more superior.

7 DR. KELLER: I suppose you would, but our
8 preference is that a veterinarian contact the company and
9 ask them to get that indication approved.

10 DR. BARKER: That brings up the next issue.
11 Scientific data in the literature, would it be reasonable to
12 expect that given AMDUCA and decisions about clinical
13 ineffectiveness, that industry might promote research
14 through universities or through its own laboratories to
15 demonstrate off-label use of a product for a particular
16 purpose relative to another product to show its greater
17 clinical effectiveness without ever having to go through the
18 approval process?

19 DR. KELLER: Oh, of course.

20 DR. BARKER: I have never seen it.

21 DR. KELLER: Actually, in what we would call the
22 preapproval area, it is actually a fairly wide area in
23 veterinary medicine because we have multiple species and
24 multiple indications, and so there is lot of opportunity,

1 once you get an original approval for something to add more
2 species or other indications in that species, and so, yes,
3 there is lots of work going on and a lot of it is in
4 academic institutions, so the word gets around and, yes,
5 there is what you might call a commercialization since the
6 product is already on the market.

7 DR. BARKER: That is not necessarily a bad thing.
8 I mean it is probably better that some of that work be done
9 on larger data sets, you know, to determine, yes, it really
10 is clinically effective for this purpose, but there is a
11 mechanism within this law that permits private industry to
12 get approval for use of a drug by proving it to be
13 clinically effective for other purposes, other doses or the
14 routes along with the veterinarian's independent decision, a
15 single veterinarian, that it is okay to use for that.

16 So, there is a lot of flexibility there. It
17 provides a lot more drugs and opportunities to the
18 veterinarian, but there is also, it seems to me, a little
19 area for abuse. As far as promotion, it is not an over-the-
20 counter medication, but a prescription drug, let's say,
21 companies are not --

22 DR. KELLER: AMDUCA would essentially, everything
23 would be prescription, even over-the-counter products would
24 have to be used within a veterinarian-client-patient

1 relationship.

2 DR. BARKER: It becomes a prescription drug. Of
3 course, companies aren't permitted to advertise for off-
4 label use, but of course that doesn't restrict the field,
5 salespersons from promotion, does it?

6 DR. LEIN: That could be a tender trap.

7 DR. KELLER: It does, but it doesn't prevent it.

8 DR. BARKER: There is no regulation against that?

9 DR. KELLER: Oh, absolutely. It is prohibited,
10 but it doesn't prevent it in the real world.

11 DR. BARKER: Is it enforced?

12 DR. KELLER: To the extent we can. We don't have
13 a lot of resources to do that sort of thing. Frankly, we
14 get a lot of the information on that kind of activity from
15 industry themselves in protecting their products against
16 competitors.

17 DR. BARKER: Thank you.

18 DR. LEIN: Keith, you were going to say something.

19 DR. STERNER: Just a couple of comments and try
20 and flesh out a bit the Agency's view on this as it stands
21 right now. As an individual practitioner, I certainly like
22 the ability to have that flexibility.

23 When I look at my industry as a whole, the milk
24 industry, the potential for a few individuals in a

1 consulting capacity to potentially contaminate large volumes
2 of the public food supply in the form of milk, or if we look
3 at the poultry industry or swine industry, where they are
4 high vertically integrated, and a few consultant types have
5 this flexibility now to impact the therapeutic decisions on
6 tens of thousands or hundreds of thousands of animals or
7 more, looking at a regulatory perspective to the public
8 health aspect, I am curious about clinically ineffective
9 criteria, no recordkeeping.

10 I realize as we look back at prosecutions in bulk
11 drug cases, the courts said, as I recall, that the potential
12 for an individual to do more harm than they could personally
13 compensate the damaged parties is very great, and I am
14 curious about the need, looking at an industry, for some
15 sort of a mechanism to account for clinically ineffective.

16 There is this pull on both ends, from the private
17 practice versus the industry's good.

18 DR. KELLER: Under AMDUCA, there is a very large
19 section of AMDUCA that has to do with food safety, and I
20 think that the concerns are covered under that area, and as
21 I said previously, 99.9 percent of the time we would never
22 look at a veterinarian's records or look for records that
23 indicate why a particular unapproved product was used, what
24 decision process resulted in a determination of clinically

1 ineffective.

2 On the other hand, if we do get into situations,
3 which is what you are talking about, where there is
4 contamination, then, in fact, we would possibly begin
5 looking around for those sorts of records, but that would
6 not be the primary focus.

7 Even without AMDUCA, I think that we have always
8 decided it would really be difficult to get into the
9 practice of medicine in pursuing a case.

10 Can I recognize Gloria Dunnavan? She is, as you
11 know, our Division of Compliance person.

12 DR. LEIN: Yes. I would like to make a statement
13 on this, too.

14 Go ahead.

15 DR. DUNNAVAN: I just want to comment that I know
16 in AMDUCA there are some fairly extensive recordkeeping
17 requirements for the veterinarian.

18 DR. LEIN: Right.

19 DR. DUNNAVAN: I think if we were following up,
20 for example, on an illegal tissue residue, we would be at
21 that veterinarian, looking at those records, trying to
22 determine the cause and the reason for that residue. So,
23 there are some recordkeeping requirements; how extensively
24 we might look at the documentation for a clinical

1 ineffectiveness may be an issue to talk about, but there are
2 recordkeeping requirements.

3 DR. LEIN: I think your last slide that you
4 projected, if there was an issue of residue on an extra
5 label drug, certainly would bring in the fact that you are
6 going to be back on the farm and to the veterinarian,
7 looking at how that extra label drug got into that menu of
8 treatment and what the records show there on the farm and
9 obviously would get back to the veterinarian with that.

10 DR. KELLER: I was dealing strictly with this
11 clinical ineffectiveness determination when I was talking
12 about recordkeeping.

13 DR. LEIN: But what triggers that is the residue
14 or maybe an animal safety situation, which would be not your
15 prerogative as much as coming in on an illegal aspect of it.

16 DR. STERNER: Well, there obviously are two
17 scenarios that come about here. One is the egregious case
18 where there has been fraud or other things concomitant with
19 the -- you know, somebody would use that as a cover to say,
20 well, I found it clinically ineffective and therefore we had
21 to go to this bulk product.

22 The other is the inadvertent or mistaken notion
23 that something might have been clinically effective, and in
24 that case, Gloria's department would likely be there, and

1 there is, in fact, that requirement.

2 But my concerns, as I said, revolve not only from
3 my personal freedom to practice, but also from the harm or
4 potential harm to an entire industry that a single
5 individual could inflict, as it were, based on their
6 clinical judgment.

7 DR. LEIN: Yes, Kelvin.

8 DR. KOONG: A quick question. There is a
9 recordkeeping system. Is there a reporting requirement on
10 extra label use?

11 DR. KELLER: For veterinarians, no.

12 DR. KOONG: Then, if I may follow, you give some
13 specific examples of the extra label use. How did you come
14 about using those as examples?

15 DR. KELLER: Many of those came from industry,
16 staff reports to us that an unapproved or competitor is
17 promoting their product. A lot of those are from the
18 literature, for instance, the antimicrobial, you can find
19 that in textbooks, the information on antimicrobials,
20 journals. The 4-methylpyrazol --

21 DR. KOONG: I guess, being a mathematician, I
22 don't understand all those details, but what I am worried
23 about, I think I agree with you --

24 DR. LEIN: The subjective world.

1 DR. KOONG: -- the continuum is what concerns me,
2 and in many of those examples, I am not picking on any one
3 specifically, and how do we know where those examples are on
4 a continuum, you know, in terms of effectiveness and
5 ineffectiveness, if we don't know that, how do we quantify
6 that.

7 I recall and Lord Kelvin -- actually, this is true
8 -- has said that if you can't quantify, you can't understand
9 it.

10 DR. KELLER: We are in trouble.

11 DR. LEIN: Kelvin, you will never get in practice,
12 I can see that.

13 Dr. Fletcher.

14 DR. FLETCHER: Just a comment about the records.
15 I think what has been said is important and we need to
16 emphasize that it may not be an FDA requirement, but I think
17 it is from a professional standpoint a requirement that the
18 veterinarian be able to produce that record that would
19 document why that decision was made.

20 I had a question which you may have answered, that
21 related to the scope of this question that you are asking us
22 to address this morning, and that was whether we were down
23 to the level of one veterinarian making a decision, an
24 independent decision that this is clinically ineffective,

1 and I am hearing the answer being yes by the way things are
2 written all the way to what happens -- this again is a
3 continuum -- how many veterinarians are making those
4 independent decisions that feed into something then becomes
5 an issue of now there is substantial evidence that this is,
6 in effect, ineffective, and that group might, in my case,
7 broiler veterinarians or turkey veterinarians or swine
8 practitioners or bovine practitioners group.

9 You get a big enough group that says in our
10 collective wisdom and clinical experience, this particular
11 drug is ineffective, and it would seem to me at some point
12 there, it might trigger the Agency to say, well, wait a
13 minute, it looks like there is substantial evidence from the
14 practicing veterinarians that this is ineffective, and then
15 what do we do?

16 I see that kind of continuum. I don't know how
17 many it would take to make the Agency look at now we have a
18 serious problem, because I would expect the individual
19 veterinarian to have within the medical record for that
20 flock or herd, or that case, the kind of data that would
21 support why that decision was made, whether or not it is
22 reported to FDA for the reasons we have already talked
23 about, and I just don't know how many it would take to raise
24 a flag that says yes, there is a problem with this

1 particular product even though preapproval and everything
2 else indicated that it was going to be successful.

3 DR. KELLER: I can't tell you how many. I perhaps
4 shouldn't tell you, but there are dozens and dozens of
5 examples of products and the one I showed, penicillin, is a
6 classic example. Everyone knows that it has limited
7 effectiveness at the dose on the label. Have we don't
8 anything about it?

9 DR. LEIN: One thing in at least the diagnostic
10 laboratories, we are struggling with what do you report on
11 antimicrobial sensitivities. Our committees basically now
12 are working with that and trying to come up with a decision.
13 Certainly it is quite easy where there is licensed drugs
14 that you are going to put those out. Then, you have the
15 extra label, and then you have forbidden drugs that can't be
16 used.

17 Some laboratories are putting this out in a menu
18 that would give the extra label, as well as the licensed
19 drug. Some of us are putting out only the licensed, and
20 then if there is at least resistance there, are offering the
21 extra label to come up and be put out, and some of that
22 including depending on species, but usually not even looking
23 at that, looking at the human drugs that would be available,
24 too.

1 So, there is different menus that are being
2 offered out there, and we are trying to come up with
3 something that would be standardized, but haven't I don't
4 think got to that point yet between the labs.

5 DR. KELLER: We talked about getting some sort of
6 -- and I think maybe we have worked a little bit -- getting
7 some sort of understanding with the veterinarian diagnostic
8 labs, and that would seem like a wonderful thing to do
9 except that we quite frequently see results of materials
10 sent to human diagnostic labs, and of course they don't
11 care.

12 DR. LEIN: The practitioner frequently, if he is
13 not keeping up with the literature and with AMDUCA, if you
14 gave him the full menu, may feel that is license to use
15 these. We hope that is not true.

16 So again I think what AVMA had done, and FDA and
17 FSIS now, in putting out information basically on AMDUCA has
18 been important. Your telecasting that was done, I certainly
19 would like to see that followed up again with another
20 format, saying where that is going today to the
21 practitioner.

22 Other questions? Steven.

23 DR. BARKER: Does the responsibility of the FDA
24 for the efficaciousness of a drug and allowing it to

1 continue to be marketed stop with the approval process?

2 DR. KELLER: No. That provision in the Act
3 clearly states that substantial lack of efficacy can be a
4 reason for withdrawing a product.

5 DR. BARKER: But from what I understand, you are
6 relying on just information from industry, your publications
7 to make that determination, and not records from individual
8 veterinarians who are making determinations and using other
9 drugs.

10 DR. KELLER: Well, ultimately, those would feed in
11 to the industry records and whatnot. That is where they get
12 their information.

13 DR. BARKER: The point Dr. Fletcher made about how
14 many veterinarians does it take, you know, where it turns
15 out that a determination of something being ineffective is
16 known in one region of the country, and not to the rest, it
17 is still being taught to students that this drug is
18 effective when it is really not, and taking six months to a
19 year for a publication to reach the general public, how do
20 you meet your responsibility for monitoring efficaciousness?

21 DR. KELLER: Well, as I said, we have dozens and
22 dozens of examples of products that are not effective or
23 have limited effectiveness, and it comes down to a matter of
24 resources oftentimes. If veterinarians have already moved

1 on to other products, what are we achieving by spending a
2 great deal of time, and as I showed in my presentation,
3 products have a lifecycle, and they come off the market if
4 they are not being sold.

5 The exception to that -- and it is an important
6 exception, and perhaps penicillin is another example -- when
7 people double, triple, or whatever the dose in a food-
8 producing animal, there is a substantial tendency to get
9 more residues, maybe is why we feel somewhat uncomfortable
10 about penicillin, but that would be an instance where we
11 would probably consider some sort of action, but we haven't,
12 at least I can't think of any right offhand, but food safety
13 would be a time when we may invoke the lack of efficacy
14 provision, because residues have become a problem.

15 DR. LEIN: Diane.

16 DR. GERKEN: Is there any human corollary, in
17 other words, the human side of FDA, have they tried to
18 define clinically ineffective? I can see where they don't
19 have AMDUCA specifically, most of the issues with AMDUCA to
20 deal with, but the issue of dosage they might, because a
21 dosage that is on their label may be ineffective, if you
22 will, and they may have to go to either a higher dose, and
23 so is there any precedent on their side for dealing with
24 this?

1 DR. KELLER: Well, with antimicrobials, yes, they
2 do have problems with resistance. There is something going
3 on right now -- is it Seldane -- there is an antihistamine,
4 I believe. Yes, Seldane is what I thought.

5 It is a fairly big issue because the Agency has
6 said that this product Seldane, which was established as
7 safe and effective, is not as safe as a recently approved
8 product, and it happens to be by the same company, so there
9 is some discussion in FDA about taking this product off the
10 market. That is not an efficacy issue, it is a safety
11 issue, comparative safety issue.

12 But there is considerable debate because the
13 Agency has never done that before, they have never compared
14 products and said, okay, we have one that is better, more
15 effective or safe, or whatever, so we are going to get rid
16 of this one.

17 As I said, it is typically a product lifecycle
18 thing. Product come on the market, they are good --

19 DR. GERKEN: So economics dictates.

20 DR. KELLER: Well, in that case probably the HMOs
21 just won't buy it.

22 DR. LEIN: Keith.

23 DR. STERNER: Just a comment. When you talked
24 about older drugs, penicillin certainly falls in that

1 category, and yet there are some clinical indications for
2 which there are no approved drugs currently, and as a cattle
3 dairy practitioner, metritis is certainly one that we are
4 called to deal on.

5 The organism that is most commonly isolated
6 continues to be sensitive to it, and so certainly, you know,
7 clinically, I think I can justify and rationalize its use,
8 and even though at the therapeutic dosage indicated at the
9 label, I think I have good medical rationale for its use,
10 and I am comfortable with its use in individual practice
11 because it is usually used on a case-by-case basis. We
12 aren't mass medicating thousands or tens of thousands of
13 animals at a time, but there may be a few individuals in a
14 herd where there is a particular problem with it.

15 So, you know, again if you exercise regulatory
16 discretion here and went after that because people reported
17 that it was ineffective for respiratory disease, and
18 certainly the metritis indication is not there on the label,
19 you would hamstring, in my opinion, my and my industry's
20 therapeutic regimen.

21 DR. LEIN: Sue.

22 MS. HUDSON-DURAN: We have talked about this over
23 the years. Is a deterrent that it is really expensive to
24 change a label, because just like with penicillin, it would

1 look like to me the drug companies would have an advantage
2 if they increased the dosage and the frequency like we use
3 it, they are going to sell more product maybe, and then we
4 have a legitimate labeled drug that has a withdrawal on it,
5 because if you see the drug is sold OTC, all of the farmers
6 that may choose to buy that OTC, even though the label reads
7 3,000 units per pound, are not giving 3,000 units per pound,
8 and then they may call us and say, okay, what is the
9 withdrawal date, and they haven't given the dosages or maybe
10 they gave, instead of every 12 hours, they may have given it
11 every 12 hours for two days, and then 24 hours for one day.

12 I had thought over the years we had really
13 concentrated on some of that labeling, rather than playing
14 guessing games, to really have a legitimate label with the
15 right therapeutic dosage.

16 Again, is it very expensive to change a label?

17 DR. KELLER: Well, there is a process involved,
18 and it involves a supplement, so there is time and company
19 resources that goes into that. If it is an efficacy
20 supplement, then, there would probably have to be some
21 research involved.

22 As far as just the simple label change, we usually
23 work with the sponsor and tell them something like the label
24 change should occur at the next printing or within the next

1 six months or something, and these labels, depending upon
2 the label, can run anywhere from 10, 20, maybe even 40 or
3 \$50,000 printed at a time, so there is a little bit of money
4 involved, but we usually let them use them up as much as is
5 reasonable.

