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M O R N I N G S E S S I O N

(8:30 a.m.)

SESSION 2: DISCUSSION ON RISK STANDARD

INTRODUCTION

Dr. Keith Sterner

DR. STERNER: Good morning. I am Keith Sterner. A couple of ground rules if we could. Yesterday, I noticed a number of cell phones going off. Those of you who have cell phones, if you would switch them to vibrator mode or some other form of notification other than distracting from the proceedings, it will help for an orderly proceedings this morning.

I would like to welcome you to the FDA Center of Veterinary Medicine Workshop. I always look forward to Fridays because my favorite radio program is "Science Friday" on NPR. And I think yesterday and today have been and will be about science. Not perfect in everyone's eyes, but this workshop is everybody's opportunity to contribute to the dialogue.

I want to echo Dr. Sundlof's comments that it is of paramount importance to keep differences of opinion to an objective criterion and not to those of a personal nature. Yesterday, we listened to numerous eloquent presentations on the risk assessment. And there appeared to be general agreement from the presenters as well as the panel that the

model was workable within the parameters of the given assumptions.

Today we have a very full agenda. And I intend to be relentless in keeping us on task. Given the intellectual prowess and the large volume of information our speakers wish to convey to us today, my task is somewhat akin to that of trying herd cats.

We all have to eat. As biological entities, it is not an option to opt-out. We do as individuals, however, have choices. Our deliberations here will have significant and far-reaching impact on many individuals and industries not only in the Untied States, but also in the rest of the world.

These workshops that the CVM is sponsoring will help to set policy that will hopefully emphasize and ensure a meaningful, positive public health impact while not creating too great a barrier to the animal, agriculture and pharmaceutical industries that will most directly be affected.

It should be apparent to almost everyone that it is entirely possible that the human health problems discussed yesterday could be far more easily impacted through food processing technology that would render foods of animal origin sterile, at least as far as the point of purchase and that removal of fluoroquinolones entirely or

for that matter all antimicrobials would not ensure that human illness would not or could not occur.

That fact has long been recognized in one food of animal origin. That is milk. Indeed, pasteurization has helped to ensure that a nutritious food product that was safe for human consumption.

Food production and processing, however, are not the subject or the focus of this workshop. We are here to comment on the current state of knowledge as it would apply to the veterinary antimicrobial drug approval process.

If by some small miracle we complete our dialogue on the risk assessment model, we may even broach the subject of thresholds. That may prove to be at best an illusory promise. Speaking as the moderator of this session, I do intend, however, to try and attain that goal. I will remind the speakers to try very hard to stay on time so that we can stay on schedule.

With that, our first speaker this morning is Dr. Alan Rulis. He is with the FDA since 1977. He holds a B.A. in chemistry from Logastana College in Illinois and a Ph.D. in 1972 in chemistry from the University of Wisconsin. Prior to joining the FDA, he did post-doctoral research in chemistry in the Netherlands and Canada and taught chemistry at the University of Toronto in Canada. He will be under assessment of risk looking at food additives. Alan.

ASSESSMENT OF RISK: FOOD ADDITIVES

Alan Rulis, Ph.D.

DR. RULIS: All right. Thank you. Can I be heard in the back there? Am I clear here. Okay. I am going to spend my time to give a broad overview of the safety standard that is used in the food additives area. My responsibility ---

(Audio missing due to technical malfunction.)

--- we are in the Center for Food Safety and Applied Nutrition.

(Slide.)

And the statute that governs --- all the way back to 1938 had an adulteration standard, which you can see up here, 402(A)(1). Food is adulterated if it contains any -- if it bears or contains any poisonous or deleterious substance which may render injurious to health.

But in the case of substances not an added substance, such food shall not be considered adulterated under this clause if the quantity of the substance in such food is not ordinarily rendered injurious to health. So that is the adulteration standard that had been in effect since 1938.

In 1958, Congress enacted the Food Additives Amendment to that statute. And on the bottom, you will see -- and we will raise it up just a little bit -- you will see

a Section 402(A)(2)(c) says it is adulterated if it is or bears or contains any food additive which is unsafe within the meaning of 409. So that clause was added in 1958. Okay. Go ahead and change the slide.

(Slide.)

Now, the Act as we use it in the food additive area, in '58 and '58 amendments, defines food additive. It requires pre-market approval for new uses of food additives. It establishes the standard of review which we will talk about briefly. It establishes the standard of safety which is one of the topics that you are interested in this workshop. And it establishes formal rule-making procedures for effectuating our decisions. Okay, next.

(Slide.)

Just for your edification, there are some characteristics of food additive approvals that are unique, a little bit different from some of the other approval activities that FDA engages in. And I want to just focus on a few of this at this time. The first one is that approvals are safety-based only. There is no explicit balancing of risks and benefits. Okay? Safety per se is the standard.

The kinds of substances that we review for safety in the food additive area are generally not very toxic in comparison to what you might think of industrial chemicals or possibly drugs that have distinct pharmacological effects

on living systems. These effects that we study are generally subtle and chronic.

Food additives are consumed for a lifetime by all segments of the population. So the target population is everybody from infants to aged people. The statute requires that a food additive cannot be approved until a regulation is published in the Federal Register. So there is rule-making required by Section 409. It is formal rule-making and there is an opportunity for objections, hearings and court challenges.

And a Federal Register preamble is usually prepared laying out the rationale for FDA's approval or denial of a petition. Further, the regulations that are issued are generic. They are not licenses in the drug or devise sense. Anyone who is in compliance with the conditions of use laid out in a regulation may add that additive to food, although some additive approvals are protected by patent legislation or patent -- existence of a patent.

Careful consideration of these conditions of safe use is therefore required prior to any decision. And usually in our area, there has not been a lot of extensive pre-filing interaction, although I think we are moving more in that direction. This is in contrast to the drug approvals that the Agency gets. Okay.

(Slide.)

Now, the term, "food additive", is very broadly defined. It is any substance, the intended use of which results or may reasonably be expected to result directly or indirectly in its becoming a component or otherwise affecting the characteristics of any food.

And then there are exclusions. And of course, pesticide chemicals are excluded, animal drugs are excluded.

But it is a broad definition when you are in the food area itself.

We exclude a huge category of substances, those that are generally recognized as safe. And that is a common-sense exclusion that Congress realized they had to put in there because otherwise if you make the food by mixing foods, by this definition, of butter and eggs and vegetable oil, it would be food additives. And, of course, they are not. Okay, next.

(Slide.)

Now, the statute talks about safety, but rather circuitously and in a not very helpful way. It says in effect that the food additives shall with respect to any particular use be deemed to be unsafe unless there is in effect a regulation prescribing the conditions under which the additive may be safely used. But it doesn't here define safely.

(Slide.)

And in the next overhead, you will see, again, it says that the Agency shall by order establish a regulation prescribing the conditions under which such additive may be safely used and the reasons for such action. But again, no definition of safely. Okay.

(Slide.)

Just for your edification, in the process that goes on in the food additive area, petitioners responsible for establishing the safety of the requested use, the burden is on the petitioner. This is a pre-market approval system. FDA is responsible for conducting a full and fair evaluation of the data and issuing a regulation if we believe that the use is, in fact, safe. We do not consider the benefits of the use of the additive.

(Slide.)

The standard of review is a fair evaluation of the data. That is a legal standard, fair evaluation of the data. There is some legislative history behind that. Next overhead.

(Slide.)

References a House report back in 1958. "The Committee feels that the Secretary's findings of fact and order should not be based on isolated evidence in the record which evidence in and of itself may be considered

substantial without taking account of the contradictory evidence of equal or even greater substance." In other words, the whole record has to be looked at.

(Slide.)

Again, the statute, "No such regulation shall issue if a fair evaluation before the Secretary fails to establish that the proposed use of the additive under the conditions to be specified will be safe." Again, no definition of safety here.

And the last part of that long version that I have up there is, in fact, a food additive part, the food additive version of the Delaney Clause which says that a food additive cannot be a carcinogen. Okay.

(Slide.)

The help on the safety definition came from Congress in the legislative history of the Act. And so here we see that safety finally is defined by Congress for us in the legislative history. "Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive."

Reasonable certainty of no harm thankfully was what Congress gave us as a handle to help us deal with this definition of safety. And it has been -- I think some folks have felt it to be not that helpful. Actually, it turns out I think with the tradition of 40 years of experience in this

area and with a lot of thought, the reasonable certainty of no hard standard has become I think a useful tool.

Congress went on in their legislative history to the '58 Act and said that in addition to saying that safety is reasonable certainty of no harm, that the standard does not and cannot require proof beyond any possible doubt that no harm will result under any conceivable circumstance.

So this is an admission, in fact, that science cannot prove things with absolute certainty. Certainly, you cannot prove, you know, a lack of any risk with absolute certainty. So reasonable certainty is what you have to work with. And it is, in fact, a no harm standard.

So what you are after is no harm, but you know that you can't get there except by reasonable certainty. And that means there will be some uncertainty. There will be some residual uncertainty in the decisions. Next.

(Slide.)

So the standard of safety is that the petitioner has the burden to demonstrate a reasonable certainty of no harm from the intended use. And one of the ways we describe this is to say that the -- this requires that the FDA assess whether it has received adequately documented answers to appropriate questions of probative value. Okay, adequately documented answers to appropriate questions of probative value. Okay.

Now, to help tease out this reasonable certainty of no harm definition, we have tried to put a few points up here about what we think it is not. What it is not is it is not an academic inquiry. We are not after the answer to every conceivable question.

It is not a search for complete knowledge. It is not intended to assure, nor is it possible to ensure safety with absolute certainty. In other words, reasonable certainty of no harm is the goal. And what we are not after is certainty of no theoretical possibility of harm. That is sometimes what people think it is, but that is not the goal.

It does not weigh risks and benefits. And it is not intended to enforce or limit consumer choices among safe foods. It is not an ethical standard. It is not a value standard about what foods people should select to eat. Okay.

(Slide.)

What it is -- what it does do, in fact, is ensure safety. It is a consensus decision among our reviewers made under uncertainty. And that provides a fair evaluation of all the data of record. Remember the standard of review.

In the end, it has to protect public health. It is made in the absence of complete knowledge. We admit up front that there will be residual uncertainty. It will withstand scientific, procedural and legal challenge from

all sides. And there will be residual uncertainty, but we try to keep that residual uncertainty not out of line with what has been previously tolerated in the context of all previous similar safety decisions.

So the idea here is that once you have developed an institutional framework and a base of institutional knowledge, you can gage your decisions on whether or not the residual uncertainty is out of line with the decisions you have made in the past. And this is very helpful, although in new areas this can be perplexing because we don't always know all the questions that have to be asked and we are not always sure that the answers purport with the standard of safety. And so in some cases in the new areas, we have to feel our way.

(Slide.)

My last slide is along those lines just to point out that as we move from the trivial situations of tiny exposures to, let's say, even packaging materials. In the upper left, we have low exposure. And at the lower right, we have high exposure. Think of this little road way, sometimes people refer to it as the yellow brick road -- this little road way as a spectrum upon which food additives are laid out from low exposure to high exposure.

The low exposure, we have maybe packaging materials that migrate into foods in minuscule quantities,

parts per billion or less. And in the lower right in the large part of the road way, you will see whole foods, additives that are added in large quantities, macro-additives.

Of course, we don't regulate whole foods as food additives. But there are macro-additives that are added to food and can be regulated that way.

And in the traditional low exposure part of that spectrum, we apply what we call a toxicology-based review. It is a classical toxicological approach that basically uses animal feeding studies, assesses the lowest -- assesses the most sensitive, longest duration study to determine what is the dose, what is the highest no-effect level. In other words, what is the dose that is known not to cause an adverse effect and what is the highest value of that dose in the animal species of the longest duration, most sensitive study.

And that highest no-effect level then is reduced by an uncertainty factor. Typically, it is a factor of 100 that is really two factors of ten that have to do with the variation among humans and the translation of the data from animals to humans. And what you arrive at is an acceptable daily intake, ADI which many of you are familiar with.

That ADI is compared with the likely exposure. We are charged by the statute to determine the probable

exposure to humans in the course of our safety evaluation. The probable exposure is sometimes called the estimated daily intake, or the EDI.

The ADI and the EDI are compared. And when the estimated daily intake is determined not to exceed the ADI, the acceptable daily intake, then we have determined as a matter of science and as a matter of law in this case that we are in compliance with -- the petitioner has met the standard of reasonable certainty of no harm. So that is the classical picture.

Now, when we move into the macro-ingredients where there are lots of other kinds of questions than just simply classical toxicological end points, the picture gets a little more complicated. And in the newer types of additives that we have had to deal with that push more in the direction of macro-ingredients or functional foods, we are also considering nutrition-related questions such as vitamin depletion or gastrointestinal effects.

And Olestra is a good example of an additive that we reviewed that is also -- was subjected to toxicological review in a classical sense, but had, as well, a nutritional component to its review. Nevertheless, the safety standard was the same reasonable certainty of no harm.

And the decision was made in that light and was described. And all decisions on that end of the spectrum

are described in the same way in the Federal Register. Here is the standard; how did we get there, just the logical series of steps that leads you to the conclusion that you have met reasonable certainty of no harm.

So this was just a quick overview of the statutory framework, the standard of use in the food additive area; some glimpse at how it is evolving to take into account new kinds of additives that we have to deal with. And I hope it is helpful to your workshop. And I would be happy to take any questions that you have.

(Applause.)

MS. : I wanted to know what the responsibility of CFSAN is after a food additive has been approved to monitor whether its use is coming up as anticipated? And also, what are the regulations that they are required to go through if they want to withdraw a food additive?

DR. RULIS: Right. Okay. Well, safety is really a function of time. It is not static. So once something is approved, it is not -- it is on the books. And if nothing else happens, it is on the books forever. But we know that safety is a function of time.

So new toxicological information could come up. The exposure could change. And so as a result of that, we monitor the use of food additives over time. We keep track

of their exposures in the population. We monitor literature to determine if anyone has done any studies to raise questions that were not even anticipated when it was approved.

If -- and in particular for the macro-ingredients where we are into new areas of safety evaluation, we will often work with the companies to determine whether they can and will be able to do post-market surveillance and will monitor the use of the additive in the public in a very conscious and explicit way. So there is monitoring. There is kind of assessment of the safety over time of all additives.

If an additive is determined to be unsafe at some point in time, then there is a procedure for getting it off the market. Anybody can file a petition that says here is the safety data. This additive is clearly unsafe. The Agency should pull it off the market. We get petitions like that.