6 So, I think that the main thing would be the
7 resources that go into the supplement, developing a
8 supplement, submitting it to us, getting it approved.

9 DR. LEIN: Dr. Vaughn.

10 DR. VAUGHN: I want to just add a few details onto
11 what Bill already said. If you also use that concept of the
12 continuum, the older a product is, obviously, the older the
13 data is that is in the NADA, and for very old drugs, like
14 penicillin, they are probably going to have to redo, not
15 only the efficacy section, but a lot of other sections
16 including the human food safety. It may or may not be in
17 environmental assessment that had been done. The target
18 animal safety, all of those things.

19 So, it could be literally the same as a brand-new
20 NADA, and at the same time, you have to look at the other
21 side of that, and that is will they achieve any new market
22 status by going through that process.

23 So, you know, back to Dr. Gerken's comment, I
24 think economics does play a factor in this.

1 DR. LEIN: Yes.

2 DR. LANGSTON: I just had a question. When you
3 take a product through with the clinical trial, say, you are
4 using a positive control of an older drug that is approved,
5 and presumably it comes out to be much less effective, how
6 do you view that, does it occur, or how do you view that and
7 could that be resource for ineffectiveness?

8 DR. VAUGHN: I am sorry. Could you ask the
9 question again?

10 DR. LANGSTON: In an approval process with the
11 clinical trial, where you used a positive control,
12 presumably an older drug, and that older drug turns out to
13 be much inferior to the new drug, how often does that occur
14 and could it be used as a resource to point toward
15 ineffectiveness of that older drug?

16 DR. VAUGHN: It could be. It would depend on how
17 we designed the trials. Generally speaking, there are some
18 disadvantages to using a positive control design in a study.
19 It certainly takes a lot more animals. We are actually not
20 benchmarking against disease symptoms necessarily as much as
21 we are the relative efficacy.

22 In those cases where we have used positive
23 controls and design studies in that way, it certainly would
24 have to be as good as or greater than the approved positive

1 control.

2 DR. LEIN: I think some of what you are talking
3 about there would be better designed -- not designed -- but
4 worked really from an epidemiology standpoint and in
5 clinical cases that would be presented and least put into
6 manuscript showing outbreak and where one drug was
7 ineffective in an off-label drug or extra label drug was
8 used and was effective.

9 DR. KELLER: Dr. Larkins is going to talk. The
10 companion animal area is a little bit different.

11 DR. LARKINS: We use more positive controls in the
12 non-food animal area probably than Steve does, and my
13 experience, as Steve mentioned, the new product has to be at
14 least as good or better than the positive control, and I
15 have rarely ever seen a new product, you know, so
16 dramatically superior to the old product that we questioned
17 its efficacy.

18 DR. LEIN: Any other questions? Yes.

19 DR. KEMP: Well, I hate to bring Uga back into
20 this, but I have this strong feeling we are out here chasing
21 our tail against a definition we are not going to come up
22 with. Effective and ineffective are relative terms. Every
23 practitioner is going to have some endpoint you are working
24 toward. If you reach that endpoint, you say it's effective;

1 of you don't, it's ineffective.

2 Like Dr. Barker was saying, some are more
3 effective than others, and maybe effective is that you reach
4 that endpoint that you want. Now, FDA is going to react to
5 notoriously bad outcomes as ineffective, and you may react
6 to notoriously wonderful outcomes as something you need to
7 seek having approval for said use, but in the middle of this
8 thing, you have got this big gray area that is going to be
9 based on reasonable professional judgment by the
10 veterinarian that is involved there, and a lot of times on
11 clinical impression. Kelvin is not going to have his data.

12 My wife does nurse practitioner stuff in an ER.
13 You can have a kid come in with 104 fever, you know, red
14 lights come on and everybody gets upset. If that kid grabs
15 a sucker that she hands to it, and eats it, and sitting
16 there talking and playing ball, she is not real concerned.
17 You can't put that into numbers.

18 So there is this big area there, and we are trying
19 to define something, I don't think we are going to define,
20 because it is just very moot, very difficult to hold onto.

21 DR. LEIN: Dr. Mitchell.

22 DR. MITCHELL: I would like to follow what Dr.
23 Kemp has to say. He has an impressive rationale, and he
24 always has in his analytical process.

1 DR. BAKER: Mr. Chairman and Distinguished
2 Committee, I appreciate the opportunity to have a few minor
3 words of wisdom to give you I hope. I am a swine
4 practitioner by trade from Bowling Green, Kentucky. We
5 don't have many pigs in Kentucky, so I practice in several
6 states.

7 I represent the swine practitioners on the DAC
8 Committee, which consults with COBTA of the ADMA. I
9 currently consult for around 70,000 sows. I see
10 approximately 1 1/4 percent of the pigs that are marketed in
11 the United States annually, so I do see a lot of pigs.

12 Those of you that are not too familiar with the
13 industry, I wanted to make four points. First of all, I
14 want to educate you a little bit about what is going on in
15 the swine industry in my minute role and example.

16 In my own practice, in the last 15 years, I have
17 gone from a part-time swine practitioner with over 200 swine
18 clients to a full-time swine practitioner and consultant
19 with seven clients with 70,000-plus sows.

20 The industry has changed rapidly. We have gone
21 from small, continuous flow production to all in/all out,
22 three and two-site production, and now to what we call
23 multisite production, which means each site is all in/all
24 out by age group with total depopulation between each group,

1 and this has created a rather dynamic situation, both from
2 emerging new diseases and changing diseases.

3 We have many diseases, like erysipelas, that we
4 had labeled usage of certain drugs that no longer respond to
5 those drugs in these type situations even with vaccinations.

6 We have diseases, such as Actinobacillus suis,
7 which we at one time considered a mercy disease of pigs. It
8 just killed off the 18-month-old junker that just couldn't
9 quite get to market, it finally put him out of his misery,
10 and now we see clinical outbreaks involving thousands of
11 pigs with this organism, and we don't have any drugs that
12 are really approved for use in this situation.

13 Hemophilus parasuis is another disease that we
14 rarely have approved products that work. We have no vaccine
15 that is very effective. And MICs are relatively meaningless
16 with this disease. We have Helicobacter intracellularis,
17 which is a relatively new disease that we also have no real
18 way to measure drug sensitivity. We do have a drug that has
19 a label claim.

20 So, in the field, we frequently see more pigs that
21 are ill at one time and one site than all the research that
22 was done to get a product approved, so the field
23 veterinarian may actually understand the disease and
24 clinical ineffectiveness better than anyone on earth.

1 The other point that I would like to make is the
2 special situation of MEW, medicated early weaning or
3 segregated early weaning. It is a process that has become
4 pretty essential in our industry. It can be used to salvage
5 costly genetics or valuable genetics in the case of an
6 economically important disease entry into a system.

7 It also can be used in the commercial level to
8 produce virtually disease-free pigs from a breeding herd
9 that is heavily infected with economically important
10 diseases. I keep using the word economic. To me, it is
11 very important. I know for the FDA and the CVM it is low on
12 the totem pole, but for us it's one of our more important
13 criteria for determining ineffectiveness.

14 But in the MEW situation, it creates a whole new
15 or different meaning for clinical effectiveness. In this
16 case, we have to have an antibiotic that not only treats a
17 disease, but it also has to eliminate a disease organism
18 from each individual animal.

19 It is coupled with the early weaning process we
20 don't fully understand, but we do know that weaning pigs at
21 various ages will help us remove certain disease organisms
22 from these pigs and certain drugs, and there is very little
23 published, although there is a good bit of data that
24 circulates among the veterinarians in the industry which

1 drugs are effective.

2 So, in these cases, frequently we don't have any
3 prior records to fall back on. We have to make a phone call
4 and say, hey, what did you use to get rid of APP serotype V
5 in your herds and what age did you wean the pigs.

6 So, that is a very special case. The other case
7 when we are determining clinical ineffectiveness or
8 effectiveness, we have very sophisticated record systems in
9 all these large swine enterprises, and we can evaluate drugs
10 based on how long it takes to finish a group of pigs.

11 If we have an HPS outbreak -- which we frequently
12 have in these systems -- we can evaluate penicillin versus
13 another drug just based on these record systems. It
14 certainly works well with feed additives.

15 In conclusion, I think it is extremely important
16 for us in our industry for the CVM to exercise a good deal
17 of flexibility when they look at the veterinarian and how he
18 determines clinical ineffectiveness.

19 I think the critical part is a valid client-
20 patient relationship, but frequently, those of us in the
21 field are the experts in clinical ineffectiveness. It is
22 not the university. The industry has changed so fast that
23 we have very little published data to rely upon.

24 Thank you.

1 DR. LEIN: Thank you, Dr. Baker.

2 Questions for Dr. Baker? Sue.

3 MS. HUDSON-DURAN: I guess what I am hearing you
4 say is what we really have done for years in human medicine,
5 we look at a small population, we get the drug approved, and
6 then we look at a large population, and we get a report
7 back.

8 What I see over and over we are missing here is
9 that you should be sending that information in to someone,
10 whether it be the USP or the FDA adverse interaction, but
11 somehow we are missing the boat by not getting that
12 information.

13 DR. BAKER: That information and I think
14 gradually, it will fall back into the university and the
15 industry's hands, and it will be looked at, but, you know, I
16 was involved in the first medicated early weaning trial that
17 was done in this country, and it was to get rid of
18 Actinobacillus pleuropneumonia, and we weaned pigs at five
19 days of age, because we didn't know any better, we didn't
20 what would work, and we eliminated Mycoplasma pneumonia, we
21 eliminated APP and HPS from these pigs, and it was a large
22 population of pigs. We created about 1,500 of these pigs.

23 Then, of course, gradually, that particular herd
24 deteriorated as these diseases reentered, but it was

1 interesting to see a group of pigs that were virtually
2 disease-free, and the outbreaks that we had, especially HPS,
3 were pretty dramatic. The drug that we found that was
4 clinically effective for this disease at that time was
5 combiotic, it was Pen-Strep, and still today I wish I had
6 that product because it was the only product that you could
7 give a daily injection three days in a row and treat these
8 pigs, and we don't have product today that works as well.

9 DR. LEIN: Butch, do you have the feeling that at
10 least in successful trials, where this becomes a method,
11 that through the swine practitioners, this would eventually
12 surface as the method to be used, would that be true? Would
13 be the best place for it to show up?

14 DR. BAKER: A lot of that stuff has been -- I mean
15 speakers have gotten up and talked about their trials and
16 what they did, and a lot of that was published in
17 proceedings, but very little of it can be found in refereed
18 trials.

19 DR. LEIN: Exactly. I think in a lot of the
20 specialty groups, at least in their meetings and
21 proceedings, is where a lot of this material would exist.

22 DR. BAKER: Our specialty group is a very small
23 group. The board certification process just in swine
24 production medicine just began a few years ago, and there is

1 only about 15 in that group at this point, but there will be
2 more as it develops.

3 DR. LEIN: Any other questions?

4 DR. FLETCHER: Just a comment. Much of what Dr.
5 Baker said about swine would apply with some variations in
6 terms of disease and certain practices to chickens and
7 turkeys, and the same would apply to the development of a
8 base of information shared by those practitioners within
9 that specialty, whether it is at a national meeting or in a
10 more or less closed session for just those people.

11 DR. LEIN: Exactly.

12 DR. BAKER: Well, I would like to hope that the
13 swine practitioner doesn't become like the poultry
14 veterinarians, you know, which is a very small in-house
15 group of veterinarians, and that information is probably
16 mostly owned by the different poultry companies, so
17 hopefully, our information becomes general, continues to be
18 general knowledge.

19 DR. LEIN: Dr. Koritz.

20 DR. KORITZ: The example with the weaning pigs
21 clearly doesn't have a drug residue implication, but if you
22 had a situation where you wanted to use what you thought was
23 a clinically more effective antibiotic in finishing pigs,
24 where there was a potential of a drug residue situation,

1 would you consider that or would you simply feel too
2 vulnerable to do that sort of thing?

3 DR. BAKER: Many times we might have a respiratory
4 outbreak in a site that may involve 10,000 pigs or more all
5 the same age on one site, so there is more than one and a
6 half million dollars at stake there at a given moment in
7 time, so in that situation I would rely on my clinical
8 experience or if it was a Friday afternoon or a Thursday
9 afternoon, you certainly don't have time to do postmortems,
10 send that stuff to the lab, get MICs back, and wait until
11 the next Thursday to respond with treatment.

12 You have to respond that day and at that minute,
13 and you may treat with a drug that you have available in
14 that quantity. That may determine what you start with. You
15 may just use your clinical judgment on what is best, and you
16 may call a veterinarian that you respect, that you know has
17 gone through this particular outbreak before and has some
18 clinical experience, but that is going to be the sources of
19 information that determine how you react. It certainly
20 won't be in the literature.

21 DR. KORITZ: How would you estimate a withdrawal
22 time in that situation, when it is a drug without a label?

23 DR. BAKER: Generally, we use approved drugs or
24 almost always we would use an approved drug. We would use

1 it in an extra label fashion, maybe dosage or the way we
2 administered it. For example, HPS, really the only
3 treatment we have available to us, that is economically
4 feasible, is to inject every pig in the barn daily for three
5 to five days.

6 With combiotic, we could knock it out with a
7 three-day treatment with penicillin. Sometimes you have to
8 go seven consecutive days. When you start treating 10,000
9 pigs a day with an injectable antibiotic, it is a huge
10 effort. It takes quite a bit of organization and commitment
11 to go after it, but if you don't, you may lose 20 percent of
12 those pigs plus have another 50 percent that are stunted,
13 that don't finish well. So the economic outcome on that
14 disease is critical in how you react.

15 We seldom use unapproved drugs. In the MEW
16 situation, we may see unapproved drugs. In the past we have
17 seen unapproved drugs used, and so there is some data on
18 those drugs available to us.

19 DR. LEIN: Dr. Fletcher.

20 DR. FLETCHER: To expand that just a little bit,
21 the Food Animal Residue Avoidance Databank, FARAD, provides
22 a source of information to practitioners about withdrawal
23 times and residues in a number of different situations, so
24 that is a resource that is available to veterinarians across

1 the country, and is getting I think a lot of hits in the
2 sense of inquiry, so there is a bank of information that
3 could be drawn on for that kind of data.

4 DR. BAKER: USP also has data and we might could
5 get some information, but yes, we use FARAD a lot, and they
6 have a diskette and I have that, that you can put on your
7 computer or your laptop, so you can pull some of that data
8 up pretty fast and look at it without even making a phone
9 call now.

10 We print that. In fact, most of the herds I have
11 got the extra label drugs that we use, I have printed the
12 FARAD withdrawal times for my producers, because when you
13 are dealing with farms this size, you have got a multitude
14 of people that have their hands on drugs, and so you want
15 that information to be generally available to them, so they
16 know where to go if they can't reach me by phone and they
17 want to give a sow a shot of ace promazine because she is
18 eating her pigs, for example, they know what the withdrawal
19 is on that sow based on the FARAD data.

20 DR. LEIN: Sue.

21 MS. HUDSON-DURAN: A point of clarification. We
22 cannot get streptomycin, not because of anything in
23 marketing, it was a public health issue because we have 2.5
24 million active cases of TB in the U.S. and CDC says a good

1 percentage of those are only sensitive to streptomycetes, so
2 they not only pulled it from the vet market, hospitals don't
3 have that. You have to go through CDC.

4 DR. BAKER: You can still get that through the
5 hospital in very small quantities and it is used somewhat --
6 I think it is still used in embryo transfer business
7 although I am not close to that industry right now, but I
8 wasn't complaining that that product had been removed. I
9 can make some big complaints about the iron dextran
10 situation, and that was yesterday, and no one asked.

11 That is an example of a situation where it is
12 difficult for us to take the label approval and make those
13 things fit for us in this new swine industry that we are
14 working in, because all the rules have changed for us, the
15 diseases have all changed.

16 The old diseases are emerging as completely new
17 diseases, and then we have got this purge virus that has
18 completely changed the outcome of diseases that once weren't
19 an economic problem, like strep suis is a huge economic
20 problem for us and we really don't have any drugs that --
21 when you have a 10,000-head nursery, how do you go through
22 and inject every pig strategically every day for five days
23 with Naxcel and make it work. It is an impossible thing and
24 they have to feed, water, and care, and do all the regular

1 things with those pigs.

2 I mean you have to throw an army in there, and
3 then in a company situation, where you have an isolated
4 nursery, and you have security rules trying to protect the
5 health status of those pigs, where do you find the extra
6 people from your system. You know, you can't get them from
7 the sow farms, and you can't get them from the finishing and
8 get them in there. You know, you have to bring in the
9 office staff, the secretaries and the bookkeepers.
10 Literally, that is what happens.

11 DR. LEIN: Any other questions for Dr. Baker?

12 Thank you very much.

13 Dr. Gatz Riddell.

14 DR. RIDDELL: Thank you, Dr. Lein. Maybe I might
15 add a little bit of something to one of the questions that
16 Ms. Duran asked about getting this information in.