It has to meet all the standards, of course. And you have -- the scientific basis for that decision has to be solid. But we would entertain a petition for that. And there is a regulatory and legal process then for removing an additive. We have done it. It doesn't happen very often, but it has happened.

DR. STERNER: Yes, our next speaker to address the

assessment of risk with regard to drug residues is Dr. Kevin Greenlees. He received his doctorate in cardiopulmonary physiology from Colorado State University in 1983. He joined the FDA Center for Veterinary Medicine in 1989 and has been involved in the review of new animal drugs ever since. He is a diplomat at the American Board of Toxicology and a member of the toxicology team in the Division of Human Food Safety. Kevin.

ASSESSMENT OF RISK: DRUG RESIDUES

Kevin Greenlees, Ph.D.

(Slide.)

DR. GREENLEES: I want to start by thanking Dr. Rulis for laying some very nice groundwork for this talk which was -- we didn't coordinate this. We really didn't work ahead of time. And it is just -- he set such a very nice basis just to make life much easier for me.. :

This talk is really to talk about how we evaluate the risk for the chemical residues ---. It is not going to address anything towards the purpose of this meeting which is a risk assessment or the safety of the consumption of a resistant microorganism.

(Slide.)

When we are trying to put this in a framework of a risk assessment type approach, the evaluation of new animal drugs just like food additives evolved before the current

concepts of risk assessment and how you do risk assessments. But I think you will find that the approach really still fits a lot of the paradigm once you have looked at all of the boxes you need to fit and all the pieces that need to fit together.

It is going to deal with problem identification, the identification and characterization of the hazard that you have concern for, how large is that hazard, what is the acceptable risk level that you are trying to deal with, what is the exposure and how are you going to deal wit that exposure. And I am going to admit right up front that I am going to mix in this both management of the risk and assessment of the risk because I think that gives you a more complete picture of how we ---.

(Slide.)

The problem that we are dealing with is exposure of the human consumer to an unsafe chemical residue of the new animal drug. We heard definitions given of what residues are. And I am going to just briefly tell you that the residue that we are dealing with is the residue of new animal drugs, any added substance that is present in or on the commodity or food primarily as a result of metabolism or the degradation of the new animal drug.

So in other words, it is the drug you administer and all its by-products. You are going to get more about

the definition in the next talk by Dr. Tollefson. I am going to leave it there, again, emphasizing we are talking about the chemical residues.

(Slide.)

When we are talking about what is the hazard, what is your concern, we need to identify what we actually have concern for. Is it the active ingredient? Is it the metabolite in the active ingredient? Is it a second or third order metabolite? Where does your concern lie?

And there are a whole battery of studies which were alluded to in the previous study -- in the previous talk on what are those -- how do you go about doing that. So there are oral toxicity studies which are the standard, you know, rodent assays, 90-day studies, the development toxicity study, reproduction toxicity studies and any special studies that are needed to address the specific nature of that compound.

And for a given compound, you may look at that and decide we don't need one of those studies, again, because of the nature of that compound. The -- in addition to identifying what is it in the residue that we have concern for, what are its characteristics, we are also assessing what is the nature of that toxicity. It is developmental toxicity? Does it cause birth defects? Does it cause damage to the liver? What kinds of toxicity do we see?

We look specifically at the carcinogenic potential of compounds. This is done through assessment of the oral bioassays, the literature and through looking at specific immunogenicity assays. And if necessary, we will go on to make quantifiable assays where we actually are looking for development of cancer in animals.

In recent years, we have started to look at the effects of the drugs residues, the chemical residues in food on the human gut and flora recognizing that it is possible that it may have effects on the gut and flora at lower levels or different levels than you might see in systemic toxicology where you have effects, again, on one of the organ systems of the body indirectly.

And also part of the same characterization process is the residue studies that are required. And I listed here the --- metabolism study because that is probably the big gun is usually where you typically will do a carbon-14 study looking at what are all of the residues, where do they go and what are all the pieces that are in the animal.

But it also is based on other studies which will again characterize the nature of the residues that are in the animal. And between those studies, then you can get a handle on where you have your level of concern and what concern that would be.

(Slide.)

When you have completed that process, you then have to go through each of those studies, evaluate what that information is. And as was again talked about previously, our typical approach is to try and establish a dose to the animal in the animal studies that would have a no observable effect level.

In some cases, you may actually have an effect. And that would be a --- effect level. There are also other approaches such as the benchmark dose which allows you instead of just saying, well, what dose do you not see an effect, it allows you to use the dose response relationship from those doses we see an effect and calculate back to a -- the level which is comparable to a low effect level.

These in turn allow us to calculate or determine acceptable daily intake. And there are other end points such as the reference dose or safe concentration which are also -- again, these just come to say how much are we going to allow in the diet. That's what these numbers mean.

(Slide.)

There is some difference to how you deal with a carcinogen than a non-carcinogen. For a non-carcinogen, we -- as I mentioned, we go through the sub-chronic toxicity study, reproduction, development toxicity. It goes through safety of gut flora. You evaluate all of those studies,

establish the NOEL and you eventually come up with an acceptable daily intake.

If a compound is thought to be potentially carcinogenic, then we also have to evaluate its potential to cause cancer in rodent bioassays. We also make look at some alternative assays. But these are assays the studies insist we design to show does it cause cancer and can we establish a dose response relationship to that cancer.

If the answer is, yes, it does cause cancer and you can then still calculate a dose relationship, then our approach is to determine a one in a million risk level and test --- using a linear low dose extrapolation. We calculate what is the equivalent of acceptable daily intake and the equivalent of safe concentration. So it just builds on what you do for a non-carcinogen.

(Slide.)

The way to use that is you have to have some standard. The standard is the same as that for food additives, that it is the reasonable certainty of no harm. For carcinogens, this is the upper bound of the dose resulting in a one in a million risk level -- the dose -- this can be interpreted as saying the safety of no harm is that dose which will have a risk of one in a million of causing cancer in the rodent that you studied it in.

And the reasonable certainty is established by

having the upper bound, the variability accounted for in that calculation.

For non-carcinogens, it is based on the acceptable daily intake which uses safety factors as we talked about before and to calculate a no effect level.

Unlike food additives where they have an estimated exposure daily intake or an estimated exposure, we assume that all the animals are medicated with the drug. So if this is a drug intended for dairy cattle, we assume all dairy cattle are medicated. We then assume that all of the edible tissues are at the maximum allowable concentration, the tolerance concentration.

We then also -- and this is not on the slide. We also then assume that people are going to consume a specific quantity of that daily. So for muscle, it is 300 grams. For liver, it is 100 grams and so on. The latter -- the consumption factors are based on data, based on --- surveys.

The other assumptions are just that, they are assumptions. But they are very conservative assumptions.

(Slide.)

When you have all that information, we then -- because we are working to a standard to say we are going to have to meet that end goal, we then use other studies to help us get there. So we look at the drug metabolism studies to say, okay, we are going to want to measure this

compound. So you have to -- and we did all of our toxicology based on all of the residues.

We can't measure all of the residues. You've got to have something you can actually get a handle on. So we establish a marker residue which is something that you can actually measure by an assay and say what is the relationship of that marker residue to the total residue. And then you actually develop the assay to go with that so that you can go and measure how much of that compound is actually in the edible tissues. And note how that refers to all the edible tissues.

We establish a regulatory tolerance which is the safe concentration which was calculated in the acceptable daily intake as is all the residues. The tolerance is what you can actually measure of that safe concentration. And you establish a ratio to that. So from the tolerance, you can take a direct line back to say what would be the safe concentration. And then you know whether you are or are not within the acceptable daily intake ---.

We calculate a withdrawal period based on withdrawal studies. So we have already established how much is allowed in the diet. If we say, okay, how long do you have to take the animal off the drug and allow the drug to deplete until you have actually reached that level. And, again, there are conservatisms in here so that we are

confident that not only do you have a safe concentration in the diet and you calculate the safe amount, but you actually are confident that the animal population will have reached that dose, that concentration in the animal tissues.

And there are also other mitigating or management factors. And this is all dealing with risk management. But you notice it is also data analysis at the same time. Where you might have restrictions on the label, there certainly are indications on the label and instructions on the label all of which will assure the commodity is the drug product that is used appropriately.

And there is a post-market surveillance and compliance, again, to be sure that the compound is used appropriately and that they are following the label.

What I did not talk about earlier in the talk, but it takes place throughout the entire process, is the communication process between the Food and Drug Administration and the drug sponsor so that there is interaction throughout this entire process to ensure that we have got the best information and are really on board with what --- the compound and what would be a safe criteria for approval.

Once a product is approved, then it turns to external communication with the rest of the public. And we are dealing with -- we have the label information. You have

freedom of information summaries which summarize all the bases for the approval. And then we also have communication from the drug sponsors on safe and appropriate use of the compound. Thank you very much. I am going to stop there.

DR. STERNER: Questions for Kevin?

MR. : Yes, I've got one. I wonder if you would clarify or elaborate a little bit on the use of the low observed effect level in calculating the acceptable daily intake.

DR. GREENLEES: For some compounds and in some circumstances, you may, in fact, have studies which do not have a no-effect level, but in fact show a low effect level. In other words, you have actually -- the lowest dose administered has some effect.

If you look at the sum total of the data you have, you may elect -- you may determine that you can appropriate establish the safety of the compound by simply using a larger safety factor, a larger uncertainty factor. No effect levels are to some extent a -- it's a product of study design.

How close did you estimate what would, in fact, be a no-effect level dose when you designed the study? You may be right there. You might have missed it. You could -- the no-effect level could be 100-fold lower than the threshold which would actually not show an effect.

So you have to evaluate the study on the basis of your sum total of information on that. But in the cases where low effect levels of used, then an increase is added to the safety factor, usually using ten-fold instead of using 1,000-fold that you would otherwise have been 100-fold safety factor.

DR. STERNER: Thank you for staying on time as a small subtle reminder to our next speaker. Our next speaker is talking about assessment of risk with regard to pesticides is Dr. Roy Sjoblad. He has been at the Office of Pesticide Programs -- see, I am off already -- Pesticide Programs at the U.S. EPA since 1984.

He is currently a Senior Microbiologist in the Biopesticides and Pollution Prevention Division. He is involved in a number of policy issues related to safety and use of genetically engineered microbial and plant pesticides.

And he received his Ph.D. from Pennsylvania State University. And prior to joining the EPA, he was a faculty member in the Department of Microbiology at the University of Maryland. Dr. Sjoblad.

ASSESSMENT OF RISK: PESTICIDES

Roy Sjoblad, Ph.D.

(Slide.)

DR. SJOBLAD: Today I am going to try to give you

some fundamental concepts of how risk assessment and risk management is applied at the Office of Pesticide Programs to pesticides and focus on gentamicin as a specific example of this process and how it normally might function in some of the unique issues that are brought to bear when gentamicin came in.

Please, microbiologists out there, ignore the capital A in amylovora. I know that just drives people crazy if you are a microbiologist. But I a non-microbiologist did the overhead. So forgive me.

I think that we all know that gentamicin is a glycoside antibiotic, very important. The World Health Organization considers it one of the 15 or so essential drugs. So I won't belabor that point.

In this short talk, we are going to be condensing a five-year process into a little over ten minutes. And so I am going to focus on some essential concepts. Basically, gentamicin came in as a conventional chemical pesticide. Okay? And the proposal basically let's say for simplicity was in the aerial spray on apple orchards to control the gram negative Erwinia amylovora which is an enterobacteriaceae.

The use rate was a very low rate, about six grams AI per acre if I recall, and up to nine applications for a growing season. Pretty much if there is a -- whether a

model would be used to determine whether Erwinia might be a problem and, therefore, the spraying schedule started as sort of a prophylactic treatment.

To understand the risk assessment and risk management process with gentamicin, I think we need to see a little bit about the structure and the function of the risk assessment and risk management branches in the Office. And I have listed six of the ten divisions are shown.

(Slide.)

Starting in the upper left, the Environmental Fate and Effects Division is a risk assessment division. They review data that the registrant submits on nontarget organisms, birds, fish, honey bee. They also look at data that are submitted, studies that are submitted on the fate of the particular active ingredient or pesticide in the environment.

Going down the Health Effects Division, they reviewed data that are submitted on mammalian toxicology. They also review product chemistry data, mainly the impurities in the formulation and also exposure data.

The Antimicrobials Division is a risk assessment and risk management division combined in one division. They basically perform the risk characterization of chemical disinfections with public health uses. And almost all of their products do not create that microbial resistance as

would a standard clinical drug or veterinary drug wouldn't.

And Dr. Nulent here who is doing the overheads can answer any questions you might have on that particular newly formed division.

I am in the Biopesticides and Pollution Prevention Division. It is a risk assessment and risk management division. We handle the microbial pesticides whether they are genetically engineered or not, --- plant pesticides and biochemical pesticides. And biochemical pesticides are naturally occurring materials that control the target pests by a nontoxic mode of action. And these would be things like phermones for instance.

Going down here, the Registration Division is a risk management division. And they -- all the information first comes into them for distribution to the relevant divisions for conventional chemical pesticides. Okay. If I could have the next overhead.

(Slide.)

I am just going to focus a little bit on the types of information that the Health Effects Division reviewers would be reviewing and summarizing and characterizing just as the previous speaker pretty much said. So that was -- you could say this data would be used, too, in a similar fashion.

Notice we have a battery of acute, sub-chronic

studies, chronic studies in a number of different types of animal species. I don't want to focus -- I don't have time to focus on the specifics. I just want to get some concepts across, that the registrant is responsible for having these studies conducted. And they are done under GLP.

The registrants can request waivers based on scientific rationale. And the Agency will consider those requests for waivers. And, again, the data are used to identify hazard to applicators, workers, pregnant women, children. Dietary risks are evaluated in much the way that we heard previously.

Now, this is the type of information that was sent in for gentamicin, to support the registration of gentamicin in pome fruit orchards. Now, if I could go back to the previous overhead.

(Slide.)

The information when gentamicin came into the registration division, they take the data packages and distribute the relevant studies to the Health Effects Division or the Environmental Fate and Effects Division. And those go out for review. The reviewers then will summarize the data and the risk assessment will be done in the divisions. And then that is sent back to the Registration Division.