17 The swine practitioners do have a pretty good
18 network of information. Some of the information could be
19 put together into statistically evaluable packages. If you
20 look at drug availability, I know we are covering AMDUCA
21 today, but you have to look at drug availability as being
22 attacked by a three-pronged spear, that being AMDUCA, ADAA,
23 and professional flexible labeling.

24 Possibly under ADAA, there could be some

1 innovative evaluation of scientific data sets like that to
2 be utilized in the drug approval process.

3 Like Dr. Baker, I am representing the Drug
4 Advisory Committee here today. I am the representative from
5 the American Association of Bovine Practitioners, and we act
6 in an advisory capacity to the Council on Biologic and
7 Therapeutic Agents.

8 Like Ms. Duran, I work at the large animal clinic
9 at Auburn University, and probably like Ms. Duran and Dr.
10 Ravis -- no offense, Dr. Kemp -- we weren't totally insulted
11 by the reference to Uga yesterday in the presentation, and
12 to be truly politically incorrect, I probably wouldn't have
13 been offended if they had used the Florida gator as the
14 mascot.

15 [Laughter.]

16 I really do appreciate the opportunity to provide
17 input here today. AMDUCA has been hailed in the profession
18 as decriminalization of the extra label use of drugs in
19 veterinary practice, and Dr. Sundlof very eloquently
20 described the progression from the Compliance Policy Guide
21 through AMDUCA, through the proposed rule, through the
22 invitation for comments particularly on this area of
23 clinical ineffectiveness, to the publication of the final
24 rule, and now to what we have to consider, what really is

1 clinically ineffective.

2 I would also like to say that very many segments
3 of veterinary medicine were very gratified that that type of
4 invited response was utilized to fulfill all the tenets of
5 AMDUCA and to allow inclusion of that phraseology in the
6 important sections in the final rule.

7 I would like provide a little bit of input to the
8 committee as far as the application of the term clinically
9 ineffective. I know you are faced with two questions: how
10 should clinical ineffectiveness be defined? You could maybe
11 addend that with really should it be defined.

12 Dr. Sundlof said we would like to have some solid
13 guidelines, and I guess I would probably like to present to
14 you some information this morning that would say solid
15 guidelines are really going to be a moving target.

16 They are going to be something we are really going
17 to have to sit back and use some judgment on, and it is
18 going to be really difficult to confine a definition of this
19 term into a limited box, so we are going to have to look at
20 that.

21 We do very much agree that we want the profession
22 and professionals involved to be able to make the decisions,
23 and we want our practitioners to be able to utilize their
24 training, their schooling, and most importantly, their

1 experience and maybe some laboratory work that they have
2 available to be able to impact their decision.

3 As Dr. Barker said, the observations and
4 intuitions of the practicing veterinarians are going to be
5 very important in this process.

6 And then the other question: how should a
7 veterinarian make this determination? That is a very, very
8 valid question and I don't think we can be flip about it. I
9 think we have to really discern is it on a case-by-case
10 judgment, is it totally your opinion, is it intuition, is it
11 your past experiences.

12 Maybe is it something you heard at a meeting,
13 maybe is it something in the published literature that has
14 not been included into a package insert, possibly in
15 proceedings somewhere, maybe from talking to a highly
16 respected colleague, maybe it is retrieved from a scientist-
17 to-scientist transfer like he might get from a technical
18 consulting veterinarian from a pharmaceutical firm.

19 There are a lot of means whereby you can obtain
20 this information, but I think the bottom line is that the
21 word flexibility has to be the byword. We really have to
22 build flexibility in to any determination or consideration
23 of what clinical ineffective is.

24 So, let's consider a couple things today. One,

1 the situations that veterinarians are going to address and
2 be exposed to in practice are very varied, of course; and
3 two, there are already specific examples where we can talk
4 about the use of an approved product being clinically
5 ineffective, maybe scientifically illogical, whereas the
6 extra label use of another approved product would be the
7 appropriate or logical therapy.

8 Let's approach the situations that we may
9 encounter in practice, and let's utilize two illustrations
10 to make this point. Let's look at the veterinarian who is a
11 feed lot consultant. He works in a practice in either the
12 States of Colorado or Texas, and his typical client may be a
13 feed yard that has a one-time capacity of 20,000 head or
14 more, several which may approach the six figure -- and that
15 doesn't count the comma -- so we are looking at 100,000 head
16 of animals on hand.

17 In that particular situation, treatment decisions
18 may be made. When treatment failures do occur, in all
19 likelihood, those animals will be submitted for complete
20 necropsy and laboratory analysis. That veterinarian or the
21 practice group that he works with that consult with the feed
22 lot will have information on hand to deal with the microbes
23 that were cultured from those particular necropsies,
24 sensitivity patterns and MICs, and in future years they may

1 be able to look at drug levels in the animals themselves, so
2 that type of person may have -- and that type of
3 practitioner -- may have some really valid data from which
4 to draw conclusions that this approved product was
5 ineffective this time and will try an approved product that
6 is not approved for this use that is going to be used in
7 extra label fashion.

8 So, we have some really valid data to utilize
9 there. For a moment let me sidetrack and really agree with
10 Dr. Tollefson. She made a point that clinical
11 ineffectiveness maybe should be reconsidered, and it may not
12 take an entire cycle of a bacteria changing its resistance
13 pattern, that drug no longer being used, and it changed
14 back.

15 I am from Auburn and I hate the connotation that
16 comes from the phrase cattle from the Southeast, never West,
17 cattle from the Southeast that go into the feed yards in the
18 high plains states are not treasured entities from time to
19 time. We haven't maybe put them together like we ought to.

20 So, those animals might need to be dealt with
21 differently than cattle that come in, en masse from Nebraska
22 or Kansas of the States of Colorado or Texas themselves.
23 So, it may not only be the animal, it may be the history or
24 the background that will influence treatment decisions, and

1 there is a possibility that over a matter of months, or
2 maybe getting inclement weather, the reconsideration of
3 clinical ineffectiveness may have to be looked at.

4 So, there is a possibility that here, as with
5 everything else, we are aiming at a moving target, but this
6 veterinarian has some good information, some good background
7 work. Historical records over time is what happens when it
8 is really cold and snowing in February and March, and really
9 wet and rainy in October and November in that particular
10 feed lot.

11 So, there is a lot of information that can be had
12 but not every practitioner is in that type of situation or
13 the situation that Dr. Baker is, where you are looking at a
14 lot of numbers and have a lot of data retrieval. The
15 typical practitioner in the Southeast, who might deal with
16 bovine respiratory disease complex, much like the feed lot
17 practitioner, might look at 10 cases in a month that are on
18 five different farms. A cow herd of 20 can't really be
19 considered an operation, that's a farm. And they treat and
20 leave, they are not a consultant.

21 They probably only hear about the bad news, they
22 don't hear about the good news, but if the word comes back
23 to them that four out of those 10 animals that month died,
24 that is a 40 percent death rate. That would be unacceptable

1 in the feed yard.

2 But yet they hear about them, animals dead and
3 bloated, you can't get that animal to a diagnostic lab and
4 get any retrieval information, so where are you? You have
5 good information. Four out of 10 animals died, maybe some
6 more didn't respond, maybe two or more on one farm, so that
7 owner is looking at a 100 percent death rate.

8 You go back to that farm and say, well, let's just
9 use the same thing, and if this one dies, we will post it.
10 That is never good news that an owner is going to want to
11 hear. So, there is some indication without quite the
12 science behind it that there is some challenge to
13 effectiveness with that particular treatment in those
14 particular situations.

15 So, all you can do is say, well, maybe we will
16 change directions, use something else, but for heaven's
17 sakes, we need some more diagnostic backup. If this one
18 dies, we have got to see it. But again you are in the past
19 tense, you are dealing with somebody who has to answer the
20 same question that the feed lot consultant did, but yet they
21 don't have quite the information, and those are part of the
22 vagaries of practice that we are not going to be able to
23 change. We are going to have to deal with them, and I think
24 intelligently, with flexibility, we can deal with them.

1 Well, let's shift gears and look at a few examples
2 -- and I won't go through them, I think everybody should
3 have my document in front of them -- let's just look at a
4 few examples where even though a drug is approved, there may
5 be science, previous cases where there is a good indication
6 that that specific condition or that specific disease will
7 be ineffectively treated by the use of a product labeled for
8 that condition or that disease.

9 There is a variety of examples we can use. To
10 start off with, let's look at clinical mastitis. Now, I
11 deal with mastitis quite a bit, maybe not as much as Dr.
12 Sterner, but clinical mastitis is an enigma and we forever
13 are presented with the logic that here is a bacteria, here
14 is a compound for which sensitivity patterns suggest
15 effectiveness, but we know it is not going to work in the
16 udder of a cow, something about the bacteria, something
17 about the cow, something about defense mechanisms, but it is
18 not going to work, and probably a tremendous example would
19 be some of the gram-negative causes of mastitis, the
20 coliforms.

21 There is at least one approved intramammary
22 infusion product that says this will Strep ag, Staph aureus,
23 and other susceptible organisms for clinical mastitis. We
24 do know that coliforms will show good sensitivity to the

1 cephalosporins when you look at it in a microbiological lab,
2 but all science today tells us that the gram-negative
3 organisms, particularly E. coli, by the time we see clinical
4 signs, the numbers of bacteria are rapidly declining, in
5 fact, research shows that certain antibiotics, when put into
6 the mammary gland, can hamstring the immune system and
7 actually reduce the clearance rate of bacteria, so bacteria
8 are on the way out, so it would be illogical to rely upon
9 antibiotics to control the disease, and science shows that
10 that very ill animal may much better respond and her
11 survivability may be much better enhanced by the use of a
12 nonsteroidal antiinflammatory because she is endotoxic.

13 There are none approved for lactating dairy cattle
14 right now, and none that we may logically in this very ill
15 animal. So, that is a situation where what is approved
16 doesn't really address the problem that we are now dealing
17 with in this animal.

18 Dr. Sterner utilized the example of the metritis,
19 and I totally concur with his read on the use on penicillin
20 in this case. There are products that are approved for
21 intrauterine use in terms of antibiotics.

22 Science tells us, as we look at the reproductive
23 history of these animals and their future fertility and
24 their survivability when they are very ill, that

1 intrauterine antibiotics are probably not beneficial, and in
2 fact, in certain cases may be detrimental.

3 Maybe it is not the antibiotic, maybe it is the
4 delivery system. You may be causing more harm than good and
5 we, of course, don't want to do that, but we do know that if
6 we utilize an ecbolic agent to help contract the uterus, and
7 dump that septic material out on the ground where it won't
8 do any harm to the cow, that that would be good.

9 Oxytocin many times which could be used is not
10 effective because these animals no longer have high levels
11 of estrogen that they will have immediately postpartum
12 because they are five to 10 days following calving and now
13 they are gravely ill, but the prostaglandins have an ecbolic
14 effect, and prostaglandins are labeled for use in lactating
15 dairy cattle, but not for this use, they are for other uses.

16 So, again, this would be an extra label use when
17 there might be an improved drug available for this condition
18 that is just not going to work the way we want it to.

19 Again, there is other examples. Prepartum dairy
20 heifers commonly face a condition known as physiologic udder
21 edema. The udder, because of the rapidly changing events
22 going on immediately prior to the onset of lactation,
23 develops very severe swelling, some because of venous
24 stasis, some because of the final changes in the development

1 of the blood supply, some of it we don't know why, they just
2 get it.

3 It is called physiologic, but it is not normal.
4 That is just a moniker that has been put on it, and what it
5 can do with its weight, it can cause premature breakdown of
6 the support ligaments of her udder, and you may have an
7 animal that may be lost from the herd very early in her
8 first lactation. It is quite a waste and it is quite a
9 shame.

10 There are several products we can use, one of
11 which is a combination product that has a corticosteroid in
12 it, which in a good number of cases will induce premature
13 parturition, and it may not be good for the calf, and it is
14 usually not good for the cow because they commonly will
15 retain their placenta, and you have another condition you
16 have to deal with.

17 An approved diuretic in the thiazide derivatives,
18 in my experience and many people's experience, is not quite
19 effective at various severe cases to reduce the swelling to
20 again salvage the animal, but yet there are diuretics which
21 are approved, but not for use in dairy cattle, that can be
22 used very effectively, and so we may get in the question of
23 more or less clinical effectiveness, but yet in this animal
24 it may make the difference to whether she stays or she has

1 to meet a premature demise and has to leave the herd.

2 Dr. Sterner also mentioned the use -- I think he
3 mentioned the use of procaine penicillin G at higher doses
4 in some of our respiratory disease. Again, they are
5 approved products, but penicillin can be a very effective
6 drug, but again, science tells us at its labeled dose it is
7 just not very effective.

8 And with neonatal diarrhea it is very, very
9 nebulous area, because a lot of the concoctions in the past
10 that have worked, have worked for no scientifically valid
11 reason, but sometimes they have worked.

12 There are some products on the market for this
13 young calf, five to 10 days or less of age, that have a
14 combination of a very effective, probably too effective
15 antibiotic, and a paralytic agent, as far as the motility in
16 the bowel, the anticholinergics, and science would suggest
17 that utilizing a gut sterilizing antibiotic in this calf
18 with diarrhea may not be the best thing we can do for it,
19 because there is a normal flora that needs to be there, and
20 the internal medicine people in the small animal clinic at
21 Auburn, who think we practice voodoo on large animals, they
22 are very adamant in their thoughts that anticholinergics for
23 diarrhea don't treat the problem because the problem is not
24 hypermotility, it is actually hypomotility, and we need to

1 use drugs like paregoric or imodium that may enhance
2 segmentation type of motility.

3 So, again, there are approved products, but they
4 no longer address what we are trying to treat. Again, all
5 of these examples, and examples of the variability and
6 practice situation, really point strongly towards the
7 enhancement of flexibility in any type of system that you
8 would devise to recommend to CVM as far as judging clinical
9 ineffectiveness.

10 We would like to point out that the input of a
11 veterinarian familiar with environmental stresses,
12 background of the animals, disease processes, pharmacology,
13 microbiology, and all the animal variables you deal with are
14 going to be very important in treatment decisions.

15 There is a possibility that for the veterinarian
16 in the Southeast, treating small numbers of animals, the
17 utilization of data from regional diagnostic labs may be of
18 immense value as they look at clinical ineffectiveness,
19 where you can generate more data than that particular
20 practitioner can from his type of data.

21 The Center for Veterinary Medicine stated in the
22 preamble to the final rule that "not allowing extra label
23 drug use in situations in which the approved new animal drug
24 is clinically ineffective would produce an absurd result."

1 Likewise, it would be inappropriate and illogical
2 to construct a rigid set of criteria for establishing
3 clinical ineffectiveness in a practice setting.

4 In summary, much evidence supports a very flexible
5 approach to a definition of clinical ineffectiveness for
6 practitioners working under the varied conditions found in
7 the field. I would certainly like to thank everybody here
8 for the opportunity to provide input into one of the final
9 steps in the enactment of the regulations for AMDUCA.

10 Thank you. Any questions?

11 DR. LEIN: Thank you. Any questions for Gatz?

12 As we look at the small producer -- and I know
13 that really is a problem -- one thing that we have been
14 trying to push is more antemortem diagnostic work, and that
15 is not always easy depending where you are and what you have
16 got to work with, but certainly that has been helpful in
17 some of the respiratory situations, gastrointestinal
18 disease, and those parts of it.

19 I like your idea of at least labs trying to
20 accumulate data that would say it sure looks like this drug
21 is not working, and then if you could tie the clinical
22 success or lack of lack of success, too, that would be very
23 nice to put that together.

24 DR. RIDDELL: That is true, and don't get me

1 wrong. I don't think that veterinarians should be allowed
2 to do either free wheel and do what they want, but I think
3 they have the training and the judgment to be able to
4 utilize in a flexible circumstance their opinion and past
5 experience.

6 DR. LEIN: I agree with you 100 percent. The
7 other thing that we see so frequently in at least the
8 respiratory disease problems are, of course, a group of
9 agents and maybe the predisposing situation, a viral
10 situation or a bacterial situation, you have taken care of
11 at this point, and then you have resistant organisms coming
12 in, especially the mycoplasmas today have become a real
13 problem for us, and of course, once you are into that and
14 diagnose that situation, then, you are into an off-label
15 situation, you are into tetracyclines or other things that
16 you have to be using.

17 So again even post-treatment, coming back in and
18 re-diagnosing the case again becomes very important to move
19 you on possibly to a extra label use of drugs and trying to
20 manage that outbreak.

21 No questions? Thank you very much for your
22 presentations.

23 The next presenter will be Dr. Mel Pence with the
24 American Association of Bovine Practitioners.

1 DR. PENCE: Mr. Chairman, ladies and gentlemen of
2 the committee, thank you for your time today. My name is
3 Mel Pence. I am a full-time practicing veterinarian from a
4 rural area in Southwest Iowa. I have practiced in the same
5 area for 21 years. My practice is a mixed species practice
6 with my primary emphasis on bovine, and it is primarily cow-
7 calf, almost exclusively cow-calf.

8 I have two partners with offices in Clearfield and
9 Lennox, Iowa. I am here today to represent the membership
10 of the American Association of Bovine Practitioners.

11 My cattlemen clients tend to have relatively small
12 cow-calf herds of about 60 mother cows or so, and that
13 varies quite a bit, but I am in that area, as an industry,
14 about 50 percent of the cow-calf producers are 50 cows or
15 less. So when we think of cow-calf herds, sometimes we tend
16 to think of big western herds that have hundreds and
17 thousands of cattle, still, the majority of cattle are
18 raised by very small producers.

19 Most of our clients earn their income by selling
20 their calves at seven to 12 months of age. Food animal
21 practitioners tend to develop a very close personal
22 relationship with their clients over a period of time and
23 end up having a good working knowledge of each client's
24 abilities.

1 There is considerable variation between the
2 abilities of individual clients when we are talking about
3 what is clinically effective and what is not clinically
4 effective depending on the management abilities of the
5 client, depending upon the situation, that may change with a
6 given drug, that may change with the same disease entity,
7 the same drug regimen, the same therapeutic regimen may not
8 work on one farm as it would on another.

9 There are clients who I would be very reluctant to
10 dispense an unapproved drug for, and there are clients --
11 because I feel that their management procedures wouldn't be
12 able to handle that -- there are clients that I would feel
13 comfortable dispensing an unapproved drug.

14 This relationship enables us to work as a
15 production team member with these clients for the betterment
16 of the animals and for each member of the production team.
17 My primary responsibility in serving my clients is to assist
18 them in the production of cattle.

19 The reduction or elimination of disease through
20 preventive and proactive programs are measures that reduce
21 or eliminate the need for antibiotics. When the use of
22 antibiotics are needed, proactive measures have failed and a
23 disease process that is causing suffering and loss of the
24 client's cattle.

1 At this point, we need to evaluate our procedures
2 and take corrective measures. At times, events out of our
3 control dictate that a disease outbreak may occur. A prime
4 example of this would be our last April's snowstorm right at
5 the peak of calving season. We had about a 16-inch snow and
6 it was really cold and miserable, and the calves were just
7 soaked to the skin with this cold snow. There was mud
8 everywhere they were. It caused hypothermia in the calves
9 and this caused the death of some calves and stress-related
10 diseases in others.

11 This situation required that antibiotic therapy
12 and supportive care be given to these calves to reduce
13 animal suffering and further losses.

14 As field veterinarians, I feel that we are in a
15 unique position to evaluate and recommend management
16 procedures and treatments for our clients as members of an
17 integrated production team. Our education, background in
18 animal husbandry and a relationship with our clients enables
19 us to be in a position to recommend and implement the use of
20 specific treatment regimens for each individual case, for
21 each individual client, that will reduce animal suffering
22 and death loss.

23 When evaluating a treatment, a thorough history of
24 the problem including the effectiveness of past treatments,

1 knowledge of the client and his management skills are taken
2 into account. When the treatment for a disease process has
3 the history of poor results, resulting in the death or loss
4 of function of an animal, alternative treatments are
5 explored.

6 The first options are approved treatments, but if
7 none of these are available or have clinical experience
8 indicates the poor results using this treatment for this
9 disease process, then, other therapeutic regimens are
10 sought. Antibiotics currently approved and available for
11 the use in calves with diarrhea in the United States are
12 ampicillin, amoxicillin, chlortetracycline, oxytetracycline,
13 neomycin, chlorpromazine, sulfachlorpromazine, and
14 sulfadimethoxine.

15 Neomycin, ampicillin, and tetracycline cause
16 enough alteration of the intestinal mucosa that they result
17 in malabsorption and diarrhea even in a healthy calf when
18 given orally. The spectrum of antibiotic activity of these
19 approved drugs on E. coli is limited.

20 In our in-house results, the effective use of
21 these antibiotics is below 35 percent on isolates from our
22 own herds. These results are similar to surveys published
23 in veterinarian clinics in North America.

24 The results of 260 Iowa bovine isolates from Iowa

1 State University diagnostic lab during 1980 showed that the
2 range of sensitivities for these approved drugs are
3 amoxicillin 47 percent, ampicillin 66, sulfa chlorpromazine
4 22, sulfadimethoxine 4, neomycin 41, tetracycline 16.

5 I think that we need to understand -- and I am
6 sure you do -- that this is a regional thing, these
7 sensitivity patterns aren't going to be true for every
8 region, they are not going to be true -- my practice may be
9 different than my neighbor's practice, so that it requires
10 some clinical knowledge of what is going on within the
11 practice and what is going on in that particular farm.

12 I think that if we look at biological entities in
13 a nonmathematical way, they don't respond like when you take
14 an engine and do a certain thing to it, it always responds
15 the same. When you take a biological entity and do
16 something to it, it doesn't always respond the same.

17 To get back to our April snowstorm, calves
18 developed an enteric E. coli infection as a result of cold,
19 wet hair coats causing reduction in body temperature. This
20 stress caused a reduction of the animal's ability to produce
21 an immune response.

22 The cows, as they lay in the muddy conditions,
23 would get mud, manure on their teats, and then the calves
24 would consume this mud and manure as they nursed, and they

1 would get an overwhelming population of E. coli and other
2 pathogens.

3 These bacteria colonized in the intestine and
4 caused disease in these immunologically stressed calves.
5 This was a common problem in our practice this year, as it
6 has been in other years when unexpected weather hits. The
7 problem is not a result necessarily of poor management of
8 lack of proactive measures. The cattle are often at the
9 mercy of the weather.

10 The cattlemen's problem, in addition to supportive
11 care, was to find an antibiotic that would rid the calves of
12 the E. coli infection. The actions required in this
13 situation called for fast and decisive intervention, the
14 control of calf diarrhea. There is no time to experiment
15 with approved drugs that may be effective only 30 percent of
16 the time.

17 Another example of a common disease that is often
18 not addressed well by approved drugs is pink eye. Pink eye
19 is bacteriological infection of the cornea of the eye caused
20 by Moraxella bovis. The resulting infection is an intensely
21 painful watery eye. These calves squint and try to avoid
22 the sunlight. If you just observe them for a while, you can
23 really see the intense pain that they are under.

24 They are often blind at least temporarily.

1 Unchecked, the cornea will ulcerate and expel the contents
2 of the anterior chamber, and the pain involved would be
3 similar to being poked in the eye with a ballpoint pen or
4 something.

5 Drugs approved for the treatment of this condition
6 are tetracyclines. Clinical recovery appears to be much
7 more rapid if subconjunctival injections are given, and
8 tetracyclines are very irritating when injected in this
9 manner. Penicillins work very effectively when injected
10 subconjunctively.

11 A third example of extra label drug use would be
12 the increased dosage of penicillin used in foot rot, and
13 this problem has been addressed. Penicillin -- I won't
14 bother to read this part -- but penicillin certainly is much
15 more effective at higher dosages than prescribed by the
16 label.

17 The elimination of all drug residues is in the
18 interest of the beef-consuming public, the cattle industry,
19 and the veterinary profession. Each time the media exposes
20 a problem on our industry, we suffer the consequences.

21 The consumer is the ultimate judge of our product
22 and we need to ensure that we present them with a wholesome
23 product every time they purchase beef. That is why the
24 cattle industry, led by practicing veterinarians, are

1 actively involved in beef quality assurance programs on a
2 national level.

3 The advent of FARAD has helped the beef industry
4 to prevent residue problems with our product by educating
5 veterinarians and producers on what is science-based
6 reasonable withdrawal dates for extra label drug use.

7 The veterinarians oath that we are required to
8 take upon entering the profession of veterinary medicine
9 requires us to do all that we can to relieve animal
10 suffering. Field veterinarians need the latitude to
11 prescribe and use effective treatments to reduce animal
12 suffering and loss of lives at a time when current therapies
13 are ineffective.

14 Veterinarians in practice have the education, the
15 knowledge of the client's management skills and the
16 experience and art of practice to make these decisions. We
17 are ready and able to take the responsibility for these
18 actions and we respectfully request that this committee
19 recommend a great deal of latitude for the practicing
20 veterinarian for the use of extra label drugs.

21 Thank you for your time.

22 DR. LEIN: Thank you, Dr. Pence.

23 Any questions for Dr. Pence? Thank you.

24 The next presenter will be Dr. Tom Burkgren, who

1 will represent the American Association of Swine
2 Practitioners.

3 DR. BURKGREN: I have to thank Dick Geyer for
4 putting me on after these three distinguished practitioners
5 because even though I have some very good comments -- so, I
6 have condensed them down.

7 MR. GEYER: My assistant did the schedule.

8 DR. BURKGREN: I do have just some comments
9 outside of what I had written, and they are in reference to
10 a number of things.

11 First of all, I have been on the job with AASP now
12 for three years, and in my position as liaison between our
13 industry and CVM, it has been a refreshing experience in
14 dealing with Dr. Sundlof, Dr. Mitchell, Dr. Blackwell in
15 seeing that the trust that they are placing that the
16 veterinarians, the practitioners of the field. It is
17 evidenced in a number of the approved labels that we are
18 seeing now, with micotil, with the new term now metaphylaxis
19 in preventive therapy.

20 We see it in Palmital label 10 days before an
21 unexpected outbreak and involvement of veterinarians is
22 vital in that situation. We see it in the progress that we
23 have seen in professional flux labeling. We have seen it
24 with the passage of AMDUCA, and now within this definition

1 of clinical ineffectiveness, I think that the committee will
2 hopefully follow the direction and recognize the experience
3 of the veterinarians and the need for professional
4 discretion in determining this.

5 As you have noticed from our practitioners here,
6 the situations we deal with in the field are complex. There
7 are a number of factors that enter into it. It is not
8 always simple. The label directions are very direct, they
9 are black and white. Unfortunately, what we deal with on
10 our farms and our production systems are not. We cannot
11 quantify it. So, we need that professional discretion to go
12 out on the farm and determine what is clinically
13 ineffective.

14 As far as the information transfer that was
15 brought up, within AASP a vital function of our association
16 is information transfer. We have a peer-reviewed journal
17 that has a turnaround time right now of article submission
18 to publishing of three months. It is probably tops in the
19 industry for peer review. We get the information out fast.
20 Informally, we have a list server and currently are
21 developing another one.

22 If there is a drug out there that is clinically
23 ineffective, that has just popped up, our practitioners find
24 out about very quickly, and informally, just between

1 practitioners, our network I believe is second to none in
2 the world.

3 And we have heard economics talked about. That is
4 another refreshing change. You may recall in the mid-
5 eighties of having a very heated argument with the FDA field
6 investigator about extra label use and economics in food
7 animals, and that field investigator told me I don't care if
8 every pig farm in the United States goes broke, you cannot
9 use extra label drugs for economic reasons.

10 So now, here, I kind of feel that door has been
11 cracked open now, and that's great, because that shows the
12 FDA and specifically CVM, has intellectual integrity, the
13 intellectual integrity to recognize the world the way it
14 really is and what we deal with on a daily basis. Economics
15 enter in sometimes into our decisions, and so I think that
16 is another ray of light.

17 I guess finally, I would say that for
18 practitioners, there is not going to be any recipe of steps
19 for us to go through to determine when a drug is clinically
20 ineffective. I cannot see that happening. Variability
21 between production systems, not only between species, but
22 within species, within swine, for example, what might go on,
23 on the farm with 100 sows may be quite different from the
24 Murphy family farm with 260,000 sows.

1 So, we need that discretion. I would like to see
2 the policies of CVM, as I mentioned before, extended down
3 through the clinical ineffectiveness. And that's it.

4 DR. LEIN: Thank you very much.

5 Are there questions for Dr. Burkgren? Yes,
6 Steven.

7 DR. BARKER: So let me put the question to you.
8 How should the term clinically ineffective be defined for
9 purposes of AMDUCA?

10 DR. BURKGREN: Left up to the discretion of the
11 primary care veterinarian.

12 DR. BARKER: How should the veterinarian go about
13 determining whether a drug is clinically ineffective?

14 DR. BURKGREN: They will know it when they see it.
15 It's a moving target. I can't tell you. Even within the
16 farms that I deal with, to go from one farm to another and
17 say where one drug is ineffective and where is it effective,
18 it is a case-by-case basis. I don't have a recipe. I don't
19 have an algorithm in my head that says these are the steps
20 we are going to go through.

21 On a specific farm, I will know that the last time
22 Genocin didn't work in the defurring room, and so I have to
23 go with another drug.

24 DR. LEIN: Diane.

1 DR. GERKEN: I have a question. Do you or any of
2 the swine practitioners report the ineffectiveness to FDA or
3 USP?

4 DR. BURKGREN: As an adverse reaction?

5 DR. GERKEN: Yes, unexpected reaction.

6 DR. BURKGREN: I believe some of our practitioners
7 might, but a very small number. It has not been, to my
8 knowledge, a widespread event.

9 DR. GERKEN: So there is no history in any agency
10 that this has been ineffective, it is just a very well-known
11 fact among you?

12 DR. BURKGREN: Yes.

13 DR. LEIN: Yes, Janis.

14 DR. CLELAND: This is just a comment. Since all
15 of the public speakers have been large animal oriented
16 individuals, and have spoken very eloquently to the issue, I
17 would like to say that the same thing evolves as far as
18 small animal practice. It is on a case-by-case basis
19 whether something is ineffective or not.

20 We don't have the herds and that sort of thing,
21 but we do have disease processes run through like
22 respiratory disease in cats, and so the same type of thing
23 definitely applies to small animal medicine, as well.

24 DR. LEIN: Other questions? Thank you, Dr.

1 Burkgren.

2 The next presenter will be Dr. Richard Carneval,
3 who will speak for the American Health Institute. Is that
4 right?

5 DR. CARNEVAL: Animal Health Institute.

6 DR. LEIN: Animal Health Institute, I am sorry.

7 Richard will give us his thoughts on clinical
8 ineffectiveness.

9 DR. CARNEVAL: First of all, let me thank the
10 chairman and the committee and CVM for allowing the Animal
11 Health Institute to comment today. I am Dr. Richard
12 Carneval. I am Vice President of Regulatory, Scientific,
13 and International Affairs at AHI.

14 I would like to submit a short statement for the
15 record regarding the matter today. The AHI represents
16 manufacturers of animal drugs and biologics used to improve
17 the health of food-producing animals and increase food
18 production, and to keep pets and other non-food animals
19 healthy.

20 The Institute is pleased to be able to comment on
21 the matter before the committee today, that is, the matter
22 of clinical ineffectiveness as it relates to the current
23 regulations permitting extra label use of animal and human
24 drugs by the veterinarian.

1 AHI believes that the passage of AMDUCA was
2 important in legally allowing veterinarians to prescribe or
3 administer drugs that may not be approved for species or
4 indications to relieve pain and suffering in animals.

5 The FDA published implementing regulations
6 interpreting AMDUCA and establishing the conditions under
7 which such extra label use is permitted. One of those
8 conditions is when a veterinarian has determined that an
9 available approved and labeled drug is clinically
10 ineffective for the condition he or she intends to treat or
11 prevent.

12 The words clinically ineffective implies that in
13 his or her experience the drug no longer works within the
14 context of the animals under their care and an unapproved
15 unlabeled drug must be used.

16 Now, no specific instructions are provided in the
17 regulations for guiding a veterinarian or the FDA in
18 determining whether such use meets the intent of the law,
19 which is what this committee is here for today.

20 Now, this is clearly, as we have heard this
21 morning, a very complex issue, and there is no absolute
22 clear-cut answer. Fundamentally, we believe the
23 determination that a drug is clinically ineffective must be
24 made by the attending veterinarian using his or her

1 professional judgment.

2 We believe it is important that this be an
3 independent decision by the veterinarian based on his
4 personal experience and evaluation of scientific data. In
5 other words, we don't believe it appropriate for a
6 veterinarian to resort to a drug that is not approved for
7 the use simply based on anecdotal reports by others that a
8 drug has not worked in their hands or only because a drug is
9 less costly than the approved product.

10 Thus, a standard for reaching a decision we think
11 needs to be set by the profession. When a decision is made
12 that a drug is clinically ineffective, that decision should
13 be able to withstand a peer review test. In other words,
14 would a jury of veterinarians reviewing the issue support
15 the decision.

16 In this regard, we think it is important that some
17 criteria be developed to guide the veterinarian and in some
18 cases the Agency in such a judgment.

19 Now, because of the differences between
20 pharmacologic activity of animal drugs and the varied
21 disease conditions being treated, these criteria would of
22 course have to be very general, at least initially. As more
23 information is gathered, more specific criteria could be
24 developed for classes of disease conditions.

1 Now, I am not here today to propose what those
2 criteria should be, but the point is, is that most
3 importantly for food-producing animals -- and I would
4 emphasize that our comments really have to do primarily with
5 food animals -- a conscious and supportable decision should
6 be made and documented when a veterinarian selects an extra
7 label drug when an approved labeled drug exists.

8 Now, one approach could be a decision tree that is
9 developed along with criteria, which would permit a logical
10 sequence of thinking when contemplating a use. Questions
11 could be asked, such as was my diagnosis correct, had the
12 use recommendations for the approved drug been followed
13 strictly in accord with label directions, had the full dose
14 been given for the full duration of therapy, and was the
15 proper route of administration applied.