Gentamicin came in in about 1994, went into the

Health Effects Division for review. And a toxicologist with microbiology experience, Roger Gardener, in the Health Effects Division was getting -- got this information under the secondary review process that goes on and had some questions about the potential for antibiotic resistance. He had not even considered this gentamicin as going through the standard process as a conventional chemical.

He happened to -- he just called me in the Biopesticides Division. And I got together with John Cowen and we went over and talked to Roger Gardener. And the next overhead will sort of summarize the events that occurred subsequent to this.

John Cowen and I and Roger basically drafted a memorandum advising HED on some of the uncertain nontraditional hazard identification issues related to gentamicin. Now, I think it should be clear that we had no established process to address these unique issues of potential risk from pesticidal use in the environment of clinically useful antibiotics.

(Slide.)

So we did consider that antibiotic resistance development and its maintenance and its transfer were potential hazard components of the risk assessment process. We concluded form all of the available information that the proposed aerial spray and orchards will select for

gentamicin-resistant bacteria. And there was a strong possibility that the gentamicin resistance trait would be transferred to clinically important isolates. And the next overhead.

(Slide.)

This event could render gentamicin less effective or ineffective in the clinical setting. Now, right around this time, the Registration Division had gotten together -- had published in the Federal Register notice a proposed tolerance of 0.1 ppm of gentamicin in apples.

And this caused organizations like the American Society for Microbiology, Centers for Disease Control and the FDA Center for Drug Evaluation and Research to respond by showing their concerns about the potential for risk from use of gentamicin in the environment, okay, and the similar concerns as to the ones that the OPP staff generated were expressed by these agencies. And some of the key people are in the audience that were involved in some of these letters and also in an inter-agency panel that met, comprised of people from EPA, CDC, FDA and USDA.

So we concluded, too, with respect to, say, risk mitigation. That became the issue, you know, the subsequent issue. Can you mitigate this risk? We believed that there was really no amount of reasonable study, either economically or scientifically, amenable type research, that

the registrant could perform to provide reliable and predictive information to the EPA which would alleviate concerns for the risk of loss of gentamicin as an effective clinical antibiotic.

Okay. Under FIFRA, the Federal Insecticide, Fungicide and Rodenticide Act, it is really the responsibility of the pesticide registrant to provide the information and data to address identified hazards, even if they are beyond those that come under the traditional toxicology data setting.

I think to conclude, the process really thus far has been a useful model whereby there has been inter-agency communication which supported a risk management decision based on the best available scientific information and data. As a result of this process, the registrant has -- did withdraw its petition for the proposed use of gentamicin as a pesticide.

I want to say that the inter-agency panel when it did convene also was asked about exposure issues and mitigation of exposure by different types of processes that maybe an antibiotic like gentamicin could be used. And it was certainly not concluded that there could be some level of exposure which would not trigger these resistance development, maintenance and subsequent transfer. So that concludes my presentation.

(Applause.)

DR. STERNER: I can see our speaker are adhering to the threat that was made earlier at the start. We are moving along nicely. There is time for questions. Okay. Thank you very much.

Dr. Dick Whiting will go ahead and address our -- be our next speaker talking about microbiological risks. He has an active research program modeling the growth and survival of food-borne microbial pathogens. This ranges from formulating new mathematical models to composing a personal computer software program to make the models easily. Now, there is an oxymoron, isn't it, user-friendly software, and widely available.

The concept supporting the linkage of predictive modeling to a HACCP program through microbial risk assessment are currently being developed. Previous research has included the quality of microbiology of low salt meat products and the role of meat biochemistry in determining quality.

Dr. Whiting received his BS degree from the University of Wisconsin, his master's of science from the University of British Columbia and his Ph.D. from Oregon State University, all in food science. He conducted research with the USDA Agricultural Research Service from 1977 to 1998 and joined FDA CFSAN in 1998.

He has over 85 publications and 90 presentations, and was a member of the Microbial Food Safety Team that received the USDA Departmental Awards for developing pathogen models and the FSIS team that conducted the Salmonella enteritidis in eggs risk assessment.

Current activities include the Listeria monocytogenes risk assessment and the CODACS Committee on Food Hygiene. Dr. Whiting.

ASSESSMENT OF RISK: MICROBIOLOGICAL RISKS

Dick Whiting, Ph.D.

DR. WHITING: Thank you very much for the introduction there, Keith. And it is my pleasure to be here and talk a little bit about microbial risk assessment. And microbial risk assessments are really a new area. I think there has probably been less than a dozen, say, full microbial risk assessments that have been done anywhere in the world at this point.

Within the U.S. Government, we did the Salmonella enteritidis in eggs risk assessment a year ago. That was the first one. Being presented today downtown, the USDA is talking about their E. coli 0157:H7 risk assessment in ground beef. Within the Food and Drug Administration, we have a risk assessment on Listeria monocytogenes and one on Vibrio parahaemolyticus ongoing right now. So this is a new area and we are sort of inventing microbial risk assessment

as we go.

I see the risk assessment as really a pre-regulatory process. In other words, we see the risk assessment as basically an information-gathering and evaluation process. And in that, we follow the recommendations that have come out that risk assessment and risk management should be kept sort of separate.

We see the microbial risk assessment of trying to follow the paradigm that has been developed by the chemical people, that is risk assessment, risk management, risk communication. And within the risk assessment area, we talk about hazard identification, exposure assessment, dose response and risk characterization.

And in short, you know, the risk assessment determines, you know, what can happen, how likely is it to happen, what are the consequences. Or you can say the risk assessment determines what do we know and how certain are we of what we know.

Now, when it comes to trying to do a microbiological risk assessment, we have had some real problems doing this. It is a new area. The data gaps are quite large in the field of microbiology. I suspect that is because most people who have had an inclination for science decided to go into microbiology because they didn't like math and statistics. So this is now coming around to haunt

us when we try to do risk assessments.

You know, microbiologists just don't develop models when they publish papers. They don't characterize the variations and the standard deviations. And they love to do that presence-absence type of analysis which, you know, just doesn't get us too far when it comes to risk assessments.

But we do have despite saying we are following the paradigms of -- that have been pioneered by the chemical people, we do see some real differences in microbial risk assessment versus some of the others. In microbiology, we are generally concerned about acute situations and single doses. The statistics say you are likely to get a food-borne illness about once every ten years. So, you know, the chances of having two in a day are rather low.

And we also think about acute illness. But even as I say this, I realize there are some exceptions. We are beginning to talk about long-term sequelae to some of the microorganisms, Guillain Barre syndrome, HUS from E. coli or reactive arthritis from Salmonella.

And we also realize that perhaps chronic exposure to low levels of certain microbial pathogens may affect your susceptibility to when you are exposed to a large dose or is there maybe some sort of immune type response going on here. But at this point, we just really don't know enough to do

much in terms of risk assessment or modeling of this.

One big difference with microorganisms is we can't just keep diluting them. Eventually, we get to one bacteria. And at that point, we then have to start talking about probabilities of occurrence. In other words, if you have one big tank, we can talk about one bacteria surviving a pasteurization process in 40,000 gallons perhaps.

But then you begin to put it into an individual carton for retail sale. And we eventually get down to one bacteria which is now in, say, one package out of 100 or one package out of 1,000. So we have to now switch from sort of a quantitative level to more of a probablistic type of hazard assessment.