16 If another human or animal drug is selected in
17 place of the approved drug, what is known to be the safety
18 and residue profile of that product, does the risk of animal
19 or human safety concerns outweigh the benefit, and has the
20 finding -- we have heard this, this morning a few times --
21 has the finding that the drug is ineffective been reported
22 to the Agency.

23 The use of a drug not approved in a food-producing
24 animal, I think we can all agree is a serious matter

1 considering the public health consequences, whether they be
2 real or perceived, and we know there a lot of perceived food
3 safety concerns these days.

4 The goal of the industry is that extra label use
5 is kept to a minimum because there is an abundant supply of
6 effective approved products to meet the needs of a
7 veterinarian and producer. Hopefully, with recent changes
8 in the Food and Drug Act, with the implementation of the
9 ADAA, we will have that, we will get closer to our goal.

10 However, until that goal is realized, extra label
11 use should be approached cautiously in line with FDA
12 regulations, and we think the veterinarian community can go
13 a long way in providing guidance in a general way to the
14 veterinarian employed in private practice and trying to cope
15 with these vagaries.

16 With that, I thank you.

17 DR. LEIN: Thank you. Questions? Yes, Ruth.

18 DR. FRANCIS-FLOYD: Dr. Carneval, what we have
19 heard a lot the last two days suggests that there is not an
20 abundance supply of approved available drugs for many
21 indications in veterinarian practice, and I think that that
22 is something that we should be cautious about stating very
23 blatantly.

24 Again, in my specialty area, there is not one

1 approved drug. There is not one industry or drug company
2 that is willing to put the economic investment available
3 into getting an approved drug.

4 DR. LEIN: You opened an issue we brought up
5 before, this economy thing, and certainly we know veterinary
6 medicine looks at that and producers look at that, I mean
7 from that standpoint.

8 I brought it up because to me, looking at AMDUCA,
9 it appeared that that wasn't one of the choices, at least in
10 the food animal group. Now, in the non-food animal group,
11 it really doesn't say anything about that. They can go off-
12 label, they can go to other things a little bit easier. So
13 that is something that I feel, took, if we go always to the
14 cheaper drug, that is nonapproved, why would a company want
15 to approve it basically, because it is usually going to be
16 more costly. So that becomes a problem.

17 The other thing that you opened again, and we have
18 had some of that today, that I think is of interest, what
19 about increased reporting of at least ineffectiveness. I
20 don't think we probably, as veterinarians, really have done
21 that. We have done adverse reactions where we have animals
22 that really either die or are quite sick from a drug, but I
23 don't think that has been a common situation for veterinary
24 medicine to report that.

1 DR. CARNEVAL: I think that is right.

2 DR. LEIN: And what would a company do with that?
3 I mean that is the next thing, because it does fall back
4 over to again the pharmaceutical company.

5 DR. CARNEVAL: I can't answer a specific company,
6 but certainly they are required to submit those reports to
7 FDA.

8 DR. LEIN: Right.

9 DR. CARNEVAL: I think if enough weight of the
10 evidence comes to bear on it, they might look into doing
11 some additional studies or revising the label. It depends
12 on what level of concern is raised, and you are right, I
13 don't think very often -- probably people from FDA can
14 answer this better than I can -- that very often many
15 reports are received strictly indicating that a drug has
16 been judged clinically effective.

17 But I think if you are going to build the support
18 for a veterinarian using the drug extra label --

19 DR. LEIN: You would have a database at least.

20 DR. CARNEVAL: You need that information.
21 Otherwise, you are really dealing with in many cases
22 anecdotal evidence.

23 Yes, Dr. Wolf.

24 DR. WOLF: I was talking to Dr. Blackwell about

1 this earlier, and I think it does relate back to adverse
2 reaction reporting, and I really think that the CVM ought to
3 look at making access a lot easier for practitioners using
4 methods of electronic communication, and developing methods
5 whereby this information could be more easily relayed to the
6 group itself, as well as hopefully they would report it to
7 the producer of the biochemical agent or whatever, but I
8 think it needs to get back here, and this ought to be the
9 central reporting site for all of this information.

10 DR. LEIN: Dr. Keller.

11 DR. KELLER: Roughly 15 percent of our database on
12 adverse experience reports is comprised of clinical
13 ineffectiveness reports.

14 DR. LEIN: Kelvin.

15 DR. KOONG: I appreciate, Dr. Carneval, your
16 comment about the part of the decisionmaking, asking those
17 serious questions. I would like to ask my colleague are
18 students, in part of their curriculum, have they dealt with
19 the issue of those questions and also in our profession,
20 their continued education opportunity and our associations
21 at the state or national level, ABMAs, and so on, because
22 that will give me some comfort as far as they are continuing
23 subject to the continued education program.

24 DR. LEIN: I think that is just happening because

1 AMDUCA has just been passed. Now, how much that will get
2 incorporated into pharmacy, medicine courses, I am sure it
3 is going to have to happen and go forward.

4 Dr. Fletcher.

5 DR. FLETCHER: Let me respond to that from a
6 veterinary college perspective. If I would answer that yes,
7 and emphatically yes, and again say as each faculty member
8 interacts in their courses, there is a lot of variability in
9 it, but there are several points that are emphasized over
10 and over again.

11 One is the veterinarian and client-patient
12 relationship, which I think is critical in this process
13 here, however, the criteria might be defined, I mean that is
14 already pretty firmly established. It is preached I think
15 over and over again to veterinary students.

16 The second is a disciplined approach to collecting
17 information and making decisions, which I think has to do
18 with whether or not you have it in a formal written thing
19 that you go through every time in a decision tree type
20 process, but I think all of us emphasize that making
21 diagnoses and arriving at courses of action are not just
22 things that fall on you out of the sky. There is a logical
23 approach that one takes to collecting data, to analyzing it,
24 to making judgment decisions about what is done.

1 That is part of both the science and art of
2 veterinary medicine, and what we are struggling with is how
3 you bring those two components together. The other point I
4 would emphasize is the recordkeeping, and I think regardless
5 of whether FDA requires it or not, it is a professional
6 obligation that the practitioner have the kind of auditable
7 record that would allow one to go back and defend, either
8 legally or otherwise.

9 We tell our students you need to be prepared to
10 defend it legally, that if someone came back and said you
11 used something extra label, and I am now going to sue you
12 for it, how do you defend yourself, and that is maybe not
13 the best approach, but it tends to get people's attention as
14 to why you should start doing it.

15 So I would answer that question by saying yes,
16 there is a tremendous amount of emphasis on it, and
17 hopefully, it continues into continuing education. I think
18 the specialty groups, as you have seen by the testimony this
19 morning, do an excellent job in continuing education through
20 the kind of connections that they have with one another,
21 which is enhanced by things like the Internet.

22 DR. LEIN: Joe.

23 DR. GLOYDE: I have a question to ask Dr.
24 Carneval. You suggested that there should be some more

1 definitive reporting systems, and I would describe the
2 scenario whereby the representative of one of your member
3 companies walks into a practice and the veterinarian says
4 your drug X has a real problem here, and this is what it is,
5 and this is how we used it, this is the response we got, and
6 your product is no darn good and we are not going to use it
7 anymore.

8 Then, will that representative of one of your
9 member firms go out in the car and write that up and turn it
10 in to the company?

11 DR. CARNEVAL: Let's say he should, Joe.

12 DR. LEIN: Other questions? Sue.

13 MS. HUDSON-DURAN: I have one question. I reach a
14 rotation and we have -- Dr. Riddell is very adamant about
15 using veterinary products first, and we have a line that we
16 get into. We really try to go with the label, and that is
17 real pet peeve with me, I would like to go to a label and
18 use that label. We can't do that, so then we try to go off
19 label with a veterinary product, then, we move on.

20 Then, as the last resort, we compound. If we have
21 a list of drugs that we want or that the organization and
22 AVMA feels that needs to be put in the market, can we send
23 you a list of those drugs on priority, say, we have a list
24 for pharmacist and we are constantly talking about drugs

1 that we have problems with, are you open to us sending you
2 lists of drugs that we feel would be a marketable product,
3 so that you could disseminate it among the pharmaceutical
4 companies?

5 DR. CARNEVAL: Well, we would certainly be willing
6 to look at that I think whenever our companies meet from
7 time to time, and if you have information of that nature, I
8 am sure they would be happy to look at that, so we would be
9 glad to see it.

10 DR. LEIN: Ruth.

11 DR. FRANCIS-FLOYD: First, I would like to ask
12 that the committee be distributed a copy of Dr. Carneval's
13 statement if that is possible, before our next meeting.
14 Also, I wanted to ask, you mentioned that you think that ne
15 of the things this committee should consider is setting
16 standards for the profession in determination of this
17 clinical ineffectiveness, and one of the things that you
18 said was that anecdotal information is inadequate.

19 Could you characterize what you mean exactly by
20 anecdotal information, please?

21 DR. CARNEVAL: Well, I simply mean an offhand
22 remark by someone that, you know, I used this product the
23 other day and it really didn't work, so the veterinarian
24 then, based on that one comment, says gee, I don't think I

1 will use it, I think I will use something else that is not
2 approved.

3 Anecdotal, it doesn't have a lot of data and
4 scientific support behind the statement. Now, if this
5 individual reported that he used it and he had in vitro
6 sensitivity data to show that it might not have been
7 effective prior to its use, and using it at the full label
8 dosage did not work and, in fact, clinically, in several
9 animals that he treated, it did not work, but simply an
10 offhand remark that a drug may not have worked without good
11 support for that recommendation I would consider anecdotal.

12 So, I think it needs to be more than that, but I
13 am not here to tell you exactly how much more. Someone
14 mentioned a respected colleague, I think this morning, a
15 respected researcher that has done some work and reported
16 privately that in his experience, he has had problems. I
17 would think that would hold more weight than simply a casual
18 remark at a meeting somewhere by one individual.

19 I think that is what I was getting at. There
20 needs to be more of a documentation, more of a basis for
21 that decision than simply so-and-so told me it didn't work.
22 I think that is really what I was thinking of in those
23 terms.

24 DR. LEIN: Other questions? Keith.

1 DR. STERNER: I would like to reiterate or perhaps
2 paraphrase Dr. Riddell's comments earlier about in trying to
3 formulate suggested regulations or criteria for clinical
4 ineffectiveness that there has been very ably pointed out a
5 wide latitude in margin of comfort.

6 Certainly my margin of comfort with those 10 small
7 clients, where I really can't retrieve the data, is a lot
8 more marginal than it would be where I can recall data from
9 thousands of head and retrieve those records, you know, for
10 an indefinite period of time, and, you know, where I would
11 be sitting on a stand defending my clinical judgment,
12 certainly the most defensible one is where I can retrieve
13 data on scientifically valid numbers of animals versus my
14 clinical impression, and I could be made very easily to look
15 foolish in the scenario of the small number of animals under
16 widely varied circumstances versus large numbers of animals
17 under much more controlled conditions.

18 That is the dilemma with which this committee is
19 faced in trying to come up with a series of recommendations.
20 I don't blame Dr. Sundlof for trying to dump it on our laps
21 to define this.

22 I would make one other comment. To paraphrase Dr.
23 Sundlof, I first heard the phrase "weasel words" being
24 necessary to define this, because that is in fact the

1 reality of practice. As you look at this great land and the
2 wide diversity of animal species that are kept for food and
3 companion purposes, and we have to paint with an
4 extraordinarily broad brush in order to encompass that wide
5 scope of husbandry.

6 DR. LEIN: Other questions or statements?

7 Just coming back quickly to what Dr. Fletcher was
8 talking about, and Dr. Koong, I think also we are seeing, in
9 the veterinary colleges -- and I don't know how many do this
10 -- but at least in clinics, there are pharmacy therapeutic
11 boards that have clinicians, pharmacists, sitting on those
12 boards and come up with recommended treatments for different
13 things that are going to be used, and I think we will see
14 more of that now, and I have seen in some of the large
15 practices especially where there is large groups of animals
16 in feed lots or large dairy units today, where SOPs are put
17 together for at least that farm saying this is what is going
18 to be used and it will be reviewed as to effectiveness if
19 they have to change.

20 A lot of that is because of what has been
21 mentioned of a lot of people having access to drugs or
22 trying to have at least a procedure that they are going to
23 be following in treatment of animals.

24 So, I think we are seeing these sort of things

1 happening. I know at Cornell, with our decision-based
2 learning and our case-based learning, certainly that
3 decision tree is something that they work on quite a bit.

4 DR. STERNER: But there in itself lies a dilemma
5 in veterinary education in this country, and that is the
6 reality of what cases, what clinical caseloads students get
7 to see. Certainly, university clinicians, regardless of
8 their educational or academic criteria, are hamstrung by
9 oftentimes their simple geographic location and proximity to
10 -- again, I bring my food animal production bias into this
11 point -- but unless the student is put into this field
12 setting, the reality of making these decisions to see how to
13 go about that cannot happen in a university clinical
14 setting, and many universities have found that they have had
15 to close down or have made a conscious effort to do that and
16 farm that out to private practitioners, and the extent to
17 which a student sees that decision process and their
18 clinical experience may be greater or lesser depending on
19 the type of practice setting they go into.

20 DR. LEIN: Exactly, but a lot of it is working
21 with the practices now with externships basically.

22 DR. STERNER: And, of course, that is the point
23 that I am making, is that regional differences and the type
24 of clinical experience doesn't mean that every student

1 indeed has Kelvin's concern addressed.

2 DR. LEIN: But not only that, I think we had some
3 good presentations this morning saying there is going to be
4 regional differences, and I believe that.

5 DR. STERNER: There are.

6 DR. LEIN: Diane.

7 DR. GERKEN: I would go a little bit further and
8 say that it is not just in the clinical experience, that it
9 is being taught in the basic science and maybe you would
10 argue that that is basic science, and I don't want to debate
11 that, but the veterinary colleges -- and I am speaking for
12 the course that I am in charge of, in Toxicology -- has
13 really has no labeled antidotes for treatment. We are all
14 orphans and we are all -- sometimes we are compounding, and
15 so I am very upfront about what the requirements are for
16 food animals to treat animals that are intoxicated.

17 So I would say that the students receive some
18 information about extra label drug use and the requirements
19 and all the things that go into making those decisions, and
20 they are not hard and fast, as you well know, from the time
21 they enter as freshmen and for most students they have to be
22 periodically, you know, refreshed that this occurs.

23 I teach juniors and I ask them do you know what
24 AMDUCA is, and I usually ask them to put down what they

1 think AMDUCA is, and you will be surprised. They have heard
2 of it and they have a pretty good perception of what it is.

3 Now, they may not be able to do all the things
4 that you are talking about, but at least I think that we
5 have something to build on. The biggest problem that I
6 think that I see is the reporting issue. Most veterinarians
7 feel that adverse drug reporting is just that, you report an
8 adverse drug reaction, not a clinical ineffectiveness, and
9 maybe we haven't done a good enough job in trying to promote
10 the clinical ineffectiveness reporting.

11 I was just talking to Dr. Parke [ph] about the
12 electronic type of reporting, that that ought to be
13 facilitated, especially if we could report it to FDA and the
14 drug company simultaneously, so that both of them knew it
15 was already reported to the other, so there is no
16 duplication, but to make it a little bit easier whether it
17 is done through some of the -- you know, NOAA, or some of
18 the other groups, and then you have problems with
19 verification, but I think that the veterinary colleges are
20 responding in the best way that they possibly can.

21 DR. LEIN: Gatz.

22 DR. RIDDELL: I just had one comment. I really
23 understand the need to report these things when they are
24 clinically ineffective, but I would also like to underscore

1 what Keith mentioned about the regionality, because, for
2 example, PPG may not work in the Southeast, it might work in
3 Michigan, and I certainly wouldn't want my reporting of a
4 clinical ineffectiveness to impact that drug's approved
5 label, because there is so much regionality and even
6 seasonality that can factor in.

7 Somehow that has got to all be buried in there,
8 just the fact that a group of people in Alabama say
9 penicillin isn't working this year shouldn't impact the
10 FDA's view or CVM's view of whether that product is
11 appropriately labeled or not, because there are so many
12 variabilities.

13 DR. LEIN: Other statements, questions? Thank
14 you, Richard.

15 The last speaker that we have recorded here is
16 Richard Wood, that has Food Animal Concerns.

17 DR. WOOD: Trust.

18 DR. LEIN: Trust. Food Animal Concerns Trust. I
19 couldn't read that last word.

20 DR. WOOD: Thank you for the opportunity to speak
21 before you briefly. We advocate performing practices that
22 would improve the safety of meat, milk, and eggs. I know it
23 is after 12:00, although where I come from it is just after
24 11:00, so -- I will still be quick.

1 We welcome the passage of AMDUCA as a way to
2 regulate extra label drug use with food animals in
3 particular, I really appreciate the healthy discussion that
4 has happened here today.

5 We are concerned about the potential risks to
6 human health when a drug is used extra label without
7 safeguards, but in our view, with regard to food animals, to
8 use a term in this rule, it is not absurd to prohibit in
9 certain circumstances the extra label use of a drug.

10 To divide the question with food animals, it may
11 be entirely possible and appropriate for a veterinarian in
12 the field to determine that a particular drug is clinically
13 ineffective however that term is defined today or later, but
14 in our view, with food animals, it is inappropriate to allow
15 the use of an extra label drug as an alternative in that
16 situation particularly where questions of drug residue and
17 resistance are at stake.

18 The provision of extra label use related to
19 clinical ineffectiveness decisions should not be applied to
20 food animals in our view. In this case, it makes good
21 public health policy to require for the alternative drug to
22 go through the revision process before it is used in new
23 clinical situations. We feel we need to make that process
24 work.

1 To not do so is to sidestep the objective human
2 health safeguards provided by the drug approval process, a
3 process, as you know, that was recently streamlined by the
4 Animal Drug Availability Act.

5 I look forward to your discussion of this question
6 with regard to food animals.

7 Thank you.

8 DR. LEIN: Thank you. Questions for Dr. Wood?

9 DR. STERNER: I have one as it revolves around the
10 issue of resistance. I, by implication, think that every
11 antimicrobial has the potential for resistance development.
12 Do I infer that the Food Animal Concerns Trust is an
13 advocate of no approvals for use in food animals?

14 DR. WOOD: We certainly are very concerned about
15 the use of extra label drugs in food animals, and that has
16 been our position in the past, particularly with that class
17 of antimicrobial drugs.

18 DR. STERNER: That class being?

19 DR. WOOD: That class of drugs.

20 DR. LEIN: One concern, of course, and I know you
21 are interested in food and safety, what about concerns of
22 suffering of animals?

23 DR. WOOD: You bet, and that is a concern, and
24 that is why we want to see the animal drug approval process

1 work.

2 DR. LEIN: We do, too, but when it isn't working,
3 do you let the animals suffer or do you go off-label?

4 DR. WOOD: That is a very difficult decision, of
5 course, and what we want, in a structural situation where
6 you are sitting as members of the Veterinary Medical
7 Advisory Committee, we would like to see the emphasis put on
8 making the system that we all have agreed to within the
9 regulatory Food and Drug Administration, we would like to
10 see that system caused to work, and we feel that would be of
11 a benefit to the well-being of the animal and also the well-
12 being to human health.

13 DR. LEIN: Sure, but in the meantime, we are going
14 to have to probably extra label from the standpoint of the
15 care of the animal.

16 Other questions? Do we have any other public
17 statements? Yes. Please indicate your name and
18 affiliation.

19 DR. BATALLER: Dr. Bataller. You forgot me
20 already. I am sad.

21 DR. LEIN: No, I know who you are, but for the
22 record.

23 DR. BATALLER: I am a veterinarian of the CVM, and
24 I am the coordinator of adverse drug experience reporting

1 system. I just wanted to really follow up because I have
2 heard this electronic submission time and time again. Yes,
3 it is a nice feature.

4 I did want to remind you, though, we do have self-
5 mailers, a one-page document that a veterinarian can fill
6 out, has postage paid, and I certainly cannot imagine
7 anything more convenient than walking around with a piece of
8 paper rather than have them being saddled down with a
9 computer.

10 I don't know where you do your best thinking and
11 writing. The computer might not be appropriate for some of
12 those places.

13 Anyway, the electronic submission is nice, but we
14 do have the mechanism, very convenient mechanisms for
15 reporting right now, and rather than to put too much
16 emphasis on something that is kind of sexy, I think we just
17 ought to concentrate on why people aren't using what we have
18 right now.

19 DR. WOLF: I don't have any of the prepaid forms
20 for one thing.

21 DR. GERKEN: I was going to say would you like us
22 to comment on that?

23 DR. BATALLER: No. As I said, we might work on
24 that, and that is a problem we might need to work on a

1 distribution a little better than we have in the past.

2 Computers are always looked at as an easy solution to what
3 we maybe ought to be working on right now.

4 DR. LEIN: We know the USP forms are out, too, and
5 they do get to you at least either way, right, your form or
6 their form?

7 DR. BATALLER: Yes, that's correct.

8 DR. STERNER: It is clear that Dr. Bataller has
9 not bonded with his computer yet.

10 DR. BATALLER: No, it is just a machine. Just
11 remember that, it is just a machine.

12 DR. GERKEN: And his office must be a whole lot
13 cleaner and more organized than many of you.

14 DR. BATALLER: I have four computers in my office,
15 and it is pigsty right now. I have an annual spring
16 cleaning that is coming up.

17 DR. GERKEN: But you can find your forms, right?

18 DR. BATALLER: Yes, and I program, I am very
19 intimate with computers. I just find, just like with
20 anything, they can mislead people for what they can do and
21 what they can't do.

22 DR. LANGSTON: Just to comment on the adverse
23 reporting scheme, just a reminder that USP also has PRN
24 which, in conjunction with AVMA, is out there and the forms

1 are available, have been published in JAVMA. They have a
2 web site that is available, and it is a one-stop area for
3 biologicals, drugs, and insecticides, and that information
4 is forwarded to the regulatory agency and the manufacturer
5 whenever it occurs.

6 DR. LEIN: Do we have any other statements from
7 the audience? Yes, Joe.

8 DR. GLOYDE: I have been sitting back here
9 thinking for a change. Dr. Keller had a slide up there that
10 talked about some of the criteria that veterinarians may use
11 to make a decision about whether or not a drug is
12 ineffective. Dr. Riddell mentioned a plethora of instances
13 whereby veterinarians have to make a decision that the drug
14 is not effective.

15 It appears to me that maybe that is the kind of
16 thing that needs to be put down on -- maybe it is turning
17 out to be a pretty super extensive list, but at least it
18 would provide some comfort to the people that are concerned
19 about how veterinarians use drugs and what their
20 decisionmaking process is, and also provide the
21 veterinarian, who is out there with the ultimate
22 responsibility to decide whether they should use a drug that
23 is labeled for that use or another one that they believe is
24 far more effective.

1 I am not sure I have a handle on that, but I think
2 that that long extensive list is more to the point than
3 something that I think Gatz said something about putting it
4 in a box, and I am not sure you can do that.

5 DR. LEIN: Thank you. Other statements?

6 Hearing none, I think it is time for lunch. Let's
7 take an hour for lunch and be back at 1:30.

8 [Whereupon, at 12:30 p.m., the proceedings were
9 recessed, to be resumed at 1:30 p.m.]

AFTERNOON PROCEEDINGS

[1:30 p.m.]

Committee Discussion

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2
3
4 DR. LEIN: The meeting is open for discussion. I
5 think the two questions you have in front of you. We could
6 start discussion and go through and try to answer these. I
7 have been talking to a few of the people on the committee
8 and also I have talked to some degree with Dr. Sundlof and
9 Bert Mitchell and Dr. Blackwell.

10 I think as much as we can answer these questions
11 and come up with somewhat of a format, one of my thoughts
12 was to, instead of come up with a final copy of this, that
13 we would feel we would want to go forward and be utilized by
14 FDA in today's meeting, that we turn around and put this
15 back over to AVMA, run it through COBTA DAC, but also at the
16 same time, move it to the specialty groups, food animal,
17 especially the American Association of Bovine Practitioners
18 and Swine Practitioners, Equine, and AHA we have had right
19 along, and the small animal groups down through to take a
20 look at this, try to put together through that committee and
21 brought through AVMA and sanctioned through their board as a
22 positive step along with FDA's backing of it, they would be
23 at those final meetings, and do it much like we did the
24 client-patient relationship where again that was needed by

1 FDA, but really was put together and sanctioned by both AVMA
2 and FDA.

3 I think for at least our members, that is going to
4 sell better than trying to move it directly just through
5 from the advisory committee and on to FDA for them to at
6 least say this is what is going to be followed.

7 At least it would give all that group a chance to
8 look at it and give us more information. We certainly feel
9 that the outside speakers that came in from specialty groups
10 and others did a great job today, but it wouldn't hurt to
11 sit and reflect a little bit and have it go back to
12 committees and then come through basically to COBTA and DAC
13 and through AVMA finally as an official situation.

14 I also talked -- and maybe it doesn't need to go
15 that much further -- but I think AMDUCA and how it was
16 presented to the veterinarian profession through the
17 satellite conference as a joint AVMA and FDA and other
18 sponsor groups, certainly a followup with that with this
19 question and probably others that are there from the
20 original satellite conference could be very useful and could
21 be a good way of selling this and giving more education.

22 A lot of the things that we heard today on some of
23 the individual cases, things that Gatz presented, and Butch,
24 and others, down through Dr. Pence, certainly you can't put

1 that into the regulation, but those examples are so good and
2 give you an idea of why whatever we are going to put
3 together today, why it does have to be broad, at least in a
4 teleconference that could be done very well, so you could
5 have some examples given and do it on a question to answer
6 situation just like you did before.

7 So, those were some of the things that we talked a
8 little bit about at lunch, and I will open that for
9 discussion at this point if you think that is the way we
10 should go, and then I think we should get to the business of
11 trying to answer some of these questions, so there is a
12 framework for something to go forward to that committee, if
13 you want to do it that way.

14 Questions, please.

15 DR. STERNER: I would just add my endorsement or
16 recommendation that you proceed as suggested once we have
17 come up with some recommendations, answers to these
18 questions.

19 DR. LEIN: Other questions or concerns on that
20 route? Sue. Maybe the pharmacology group should get it,
21 too.

22 MS. HUDSON-DURAN: I was talking to Doug earlier.
23 Somewhere I have seen over the years, and there are, like
24 Dr. Vaughn's approach, I think we could have a guideline in

1 there or 90 categories of drugs, and the last couple of
2 those are devices, so really there wouldn't be that many.

3 Maybe a category or two really we could take out,
4 so say maybe we are talking about 80 categories of drugs,
5 because I know when we do clinical efficacy studies in the
6 hospital, each category of drug has a standard. Like an
7 antibiotic to be successful has to have improvement within
8 48 hours, decreased white cell count, decreased temperature,
9 anthelmintics, 90 to 100 percent, so cardiovascular drugs
10 are supposed to act within 4 to 24 hours, otherwise, you
11 reassess.

12 So, I think something along that line, to me would
13 be a standard that a practitioner could say okay, at least I
14 have a source that I can look and see whether or not I think
15 this category of drug is efficacious, and older
16 practitioners or more experienced practitioners might know
17 that, but that would also be a good teaching tool.

18 DR. LEIN: I think those are good guidelines. The
19 problem that you have to worry a little bit about with those
20 is that in the field situation again, that may not be
21 available to them and frequently you are working with mixed
22 infections, too, and the difficulty of saying what a white
23 blood cell count is going to do in that, because you are not
24 controlling a lot of the other problems with it, although

1 they could be guidelines if someone thought they needed more
2 guidelines to make a shift.

3 Yes, Gary.

4 DR. KORITZ: I would like to have a little
5 information to sort of direct my thinking into how I might
6 define clinical ineffective. The two questions are -- and I
7 guess they are directed to FDA -- what is the current rate
8 of violative drug residues being detected by FSIS in the
9 meat supply, and if that rate should double post-December
10 9th, 1996, how quickly would FSIS be able to detect that?

11 DR. LEIN: Steve.

12 DR. SUNDLOF: That is a good question and how do
13 you measure against some kind of standard. You have put out
14 recommendations, and then you decide whether or not they are
15 working by looking at some surrogate which would be residue
16 violations.

17 Unfortunately or fortunately, FSIS is moving to a
18 HACCP approach in which the individual plants are going to
19 be responsible for determining residues, and it is going to
20 be different. We are not going to be able to compare what
21 happens in 1997 to what is probably going to happen in 1998,
22 because the whole thing is going to shift.

23 If this all occurs at the same time as that change
24 is occurring, I don't think there is any way that we can use

1 the residue violations as a measure of how well or how
2 poorly we are doing this clinical ineffectiveness as results
3 in residues.

4 DR. LEIN: One other thing that will be happening
5 there, too, I think, Steve, is that we will probably have
6 some new tests coming out, and so we may see a blip in some
7 different antibiotic. Antibiotics are used off-label now,
8 that we don't have tests for.

9 DR. TOLLEFSON: But to get to Dr. Koritz' point,
10 for the violative residues that FDA inspects, goes out on
11 the farm and investigates, we determine whether or not they
12 are due to extra label drug use, so we would have that
13 information in the database, and the interaction with FSIS
14 and CVM is going to remain even though the structure of the
15 national residue program is going to be a little bit
16 different.

17 So, those numbers wouldn't be comparable from year
18 to year. You couldn't compare the numbers, but you could
19 compare the incidence in what you found, so there could be a
20 measure. It would actually be a measure of how successful
21 extra label use is being used, you know, by the
22 veterinarian. It wouldn't necessarily be so specific as to
23 the clinical ineffectiveness question.

24 DR. KORITZ: Well, my point is, is that I would

1 hate to establish a very restrictive definition of a
2 determination of clinical ineffectiveness if we don't have
3 evidence that a problem is indeed being created.

4 DR. LEIN: Dr. Wolf.

5 DR. WOLF: I think Sue's comments, if I am
6 understanding correctly, you are looking at drugs that
7 already in use. You pick a drug, you treat the patient. I
8 think that probably none of us has too much trouble
9 determining guidelines for what is effective and what is not
10 effective as clinical practitioners, but I think in our
11 discussions we have somewhat opened the door for recognizing
12 that certain drugs seem to be more effective or less
13 effective for various indications, and I think that -- you
14 know, we have kind of begged the question on that, looking
15 at drugs that are already in use.

16 So, how do we permit the use of these agents that
17 may be extra label because we know that under certain
18 conditions they are more effective, and leave the door open
19 for people that way, and allow also for differences in
20 different parts of the country, and that the cattle in the
21 Southeast may have resistances that cattle in Texas don't
22 have, that sorts of thing.

23 DR. LEIN: Sue.

24 MS. HUDSON-DURAN: Maybe I shouldn't have

1 mentioned lab work since we are clinical and out in the
2 field, but the bottom line is if you give any antibiotic, no
3 matter whether it is approved or not approved, and the
4 animal is not better in 48 hours, then, it is a failure, so
5 at least to have something, and, yes, everybody might know
6 that, but they really might not be thinking that way.

7 If you go out and do herd work, in two days, 8 of
8 the 10 cows you treated are not well, you are probably going
9 to get a call and say, hey, you need to come back out here.

10 The other thing is a lot of times we use a drug
11 that is off-label because a lot of the approved drugs,
12 particularly in horses, are injectable, and we send
13 something home with an owner to treat a chronic infection,
14 and it is just a delivery system.

15 Sometimes we are having to use it because people
16 don't want to inject an animal twice a day for a month, so
17 sometimes we have to go to oral off-label drugs, so we don't
18 have a choice.

19 DR. LEIN: Dr. Koong.

20 DR. KOONG: I would like also to have some
21 clarification on the first question. I guess my question is
22 directed towards FDA here. We are asked to define the term
23 clinically ineffective. It is a difficult task just as is,
24 but even if we are successful, what is this definition going

1 to be used for by CVM? What is the purpose of this
2 definition?

3 DR. SUNDLOF: I will try and answer that. Well,
4 one of the things we don't want to be using this as an
5 enforcement tool except perhaps as a last resort, so it is
6 not for that, but in the regulations, we have specifically
7 said that if a veterinarian determines that a drug is
8 clinically ineffective, then, that is a criterion for extra
9 label drug use.

10 Really, the determination is something that the
11 profession should be making. That is a professional
12 judgment, clinical judgment on the part of the veterinarian.
13 We would like to have a little bit more framework around
14 that, so that when we do run into some problems that will
15 ultimately occur with extra label drug use, and we look at
16 the conditions that cause that we want to have some basis
17 for saying whether or not that clinical judgment was, in
18 fact, exercised in making the determination that a drug was
19 clinically ineffective.

20 I think what Don Lein just said was that really
21 what FDA wants is we would like the profession to try and
22 define in very general, flexible terms what is meant by
23 clinically ineffective to give guidance to the profession,
24 so that the profession can make those kinds of clinical

1 judgments against some kind of standard.

2 This gives the profession a greater sense of
3 security. We were asked at the teleconference what do you
4 mean by clinical efficacy. There is a lot of concern as to
5 what that means and a lot of veterinarians want that kind of
6 general guidance.

7 As Don indicated, I think it would be in the best
8 interest for the veterinarian profession to own this
9 definition, then hold discussions with CVM to make sure that
10 we are in concurrence with the definition that the
11 profession has developed and that we can endorse that
12 condition or that definition because otherwise, we have
13 stated something that is so open to individual subjective
14 determination that it is very difficult for us to use that
15 as a criteria for regulation.

16 DR. KOONG: Could I followup on this? From what
17 you have described, Dr. Sundlof, that basically, a
18 definition could be as a guideline to be used by the
19 profession, the practitioner for going through a process of
20 how they make the decisions, make that judgment on an
21 individual basis, so therefore, that basically, the first
22 question leads to the second one, and if in your view, if
23 the profession, the veterinarian has come up through a
24 guideline or sequence of a question they ask themselves each

1 time they do off-label, that they have considered the
2 following questions.