But perhaps the biggest difference with microbiology is bacteria can grow. And if there is an abuse period with a food, it is not unreasonable to see 100,000-fold growth. Certainly, a 1,000-fold growth is very likely. So -- and also, we can see a similar sort of decrease. If we do a pasteurization step, we can see a million-fold or more decrease in the levels of pathogens within a few seconds.

So what we then have is trying to put together a food process model we call it or a process risk assessment in which we take the food from the raw materials and go through the various processing steps including

pasteurization, but also storage, transportation, you know, all the way to the consumer and try to model the changes in bacterial numbers as they go up and down through this whole process.

And this then becomes a very major part just in terms of size and complexity of the microbial risk assessment. But we are I think very close now to being able to do a process risk assessment like this. And despite Keith's comment on our pathogen modeling program, I would encourage you all to take a look at it. I really do think it is quite user-friendly.

And, you know, I think we are there to where this type of risk assessment can be done. And we would really like to see a PC in a program like this on every food microbiologist's desk, particularly in industry, so that people in the food industry can look at their particular food processes and do this type of calculation.

And then that kind of becomes the underpinning for a HACCP Program. Now, I don't know if you people are familiar with food industry and the HACCP, Hazard Analysis Critical Control Point Program. But I see the current efforts in this area are basically sort of qualitative.

That is, when they develop a HACCP, they look at each step separately. You look at the raw materials and you put into play certain standards and reactions to things out of

specs. for that step. And then you look at the pasteurization step. And then you look at the storage step.

But now that we can do this process risk assessment and actually model the whole flow from raw materials through, you can put all of this together. And we can compare one step in the process versus another. And maybe two processes are slightly different. But we can then evaluate at the end and say are they equivalent.

One step might rely on -- or one process might rely on good quality raw ingredients where another process might have a pasteurization step. I think about, say, fresh orange juice right now. Some people do not want to pasteurize orange juice. Can we evaluate one process that uses it versus one process that does not? And I think we are beginning to be able to do that.

This then leads us to a calculation of the number of pathogens that might be in the food at the time of consumption. So we have, say, 2,300 Listeria in a serving. So what? Is this a hazard or is this not? And this then leads us into the dose response section of the risk assessment. And I would say this is probably one of the weaker links at the moment. But, you know, we do have some idea, certainly compared to some of the chemical hazards like radon which they are trying to argue over what is a serious level.

We do know for E. coli 0157:H7 that from ten to 100 organisms is enough to be a serious threat to a child. We do know a little bit about food matrix and that that affects the effective dose. We know that there is a lot of variation between one strain of a pathogen versus another. And we also know something about the wide variation in human susceptibility to these different bacteria.

I would say these food-borne bacteria are generally opportunistic organisms. That is, they like to strike children, elderly, various immunocompromised people and pregnant women. So we are making progress in research in this area. And I think most of the gains will probably come from improved epidemiological investigations. You can't really run experiments particularly on the susceptible population that we are most interested in. But with careful investigations of outbreaks that do occur, we can get much better information.

An example of this is there was an outbreak of Listeria in Finland last spring that occurred in a hospital with severely immunocompromised patients. It was due to relatively low levels of Listeria in the butter. But we can analyze the butter. We know how many organisms are there. We know how many people consumed the butter. We know how many got sick. We can really begin to characterize the dose response for this one outbreak.

So we are at the point now we can calculate the amount of bacteria in the food. And then we can look at the dose response. And that then leads us to the question then of what kind of standards are we now going to set on this. How do we set the standards? Who sets the standards? And what sort of process do we have?

And I would say for food microbiology right now, we really have not gotten to the point of really addressing these questions yet. You know, we have talked about food, I think both from the public and certainly the government side, as saying your food is safe. And, you know, as a risk assessor, that word, "safe", is really one I don't like. I mean, safety, as your previous speaker said, is an absence of risk, an absence of something.

And, you know, to say one food is safer than another, I mean, a food is safe or not safe. I mean, in a certain sense, the word, "safer", is not really a logical term. What we prefer in risk assessment is to talk about a hazard which could be Salmonella. That is something specific. And then we can talk about the risk of that hazard, so many Salmonella per gram or a certain probability of illness from consuming a certain number. So we can talk about the hazard and the risk.

But what is an acceptable or tolerable risk from the various food-borne pathogens is a question that we

really have not begun to face yet. And I don't pretend to come up here and say I really know the answers to what that should be. I think there is a consensus we want to do better from where we currently are.

And perhaps just for discussion, I would throw out the figure that CDC statistics say that we get a food-borne illness about once every ten years. There is about 1,000 meals a year. That means your chances of getting illness from lunch today is about one in 10,000. Now, is that high or low? This is a decision, something we have to think about.

Should the risk be the same for all of the various food-borne organisms? Should Salmonella and E.coli be considered the same? I would say probably not because some of the organisms have much more severe consequences than others. E. coli, for instance, causes hemolytic uremic syndrome. It can cause death and severe kidney failure in children where Salmonella for the most part just makes people sick for three days.

Should the risk be the same for all foods? Again, I would say probably not. But nobody has really discussed this. Should we have the same risk for different populations, different sub-populations? Should we have the same standards for children? Should we have the same standards for nursing homes and other institutions?

What sort of choice should we as consumers have? If I like my eggs sunny-side up, if I happen to like raw oysters, should I have the choice to consume those foods or not? What is the acceptable level of risk? Should it be based on current standard practice? Is that a good place to start? Perhaps it is.

But then again, we have found in recent years that many of our traditional foods are not quite as safe as we thought they were. We thought eggs were safe until a few years ago. We have seen problems with fermented meat products. We have seen problems now with fresh orange juice. Foods that we had considered safe, we are suddenly finding there are some problems.

Should we base our level of standard on what is considered the best feasible technology? But then, of course, that brings the cost factor into what is feasible technology. For example, on eggs, there is about one egg in every 20,000 which is contaminated with Salmonella enteritidis.

There is a process that you can pasteurize in-shell, whole eggs with a hot water treatment. And that will inactivate any Salmonella and it costs about 24 cents a dozen. Should we mandate this for protection or not?

I really don't know the answers to any of these. But I think we must begin to, you know, face these questions

and begin to discuss them. And the answers to these are really a public and societal or political decision. This is not a scientific decision.

So, therefore, in conclusion, I would say what I am most certain of, that there is a lot of communicating that we have to do over the issues of food microbiology. Thank you.

(Applause.)

DR. STERNER: Any questions for Dr. Whiting? Yes.

MS. : Dr. Whiting --

DR. STERNER: Could you go to the microphone?

DR. WHITING: I can't hear you.

MS. : Okay.

DR. STERNER: We are fixing that.

MS. : In the risk assessments that you mentioned as having been done recently, the E. coli, the Vibrio, Listeria, the S. e. in eggs, did you take that to the human health impact like we did in the Campylobacter risk assessment? In other words, did you use the FoodNet data from CDC to look at the ill humans and try to associate that with the dose that you calculated in the product?

DR. WHITING: Yes. All four of those have tried to do that. You can find the Salmonella enteritidis on the internet if you go into the USDA FSIS, Food Safety and Inspection Service, and then Office of Public Health and

Safety. And it is available there. And it has a series of modules. And one module is called the Public Health Module.

But the Listeria one, trying to determine what we know about the dose response is one of the major parts of that risk assessment. So, yes.