3 Basically, the problem is at the end, the judgment
4 has to be made by that individual. If we provide the answer
5 to the second question, I am wondering if the answer to the
6 first question is needed.

7 DR. SUNDLOF: I would think that somewhere you
8 have to describe what clinical ineffectiveness is. What I
9 heard through this discussion is that it is not just that
10 the drug doesn't work, but it may be that the drug works,
11 but marginally and there may be other products that work
12 better, and that it is in the best interests of the patient
13 to use those products.

14 So, having a definition of what clinically
15 ineffective is, I think is an important first step, and once
16 you have defined what that is, then, I think you can start
17 looking at the decision process that gets you to that
18 definition.

19 Again, that is for this committee to deliberate.

20 DR. LEIN: Keith, you were writing. Did you come
21 up with a --

22 DR. STERNER: Wordsmithing with a pencil is not my
23 specialty. I have been working with lots of weasel words
24 here.

1 DR. LEIN: Sue has got one, too. Let's hear Sue's
2 here.

3 MS. HUDSON-DURAN: Don't laugh. Regional
4 epidemiology has shown the drug to be a failure.

5 DR. LEIN: I wrote, "The term clinically
6 ineffective means that in the experience of the treating
7 veterinarian, that a drug or treatment is not responding in
8 the normal or expected time and form and may indicate
9 rediagnosis of the condition and a change in drug therapy to
10 an extra label drug."

11 That is wordy. It could come down to something
12 further.

13 Dr. Wolf.

14 DR. WOLF: I think that, Don, your attempt is
15 praiseworthy, but I think it still overlooks the situation
16 where I may need to select an extra label drug first, and I
17 will give you an example. A cat with hemobartonellosis that
18 the packed cell volume is 7, I don't have time to wait for
19 tetracycline to work even though I know that it is an
20 effective drug if I had enough time, but I don't, so I would
21 probably treat that particular patient with carposylate
22 [ph], which is an unapproved drug. So, it would be
23 clinically ineffective if I tried it, but the cat would be
24 dead, so I wouldn't accomplish anything.

1 DR. LEIN: It could be in the diagnosis that it
2 would be clinically ineffective.

3 DR. WOLF: But the diagnosis of the disease
4 doesn't say that tetracycline would be ineffective, it is
5 the particular presentation of the disease that I know it
6 would be.

7 DR. STERNER: In that case, then, you need the
8 caveat that practitioners should use their scientific
9 training, experience, and clinical judgment to determine
10 when a pharmaceutical product has been deemed clinically
11 ineffective.

12 DR. LEIN: Or is going to be clinically
13 ineffective.

14 DR. WOLF: Or will be.

15 DR. STERNER: May be. How about "may"? Is it
16 "may," Dick?

17 MR. GEYER: Actually, I think you have some choice
18 on this at this point. What we need to know first is what
19 do you, as a matter of veterinary practice, feel is the
20 appropriate way to phrase it, and I think from the legal
21 standpoint there would be some flexibility.

22 DR. STERNER: Well, in addition, there is a
23 recognition that there is an extraordinary scope of species
24 and clinical circumstances which are of a subjective nature.

1 In general, use of the veterinarian's oath may be as good a
2 guideline as any in that determination.

3 DR. FLETCHER: I see this at maybe two different
4 levels. There is an individual veterinarian level for which
5 the definition is the professional opinion as a veterinarian
6 is this drug is clinically ineffective. That is not very
7 good necessarily from the Agency standpoint, but I would
8 back that up by saying what steps should the veterinarian be
9 taking to make that determination, and there are some
10 elements that I could see being included in that, case by
11 case, based on professional judgment exercised in a
12 veterinarian and client-patient relationship using
13 education, experience and supporting data, lab data or
14 whatever, and a second sentence to go with that is the
15 availability of information from other sources. That would
16 include consultation with colleagues, meetings, information
17 from the Internet, proceedings, publications, those kinds of
18 things that are recommended supplements to support the
19 individual professional judgment that a veterinarian might
20 make.

21 Then, there is another level which in my mind is
22 at the level of the species or the specialty where there is
23 a collective opinion by multiple practitioners within that
24 group that is defining clinically ineffective, and it is at

1 that level that it might be at a point to take into
2 consideration the points that Mr. Wood was making, that is,
3 we don't want to really circumvent the normal process for
4 drug approval by having everything done extra label, so at
5 what level can there be some Agency involvement in what
6 might be going on, and that level might be when there is
7 enough veterinarians that are saying this is clinically
8 ineffective.

9 Now, Joe Gloyde has pointed out to me on probably
10 more than one occasion that the marketplace itself will
11 determine that, but there is the issue, well, something has
12 already been approved, how come it is not being used. So I
13 could see the definition being aimed at two levels, and I
14 liked what Sue said. There are some principles that could
15 be laid down, and you may not be able to apply them in a
16 necessary situation, but they could be there as guidelines.

17 DR. STERNER: Oscar, I am personally uncomfortable
18 with the narrowing, as it were, of the definition. If you
19 think about practitioners using their scientific training,
20 by definition that alludes to what you should have learned
21 hopefully, and did learn, either in or after graduation from
22 veterinary school.

23 DR. FLETCHER: I am saying a combination of
24 things, education experience, and any supporting data. In

1 other words, it is both the art and science of veterinary
2 medicine in that regard, so not education alone, but
3 education and experience.

4 As we have heard this morning, the same judgment
5 with one client may be a different judgment for another
6 client.

7 DR. STERNER: That is correct.

8 DR. FLETCHER: So that would provide flexibility
9 to the individual veterinarian at that veterinarian-client-
10 patient relationship level. Then, I would like to see --
11 and I think we have already said this -- what steps should
12 he take. It would be the procedures that one would normally
13 employ to arrive at a diagnosis, collect the data, make a
14 diagnosis and a judgment about what the treatment would be,
15 and that would be reflected in the medical record.

16 DR. STERNER: My concern over this revolves around
17 what I, for want of a better term, will say the
18 rehabilitation of certain pharmaceutical products, and let
19 me just one that was no-brainer when I was going through
20 school.

21 You didn't give hypertonic solutions to a
22 dehydrated animal. Now it is common practice to administer
23 hypertonic saline, for example, to a dehydrated cow.

24 DR. FLETCHER: But remember education is not --

1 education in the sense I am using it here -- is not the four
2 years of veterinarian education, but the education of the
3 veterinarian accumulates in a career of practice including
4 the continuing education.

5 DR. STERNER: Correct, but what I worry is, is
6 that you hamstring the efforts of somebody who might not
7 look at the glass being half empty, but they are looking at
8 it half full, and they come up with this novel way to use a
9 product which the collective judgment of experts says, well,
10 this really shouldn't be so, and yet come on to demonstrate
11 and enjoy widespread utilization.

12 I worry that you are constraining unnecessarily
13 these innovators, these people who think outside the normal
14 convention that most of us make.

15 DR. LEIN: Dr. Wolf.

16 DR. WOLF: Could I ask Keith to repeat what you
17 have come up with as a basis?

18 DR. STERNER: Well, mine is an addendum actually
19 to what Don wrote. I think his is much more to the point
20 with regard to defining clinically ineffective, but I think
21 it needs to be supplemented with the following weasel words:
22 Practitioners should use their scientific training,
23 experience, and clinical judgment to determine when a
24 pharmaceutical product has been deemed clinically or should

1 be deemed clinically ineffective. There is a recognition
2 that there is an extraordinary scope of species and clinical
3 circumstances which are of a subjective nature. In general,
4 use of the veterinarian's oath may serve as a guideline.

5 DR. MITCHELL: So you have included in your
6 definition scientific training, as well.

7 DR. STERNER: That's right, and I believe that
8 that is appropriate to determining -- it is at the
9 foundation of trying to determine clinically ineffective.

10 DR. MITCHELL: That is my point about including
11 education.

12 DR. BARKER: I think you are saying the same
13 thing.

14 DR. LEIN: You are spelling yours out a little bit
15 more basically.

16 DR. FLETCHER: I think we are saying the same
17 thing.

18 DR. STERNER: I was trying to be more vague.

19 DR. FLETCHER: Vague is good.

20 DR. BARKER: The lowest common denominator in all
21 this is the individual veterinarian faces with a critically
22 ill animal that is a single client, single patient.

23 DR. LEIN: Dr. Wolf wrote that, as well, that is
24 dying.

1 DR. BARKER: His decision is going to be I have
2 tried this drug and it is not working. They may not have
3 the time or even the facility to go pull out everything on
4 the Internet or find all the books that address the issue,
5 but will want to make a decision to end suffering for that
6 animal and to hopefully have it recover.

7 Given what AMDUCA does, it provides a very wide
8 range of flexibility, but at the same time, addresses
9 penalties for misuse. A lot of the misuse can still be
10 regulated. The Agency will still have mechanisms by which
11 to do it.

12 So, in defining something that is clinically
13 ineffective, it must be so flexible and so broad to permit
14 even misdiagnosis, otherwise, it fails. As Dr. Koong has
15 pointed out, if we define steps, reasonable steps, that a
16 person of education in this field would take, we can provide
17 guidance, not regulation necessarily, but guidance on how
18 they should do that, and that probably should best come from
19 what has been suggested here, AVMA, and input from DAC and
20 other agencies. They better understand this, certainly
21 better than I do.

22 DR. KEMP: We need to have that in writing, but I
23 am curious whether that definition accommodates the optimal
24 therapy as opposed to pure ineffective and ineffective, and

1 whether we should address that, put terminology in there
2 that you are seeking optimal therapeutic goals for
3 pharmacologic therapy. Once again, I don't have it in front
4 of me. It may cover it just fine. I am a slow cooker on
5 these things when I hear it across the room.

6 DR. STERNER: It depends I guess on how you wish
7 to define experience and clinical judgment. From a selfish
8 food-animal perspective, if my client goes broke because I
9 made the wrong therapeutic choice for him, that is bad
10 clinical judgment, and I still have that societal obligation
11 to ensure that food products derived from these treated
12 animals do not present violative residue problems.

13 DR. KEMP: But does the verbiage, the way it is
14 written, does it allow for the selection of optimal as
15 opposed to effective and ineffective? And it might. I am
16 not attacking it, I am just asking you.

17 DR. STERNER: Good point.

18 DR. LEIN: Dr. Wolf.

19 DR. WOLF: I would just like to add I like the
20 inclusion of the veterinarian's oath because in addition to
21 relieving animal suffering, et cetera, it says "safeguard
22 the public health."

23 DR. LEIN: Yes, it does bring that in.

24 Other thoughts?

1 DR. STERNER: Would the panel have any objection
2 to a coalescence somewhat of this as a first draft to go out
3 for comment and criticism?

4 DR. LEIN: I think that is ideal. I mean you
5 would like to have something and fashioned that if we are
6 going to move this -- I didn't hear objection to moving it
7 to AVMA and the specialty groups basically, and have it come
8 back through COBTA-DAC and then hopefully, that would move
9 through the executive board and be passed by -- to be given
10 to the membership, but something simple that covers what we
11 think it should cover from the statements may be the way to
12 go instead of trying to invent a full wheel that has a lot
13 of other responses and see how the profession buys that
14 especially the specialty professions down through and
15 whether they would see that something more had to be added
16 or more of a directive or decision tree or something instead
17 of us making that up at this point.

18 DR. STERNER: Yes, but a few representatives of
19 some specialty groups -- I recognize it would be putting
20 them on the spot -- but you could ask their degree of
21 comfort. Gatz is closest to the microphone.

22 DR. LEIN: Gatz. He looks like he was very
23 thoughtful through this whole thing.

24 DR. RIDDELL: Repeat that again.

1 [Laughter.]

2 DR. LEIN: What are your thoughts on just a
3 statement going forward with the idea that this is what this
4 board has recognized as a definition of clinical
5 ineffectiveness and whether the profession feels that this
6 will be adequate or they would like to add more and we are
7 going to try to pass it through AVMA through COBTA-DAC?

8 DR. RIDDELL: And you also pass forward the second
9 question about how a veterinarian will determine --

10 DR. LEIN: Right.

11 DR. RIDDELL: -- because I think it is very
12 inherently linked.

13 DR. LEIN: Yes. We didn't get to the second
14 question. We could start to do that because that is really
15 starting to put some of the things together that Oscar has
16 talked about.

17 DR. RIDDELL: Almost everything that I deal with
18 will answer the first question in the context of what tools
19 they will have available to answer the second question, but
20 I think the AVP and DAC and all the species groups COBTA
21 included, would welcome the opportunity to pass on it or --

22 DR. LEIN: Add to it.

23 DR. RIDDELL: Add to it.

24 DR. LEIN: Or redefine it or something.

1 DR. WOOD: I am not sure it answers the question.
2 Just to echo what Gatz said, we would welcome the
3 opportunity, if you can give us something solid to shoot at
4 first in your statement. That is where we operate best at,
5 if we can get a target point and then to get the input out.

6 DR. LEIN: What do we think about at least what
7 has been stated for the first definition? Oscar.

8 DR. FLETCHER: I like it. I don't know what the
9 rest of you think about what I said about at least two
10 levels that this is operating on, the level of the
11 individual veterinarian and a broader context, almost within
12 a species group, because I think it may be a different issue
13 at the different levels.

14 The other one, just a thought about, ineffective
15 versus -- what was your term, Doug -- optimal. I suspect
16 one could make an argument that if it is not optimal, it is
17 not effective. In the way that we have to deal with things,
18 if it is no optimal, if it is not the best that we can do,
19 it is not effective. It picks at the definition a little
20 bit, but --

21 DR. STERNER: Now you get into the situation of
22 defending a clinical judgment in saying, well, why did you
23 choose this one over another, because somebody else
24 demonstrated that it was more effective. I get all kinds of

1 literature telling me why one pharmaceutical product is
2 superior to another.

3 DR. FLETCHER: And again, as you have said in the
4 definition relative to the individual judgment, you make a
5 professional judgment based on a number of factors, many of
6 which you may not even realize at the time you made it. It
7 is a debate that there is no way to win. Here is product A
8 with a label, and here is product B, and your preference is
9 A minus B, and we could debate the merits of it and not
10 resolve that issue.

11 DR. STERNER: And as was ably pointed out this
12 morning, in one area of the country, product A may be the
13 product of choice, and product B may be one in another.

14 DR. FLETCHER: Yes.

15 DR. LEIN: Steve.

16 DR. SUNDLOF: In listening to this discussion, I
17 just may offer one suggestion. That is, that if you write
18 the definition broadly enough, that each of the specialty
19 organizations could then develop their own guidelines which
20 would be within that framework, it couldn't go beyond what
21 you said is a broad framework, but for swine practitioners,
22 they could write more specific guidelines to deal with the
23 issues that are pertinent to them. Agriculture could do the
24 same thing, and I think that would address Oscar's concern

1 that you need to have more than one level.

2 The other thing is in terms of defining what is
3 optimal, really, you have three different missions that you
4 are trying to serve, and in certain circumstances they are
5 all three mutually exclusive.

6 You have what is optimal for the patient, in many
7 cases versus what is optimal for the client versus what is
8 optimal for food safety, so when you are trying to define
9 what optimal is, it becomes very confusing.

10 DR. LEIN: Yes. In defining that, too, you are
11 almost setting up an experiment which here we are treating
12 animals basically to a point, because you have got to be
13 somehow documenting why this is optimal if you are going
14 after that against treatment A, which is standard, and then
15 is now treatment B that we are using. That is more
16 difficult.

17 Other questions? Yes.

18 DR. RAVIS: I think it is a touchy area because
19 are you really trying to decide whether something is
20 clinically ineffective or judged to be ineffective, or are
21 you really trying to make a rationale to give a drug that
22 you think is better.

23 Possibly, you don't want the wording to suggest
24 that you are trying to find a reason to discount something

1 to use something else, or are you.

2 DR. LEIN: It could have all those innuendos I
3 think that you are talking about, but if you leave it, I
4 mean who is going to make the decision. Basically, it is
5 going to be the practicing veterinarian, and that is what we
6 have got to be putting this at.

7 Along with that, we are putting the caveat that
8 still we are expecting, just because you are going off
9 label, that everything is going to be met as far as the food
10 safety part and the residue part, and obviously, if he or
11 she kills the target species he is after with the drug,
12 there is another factor there that at least FDA isn't
13 interested in, but someone legally is going to be interested
14 in. So, I think all of those things sort of sit there, and
15 I am pretty sure the practitioner understands that as he
16 uses a new drug or it goes off label.

17 DR. STERNER: At least our preliminary attempt at
18 definition I think encompasses those concerns --

19 DR. LEIN: I think it does.

20 DR. STERNER: -- for as broad a species interest
21 or diversity of species interest areas as we have
22 represented here, I don't see anybody jumping up and down
23 and saying, well, wait a minute, you left me out here.

24 DR. LEIN: Joe.

1 DR. GLOYDE: I think one thing you need to
2 recognize is that the reality of whatever you define,
3 whatever you do, what it will accomplish is keep the honest
4 people honest, and those who wish to circumvent the
5 definition will continue to do so.

6 I think you have to recognize that from the get-
7 go, and that is really what you are trying to prevent, but
8 it will still exist.