DR. STERNER: Well, we have talked about food and now we are up to water, or down to water depending on how you want to look at it. And I think that the room temperature is moderating a bit. And my glass is not ice yet, but there are times where it feels a bit like it.

Our next speaker, Dr. Steven Shaub, is a microbiologist. He received his bachelor's degree from Washington State University and his Ph.D. from West Texas, University of Texas at Austin. Excuse me, a Longhorn.

And from 1992 to the present, he has been with the United States Environmental Protection Agency's Office of Water in the Office of Science and Technology. He is a Senior Microbiologist there. And he heads up the pathogen risk assessment methodology development. He supports the drinking water and recreational water regulation development. Dr. Shaub.

ASSESSMENT OF RISK: WATER

Steve Shaub, Ph.D.

(Slide.)

DR. SHAUB: Thank you, Dr. Sterner. Well,

probably a lot of you are not aware of the fact that EPA Office of Water actually is considered one of those food agencies. So we really do have a link to the food. In the President's Food Safety Initiative, we were one of the members of the governmental groups that was identified to help protect that nation's food supplies. Next viewgraph, please.

(Slide.)

Because we had a couple of questions that really needed to be answered for the panel I guess today, I kind of modified my slides a little bit to talk a little bit about some of the needs we have for the panel discussion. Within the EPA, we are actually now required by regulation to use a risk-based approach to how we actually develop our regulations to protect the general population.

And I would emphasize that generally all of our regs. are for the general population. But within the new criteria, we do have to evaluate and consider the risk of children and other sensitive populations.

One of the things that we kind of -- the approach we are using right now is the fact that if we do have a sensitive population that would have a significant or severe or fatal outcome from some chemical or microbial in water, then we will actually provide special guidance which would be presented to the people with this problem or their

clinicians or whatever so that these people would be protected.

One of the best examples we have the EPA and CDC have put out guidance to the people who are affected or impacted by AIDS so that we actually have a boiled water guidance document out to them so that they can reduce their risk of cryptospridiosis which often can have a fatal or very severe outcome. Next viewgraph.

(Slide.)

Just a couple of examples. In terms of how we are using risk as far as our development of our regulations, first of all, under the Safe Drinking Water Act which was re-authorized in 1996, again, we are trying to protect the general population.

And one of the things that is probably peculiar is the fact that we do have a risk number. Actually, we target one in 10,000 yearly risks to the general population as being appropriate for drinking water safety. And this is designated specifically against enteric diseases.

The approach that we have used is to establish a worst case organism. And this is possibly open to some suspect I guess in terms of our selection. But what we have done is established these worst case organisms based upon their probable occurrence in water, their potential to cause a disease, and their likelihood of getting through a water

treatment system and actually then causing an exposure.

Classically and even currently, we are still working with two general worst case organisms. We currently require a three-log reduction of Giardia from water and a four-log reduction of enteroviruses -- excuse me -- in the treatment process to reach this risk target level of one in 10,000 yearly risks.

In the future, in fact, what we are working right now is in a meeting earlier this week with our EPA's Federal Advisory Committee to look at enhanced surface water treatment rules which will begin to initiate within the next couple of years. And we are changing from Giardia to Cryptosporidium as the worst case target because we know that the significance of this as far as getting through treatment is much greater than Giardia.

What we are trying to do is look at whether or not we need to target the removal requirements on the water shed concentration approach. In other words, do we really stage or increase our level of treatment based upon the likely occurrence of this organism in various types of water scenarios on a water shed basis.

So you may have some systems that may only have to remove two orders of magnitude of Cryptosporidium based upon a very low occurrence of the water. Others, you may have a very significant occurrence concentration which you may have

to remove four or five logs of Cryptosporidium.

It is a very big concern of the industry and the water treatment industry because the potential cost associated with a five-log removal are very great. If everybody had to do that, basically, the additional cost to the water industry would be in the billions of dollars to implement those kinds of protection criteria.

One of the things that is unique about our -- having surface water treatment rules is that we don't have a maximum contaminant level like we do for most of the chemicals. And the main reason for that is that we can't really measure accurately the microorganisms that we are concerned about.

In other words, the enteroviruses and Giardia or Cryptosporidium, we just don't have adequate methods. So we have to use a treatment rule. So we do designate that a particular system has to have in place a capability to remove these levels of organisms which we think may occur in the source water.

One of the things also which is the fact that the states actually do the monitoring of the compliance of this. And then they report to the Federal Government or the EPA as to how well their various utilities are performing.

One of the things which is also associated with the development of the enhanced surface water treatment rule

is the fact that when we are developing this, we actually have a risk-risk kind of a trade off which we are looking at.

So our risk assessment approach is more convoluted because when we protect against Cryptosporidium, we are also going to have to make sure that we are not in that process of treating introducing large amounts of disinfectants or disinfectant by-products that could be toxic to our consuming public.

So basically it is a balancing act. We want to make sure that we have a process that is going to get rid of the organisms, at the same time not to give a toxic load of disinfection by-products which are potentially carcinogenic to the population. Next, please.

(Slide.)

As an example under the Clean Water Act, this is the other side of the EPA's water story. This is basically making sure that waters are swimmable, fishable and drinkable. And just as an example for how we are using the risk approach there, for recreational water criteria, we do have the risk-based approach. And this is against acute gastrointestinal disease.

And, basically, what has occurred in this is a number of indicators were actually tested during the late '70s and early '80s against various types of disease out-

points, and particularly the acute gastrointestinal disease in actual epidemiology studies which they showed the relationship of the indicator organism levels versus the particular level of disease outbreaks which are actually occurring.

So, basically, this, you know, gives us our risk-based approach. And what we have come up with is the fact that we do allow 19 acute gastrointestinal illnesses per 1,000 swimmers per exposure a day for green waters and eight for fresh waters. So we really do have here, again, a -- we really do allow a particular exposure level and a particular illness level that can be associated with that particular activity.

The reason we don't have as stringent requirements is the fact this is a voluntary activity. People don't have to go out and swim in our nation's waters. Obviously, we don't like to see this kind of a scenario going on. But at least the public historically has accepted this as being appropriate for this particular kind of level and they accept this amount of illness.

One of the things that is of concern to us right now and we are trying to work on this is the fact that the current criteria are not protective against upper respiratory tract, skin, eye, ear, nose, throat, severe gastrointestinal diseases. They are only really known from

a risk basis to be protective against acute gastrointestinal disease.

The way this approach works is that we do establish the criteria. And then the states adopt these. And they are actually the ones that are responsible for monitoring and ensuring that their beaches are safe. Next, please.

(Slide.)

Okay. Turning to our current approach, as Dick Whiting mentioned to you, risk assessment really is a new science for microbials. And we have been working on this for a number of years. It's rather a slow pace, but we are starting to generate more speed now, especially now that we do have to have risk-based regulations.

Through a co-op with the International Life Sciences Institute, we have been developing a framework for how we should be dealing with pathogens in various types of water media. And actually, if you want to get the full detail because I am not going to be able to really get into it in much detail today, if you look at least a reasonable summary of where we are, look in Risk Analysis Sub-volume 16.

And one of the things this is -- it does fully consider the unique aspects of microbial pathogen exposures and human health effects. We recognize -- at least we think

that the National Academy of Science-NRC model for chemical risk assessment really isn't appropriate, I guess in conflict with -- I guess we feel that really we need to address some of the more unique aspects of microbials and the host populations and the overall association of health effects and pathogen exposure.