9 DR. LEIN: Yes.

10 DR. MILLER: I am Dr. Pete Miller, and I just have
11 a comment, and I think that the real crux of the reason that
12 you are here is a regulatory issue, and not so much a
13 guidance for industry and that sort of thing. Anything that
14 you decide, I think has to be worded, so that when it is
15 enforced by the Food and Drug Administration, that you will
16 understand the consequences of that as opposed to guidance,
17 because I really believe that, as Joe just mentioned,
18 anything that practitioners are honestly trying to do, to do
19 it appropriately, they are pretty much aware of the
20 concepts, you have already said it is individual
21 veterinarian decision, and so to come up with guidance on
22 that or to come up with a definition for clinically
23 ineffective or what have you will not impact that.

24 But to directly address Dr. Koong's question a

1 while ago, the real effect of this will be in how in how it
2 is used in a regulatory sort of thing, and so that is my
3 comment. I think that is going to be really the issue and
4 how will that be interpreted by regulatory people both now
5 and in the future.

6 DR. LEIN: Do you want to respond to that, Steve?

7 DR. SUNDLOF: I think you can look at it very much
8 like the veterinarian and client-patient relationship. We
9 say one of the criterion for extra label drug use is that
10 there has to be a valid veterinarian and client-patient
11 relationship, and that begs the question what is a valid
12 veterinarian and client-patient relationship, and so the
13 AVMA more or less defined what that is.

14 As another criterion, you have if the veterinarian
15 judges it to be clinically ineffective, and that is what we
16 are trying to put some framework around, what does mean.
17 Are we going to go out and take regulatory enforcement
18 action against veterinarians that don't use valid
19 veterinarian and client-patient relationships? Sometimes if
20 it endangers the food supply and we would do similar things
21 if we found that veterinarians were using drugs that on the
22 rationale that some other drug was clinically ineffective if
23 it was endangering the food supply.

24 So, we would look at it in much the same way, but

1 you don't see FDA running around prosecuting veterinarians
2 that they feel are outside of the veterinarian and client-
3 patient relationship unless they have done something that
4 directly impacts on the safety of the food supply or there
5 is trafficking of drugs or something else of that nature, so
6 I think you have to look at it really in that respect.

7 DR. LEIN: Steven.

8 DR. BARKER: The safeguards that appear to already
9 be in place with AMDUCA and other regulations, have been
10 passed, that are kind of detailed in Dr. Keller's
11 presentation, I would think that the veterinarians
12 practicing in the field would be clearly aware of that they
13 simply can't do, and that is, one, create a violative tissue
14 residue, use prohibited drugs, create a public health issue
15 or animal safety issue, or have extra label use under cases
16 of economic fraud.

17 Those seem to be fairly clear and the safeguards
18 for all of that seem to be in place, you know, the
19 flexibility on the drug use issue is adequately or will be
20 adequately regulated.

21 DR. LEIN: Other questions? I think we are trying
22 to answer No. 1, and if we agree with what is there, unless
23 there is changes, do I see at least from the committee that
24 we go forward with that statement?

1 DR. BARKER: Could we hear it restated?

2 DR. LEIN: The term clinically ineffective means
3 that in the experience of the treating veterinarian, that a
4 drug or treatment is not responding in the normal or
5 expected time and form and may indicate a rediagnosis of the
6 condition and a change in drug therapy to an extra label
7 drug.

8 DR. STERNER: Practitioners should use their
9 scientific training, experience, and clinical judgment to
10 determine when a pharmaceutical product has been deemed
11 clinically ineffective. There is a recognition that there
12 is an extraordinary scope of species and clinical
13 circumstances which are of a subjective nature. In general,
14 the use of the veterinarian's oath may serve as a guideline.

15 DR. LEIN: Dr. Cleland.

16 DR. CLELAND: I have one question in regard to
17 your definition that you just read, Don. While I recognize
18 that this definition relates to AMDUCA, and that is our
19 charge, I am not sure that we can define clinically
20 ineffective as directing somebody to use an extra label
21 drug, because, in fact, something that is clinically
22 ineffective, we might go to another labeled drug, so I am a
23 little concerned about that portion of the definition,
24 although I understand we are dealing with this in the realm

1 of AMDUCA, but I am just concerned about that part of the
2 definition.

3 DR. LEIN: What if we just say a change in drug
4 therapy?

5 DR. CLELAND: Yes.

6 DR. STERNER: Yes, because you can go to another
7 approved drug that may be used in an extra label manner.

8 DR. LEIN: Yes.

9 DR. KOONG: I like what I heard and I think,
10 Keith, your part of that, I am not sure that -- I think it
11 should be there, but I am not sure it should be part of the
12 definition.

13 My problem is if you use that as a part of the
14 definition you are defining, you use the same word as you
15 are trying to define.

16 DR. WOLF: I think Keith's part fits for No. 2,
17 Question No. 2.

18 DR. LEIN: In a broad sense.

19 DR. KOONG: I would like to say I agree with the
20 definition you stated, the first part, and I think your
21 statement has to be there somewhere, but not part of the
22 definition.

23 DR. LEIN: Yes, Ruth.

24 DR. FRANCIS-FLOYD: Don, I am not sure if I heard

1 it correctly, but I almost got the impression from yours
2 that you started treatment and then you reevaluated. That
3 might be something we will clear up when we get a text to
4 look at.

5 DR. LEIN: It is a little bit of coming back to
6 what Dr. Wolf talked about, too.

7 DR. RAVIS: I am sure without Keith's, yours
8 primarily represents the therapeutic failure, that something
9 has not worked.

10 DR. LEIN: Right.

11 DR. RAVIS: And that we need Keith's to conserve
12 the judgment.

13 DR. STERNER: Then, it becomes the form of where
14 we find it. I am not sure you need to put it in parentheses
15 behind yours or whether it belongs in Part 2, Question 2,
16 about how --

17 DR. LEIN: Sue.

18 MS. HUDSON-DURAN: I think you could solve that by
19 not saying or redefining clinically ineffective, but
20 changing the wording to say that you are using your judgment
21 to find a clinically effective solution or problem.

22 DR. LEIN: Go to the other side of it.

23 MS. HUDSON-DURAN: Right, in a positive approach
24 rather than coming back and saying ineffective, and you

1 realize that these two broad statements are going to
2 percolate hundreds of what-if questions and these will be,
3 "Okay, this came on E-mail, this is what I do, is this legal
4 or is this not legal," because we are being real general.

5 DR. FRANCIS-FLOYD: Sue, I think if you tried to
6 be very specific, you get in more trouble.

7 DR. LEIN: Other thoughts? Do we want to go
8 further into guidelines where we talk now about diagnostic
9 tests? I mean if we put a litany of things down, is that
10 what we want to do, or do we want to stay with these broad,
11 general statements and let the specialty groups maybe look
12 at this and see if they want to define it further?

13 DR. STERNER: If you leave it broad, it takes on
14 more of a timeless nature. If you get down to specifics, it
15 will rapidly outdate itself based on technology and other
16 items that come to the fore.

17 DR. RIDDELL: I agree and I would make No. 2
18 broad, too.

19 DR. LEIN: Is Keith's No. 2?

20 DR. RIDDELL: I can't really tell. It could be.

21 DR. LEIN: Why don't you read it again, Keith.

22 DR. STERNER: I didn't change it to your positive
23 wording, Sue, but I am sympathetic to what you had to say.
24 I like to think of the half full rather than half empty

1 definition, but we are dealing with half empty at this
2 point.

3 Practitioners should use their scientific
4 training, experience, and clinical judgment to determine
5 when a pharmaceutical product has been deemed -- maybe I
6 should put "should be deemed" -- clinically ineffective. I
7 guess "should be" is more prospective than retrospective. I
8 think that addresses a concern about looking ahead.

9 There is a recognition that there is an
10 extraordinary scope of species and clinical circumstances
11 which are of a subjective nature. In general, the use of
12 the veterinarian's oath may serve as a guideline.

13 DR. RIDDELL: I think it is No. 2.

14 DR. STERNER: I think it does, yes.

15 DR. LEIN: Gatz.

16 DR. RIDDELL: I guess I have a point of procedure.
17 If VMAC were to send this to specialty groups, could it be
18 advertised to our membership as something that CVM or VMAC
19 are considering without compromising your ability to do
20 anything?

21 DR. SUNDLOF: Anything that we would do would be
22 in the open public forum. Since this will not be inserted
23 directly into any formal regulations, but may end up at some
24 later date in a guideline, policy, Compliance Policy Guide,

1 it is certainly something that is in the open public for
2 debate at this point in time.

3 DR. LEIN: Other questions? Oscar.

4 DR. FLETCHER: I still have the concern and I
5 liked what Steve said about it. I still have the concern
6 about how does the Agency, for example, collect data from
7 enough veterinarians to be able to say we think we have
8 identified a particular problem area for which we might want
9 to either take some action or we might want to inform people
10 about in some way.

11 In other words, how do you avoid having a de facto
12 process that circumvents all of the approvals? I don't
13 know, and it may be having specialty groups react to this is
14 a way to get their input. I am still trying to think of
15 some mechanism for collecting that next level.

16 DR. LEIN: I think it is the second level you are
17 talking about.

18 DR. FLETCHER: It may not be important. I don't
19 really want to pursue it without thinking about it more. I
20 am just concerned about it. To me there is a difference
21 between what the individual veterinarian is faced with and
22 what, say, all the swine practitioners might be facing or
23 all the poultry veterinarians might be facing that becomes
24 an issue. There ought to be some communication about it.

1 DR. LEIN: Dr. Vaughn.

2 DR. VAUGHN: Maybe I can confuse the issue a
3 little more.

4 DR. LEIN: We certainly need that.

5 DR. VAUGHN: Having been a practitioner before I
6 came to the Agency, and I am fortunately well-schooled by
7 Dr. Fletcher at Georgia, the approach to clinical medicine
8 is a different system than the system that we really use to
9 determine a drug is effective.

10 I think why you are struggling is because you are
11 trying to define the interface between the two. When we go
12 from a clinical standpoint, you make a diagnosis, at least a
13 tentative diagnosis, and then you decide on an assessment of
14 a lot of different factors, somewhat what Dr. Sundlof said,
15 the patient, the owners concerned, and so on, and you set up
16 therapeutic objectives.

17 After you set up your therapeutic objectives,
18 then, you determine from the available drugs which would be
19 the best match, and I would say that in the majority of
20 situations arguably, there won't be a perfect match most of
21 the time.

22 From the standpoint of the approval side, when we
23 look at drugs and determine that they are effective, we do
24 it under defined protocols where we are looking at what

1 would be a reasonably mainstream approach to treating a
2 particular disease. I will give you a more tangible
3 example.

4 Let's say we are talking about bovine respiratory
5 disease. If we are talking about treating animals once they
6 have been moved into a sick pen, and then we are looking for
7 recovery, we may be measuring sick pen days.

8 When we look at treating animals on arrival,
9 coming off of a truck, we may be looking for relapse rates
10 in determining success. So, again, if you go from feed lot
11 to feed lot, depending on their SOPs and treatment protocol,
12 your therapeutic objectives may be entirely different.

13 DR. LEIN: It comes back to staying with a general
14 statement.

15 Diane.

16 DR. GERKEN: Somehow I detect that there is some
17 kind of expectation that something would happen when a drug
18 is declared clinically ineffective for that use, and I am
19 not really sure that I understand why that might be.

20 I understand why it is declared clinically
21 effective, I mean you have to make that determination, but
22 there is nothing that you would have to do with the data
23 when it was ineffective to remove the drug or take action
24 only if there was violative residues, the things that Dr.

1 Keller talked about.

2 So, I don't think that it hurts the drug, because
3 my expectation is that every drug for every use is going to
4 have some kind of ineffectiveness at one point in its
5 career, and, in fact, it is going to be somewhat cyclic in
6 that sometimes for some drugs or for some microbes if it is
7 an antibiotic, it is going to be ineffective in one region
8 and then maybe three years from now, it will be effective
9 again. I mean there are cycles.

10 So, I don't think there is any action from the
11 ineffectiveness or at least I would hope not. Am I correct
12 about that, that you are not going to use that as an action
13 against a drug, is that correct?

14 DR. SUNDLOF: It would be unlikely. Once that
15 happens, once we have approved a drug, and it then either
16 through experience we determine it to be either unsafe or
17 ineffective, really, the burden is on the Agency to provide
18 substantial evidence that that is the case before we would
19 take any action to remove that product from the market, and
20 we are more concerned about the safety aspects than we are
21 the efficacy. That is just our priority of thinking about
22 things.

23 So, the fact that a drug was ineffective, if it
24 was so blatantly ineffective that we felt we needed to take

1 action, we would do that, but if it is ineffective in
2 certain circumstances, but effective in other circumstances,
3 you know, we may ask for relabeling to specify those
4 conditions, or there are a number of other steps that we
5 could take, or we could do nothing at all, but what we would
6 try and do would be to act within the best interests of the
7 veterinarian and the public and the animals that we are
8 trying to protect.

9 DR. GERKEN: I guess I would have a little bit of
10 concern, then, because encouraging people to report
11 ineffectiveness might be, as Keith has said many times,
12 there may be a group of people that have reported it
13 ineffective, but then another group need it, and so if you
14 see quite a few reports about the ineffectiveness from one
15 group that is vocal, if you will -- I don't mean just
16 necessarily vocal -- but I would hope that there would be
17 great discretion about whether you would remove it or not
18 because of not only what I have said, but the cyclic nature,
19 the regionalization.

20 I mean this might come back to bite you if you are
21 going to encourage people to report ineffectiveness. I
22 guess that is the down side I see of regulatory action.

23 DR. STERNER: Diane, just to respond quickly to
24 that, I guess it would be my observation that the

1 marketplace, particularly in food animal, again selfishly
2 speaking here, very quickly determines their judgment or
3 assess in terms of they vote with their dollars, the
4 clinical efficacy, and if you have a product that sees many
5 treatment failures, I assure you that it doesn't rank first
6 in the treatment regimen.

7 I think that our swine colleague, Bucky referred
8 very eloquently to how he goes about assessing that and
9 makes those judgments.

10 DR. GERKEN: I think, then, Dr. Sundlof wouldn't
11 have to take it off the market, it would take itself off.

12 DR. STERNER: Indeed, and I think his statement
13 reflects that there would be extraordinary circumstances
14 before they would initiate removal of that product's NADA.

15 DR. LEIN: Dr. Keller.

16 DR. KELLER: I might just muddy the waters a bit
17 further, not that FDA would do something, but in fact, the
18 adverse experience reports are available under Freedom of
19 Information, and we do, in fact, get periodic casting of
20 nets and screening by industry of their competitor's
21 products to find out what the adverse experience is with
22 their competitor's products, and that information is used at
23 least informally in marketing their products.

24 DR. LEIN: How devious can they be.

1 [Laughter.]

2 DR. KELLER: You could actually see if we had a
3 fairly sophisticated and comprehensive system of clinical
4 ineffectiveness reporting through out adverse experience
5 reporting program, that, in fact, the industry would not
6 hesitate to use that information against their competitors.

7 Now, how believable that would be when they gave
8 it to a practitioner, I don't know, but in fact, they are
9 aware of what is going on and they do use FOI.

10 DR. LEIN: Thank you. Any other decision
11 discussions?

12 Hearing none, do we want to accept these
13 statements basically as the form that we want to pass on to
14 AVMA and on to the specialty groups?

15 DR. BARKER: So move.

16 [Seconded.]

17 DR. LEIN: Any objections?

18 [No response.]

19 DR. LEIN: I believe it is passed.

20 I believe there is no more business in front of
21 this committee today. There is an announcement that Dick
22 would like to make.

23 MR. GEYER: The first thing, if you and Keith
24 could give me copies of your written statements before you

1 leave, I would appreciate that.

2 I would just like to go back to yesterday just for
3 a moment. Yesterday, we opened up a subject that is going
4 to be open as far as the committee is concerned until
5 November, so I would like to give you a word of caution and
6 that is, the specific subjects that we discussed yesterday
7 should not be discussed with the representatives of the
8 animal drug industry between now and the time of our meeting
9 in November.

10 If there is a need for communication, for example,
11 if you feel there is a need for additional information that
12 could come from the drug industry, let me know and I will
13 try to obtain that information. Likewise, if there is
14 information that representatives of the industry groups
15 would like to pass on to you, I will ask them to do that
16 through me.

17 I have no further announcements or other
18 information unless there are any questions about any of the
19 administrative matters concerning the committee.

20 November 11 and 12th are the dates for the next
21 meeting.

22 Thank you.

23 DR. LEIN: I want to thank the committee and the
24 special people that came in to at least represent the

1 different groups that gave their presentations for being
2 here today and yesterday also, and we will see you all next
3 fall, unless Steve has something to state here yet.

4 DR. SUNDLOF: I just wanted to thank all of the
5 committee members and especially all of the special
6 consultants who filled out all those waiver forms, so that
7 they could come and assist us here. Again, thank you. I am
8 very pleased with the outcome of this meeting. Thanks
9 again.

10 DR. LEIN: Thank you.

11 [Whereupon, at 2:40 p.m., the proceedings were
12 adjourned.]