And one of the things that did come out of this is that we pretty much followed the framework for the EPA's ecological risk assessment process which has actually gone through the EPA's risk assessment forum now and actually is considered a full-blown risk assessment protocol. Next slide.

(Slide.)

Just to show you the general approach that is being used for the framework, it is really no different than anything else that you have probably seen as far as doing the risk assessment, as far as the general approach. We have the problem formulation which the concepts, focus and the breadth of magnitude and the target end points are developed.

Then we go through the analysis phase which actually is characterizing the exposure. In other words, where is the organisms out there and then what are their health effects. And going through risk characterization after that.

One of the things you will notice, we have these arrows. We think this is a highly iterative process. We think that all the way along through the risk assessment, that they really need to look back and see how you are addressing the problems, whether or not you are getting plausible answers and whether or not they are reasonable, going to other ways you develop risk assessments for other types of regulatory procedures.

One of the things, EPA actually has a formalized approach now to how we are doing risk characterization. It is in the draft right now, but we expect this to be completed probably early next year. And this lays out all of the criteria of what needs to be done when you are doing a risk characterization.

(Slide.)

The -- to get down into the assessment end of things which is basically where I am going to focus the rest of the day, you have the characterization and exposure in which you are characterizing a pathogen, what makes it a significant concern from the standpoint of what kind of infection is it likely to cause and how is it going to be out there in the environment as to getting out into the exposure scenario and looking at the human exposure to that pathogen, and then coming up with the exposure profile where you have all the uncertainties, assumptions and various

models and things like that which are used to actually establish that final analysis of the total exposure and the characterization of the human health effects and the host characterization, looking at the dose response analysis and the health effect.

Again, one of our weakest points we have in micro. right now is the fact that we don't have a lot of good dose response data to complete our risk assessment. Anyway, coming up with the host-pathogen profile again, all your assumptions, uncertainties, models, things like that which are utilized to then feed both of these into the risk characterization. Next, please.

(Slide.)

Ilsie was kind enough to prepare -- I don't know if we can get it all in there now, yes, as you can plainly see. I just wanted to bring up -- and I realize this is too busy and too small to see. But one of the things -- actually, this is the water risk assessment framework which we have now versus the ecological framework versus the old NASA chemical risk assessment approach, CODEX approach and then -- I'm not sure what this one is. Maybe somebody else here probably knows.

But anyway, as you can see, if you look at all the various phases, I mean, really they are all pretty similar. I mean, there are little nuances in terms of how they are

implied. But really, the end product really pretty much is almost always the same. Next, please.

(Slide.)

Well, anyway, I am not going to have really a chance to really go through these in any depth. But for the analysis phase, I might just -- what I am trying to do is be consistent with where CODEX is going as far as their classical definition. So I will just -- I won't have time really to go through it anymore.

But just as far as pathogen characterization to evaluate the characteristics of the pathogen, or in our case, surrogates, we oftentimes don't deal in water with the direct pathogen. We are typically using surrogates such as E. coli or something like that to really determine the effect of the ability for the transmission to have caused disease in the host and some of the criteria and things which are incorporated into that. Next, please.

(Slide.)

And just continuing on with other things that are part of that exposure scenario. One of the things which we are really concerned about is the strain differences, especially with Cryptosporidium right now. We are -- obviously, there has been three studies now done on Cryptosporidium and oral dose response. That is EPA sponsored.

We have almost a 50-fold difference in the human dose response associated with that. So -- and those are just the animal strains. Those aren't even the human strains. Nobody has done the dose response for those.

(Slide.)

Moving on to the pathogen and hazard occurrence, this is the frequency of the appearance of a pathogen or its relationship to the surrogates in the media of concern. Some of the things real quickly that I think are really important to us is that there is a very dynamic situation in most water supplies.

It is not a constant. You have very, very large orders of magnitude, shifts in what is present in the water supply which impacts on your treatment efficacy and things like that. So it is very important from the water standpoint.

(Slide.)

One of the other things which, of course, with water is important is the fact that microbes and certain types at least of bacteria especially amplify in water. Others die off. There is persistence of some based upon various types of water characteristics, things of that nature.

(Slide.)

In the exposure analysis, it is to characterize

the source and temporal nature of the human exposure to water-borne pathogens. Obviously, we have got recreational drinking. We've got sewage, sludge, waste waters, re-use of water, things of that nature. We assume 100 mls for swimming-associated exposures. And now we have come up with a new exposure level for drinking water which is 1.2 liters rather than the old two.

(Slide.)

Some of the other things. I won't go through that. Everybody -- it is just common to every risk assessment.

(Slide.)

As far as characterizing the human health effects, we need to evaluate the ability of the pathogen, again, or the indicator relationship to cause an adverse health effect under the prescribed set of conditions we are dealing with and just some of the tools which we have available to identify those approaches.

(Slide.)

The host characterization it to evaluate the characteristics of the potentially exposed population that influences susceptibility to a pathogen. And, again, some of the tools and things which need to be considered. Next, please.

(Slide.)

Again, characteristics that influence those effects. Obviously, all the things that humans do to cause them to be exposed and the various things which influence their ability to become infected.

(Slide.)

The health effects, the clinical manifestations of disease associated with specific pathogens, we have to consider both the acute gastrointestinal disease, chronic disease, and diseases that might impact on other organs of the body, especially through various types of sequelae. Next, please.

(Slide.)

Dose response analysis, to characterize the relationship between pathogen dose, infectivity and the manifestation and the magnitude of the health effects in that population. We have the various tools, epidemiology studies, feeding studies and animal studies. We have some real concerns for most animal studies whether or not they can really prescribe the human condition.

I know I am involved in a work group of FDA to look at this. I think there is a lot of problems with using animal models. Next, please. That was -- oh, okay. Gee.

(Applause.)

DR. STERNER: My apologies. I forget to start the timer. But it was about four minutes that elapsed. Are

there questions for Dr. Shaub?

MR. : Yes, I've got one, Keith.

DR. STERNER: Thanks.

MR. : I wonder if you have any occasion to apply any standard for introduction of a pathogen into water by any kind of industrial or community activity. I am just thinking here of an analogy in the drug situation where the issue is really kind of creating a different type of pathogen by some activity. I am just wondering if there is an analogy in the water area.

DR. SHAUB: Well, certainly, we are very concerned about biotechnology, industrial things. We are very concerned about emerging pathogens from whether they are coming from, you know, other countries or whether or not they are coming from our own modification of our procedures in terms of bioengineering, modification of genetics, things like that.

We, I think with CDC, are keeping a vigilance for these kinds of things. And certainly, we have what we call the contaminant candidate list which we have identified nine pathogens which we think have emerged or re-emerged which either because of their health effects or the fact that they are now being found in the United States in water supplies and that they have the potential to defeat our current water treatment distribution systems.

We are looking at those. So if we do, we are going through the process with each one, a risk-based process to look at the potential to be a problem. If they are a problem, we will actually establish new regulations based upon their likely concern on a national basis. Is that kind of where you were going?

MR. : Just one follow-up, Keith, or -- is -- how about for current pathogens? Let's say, for example, in industry something is going to get introduced into water, treated water into the water supply. Do you sort of exercise a log reduction standard or something of that sort for viruses or bacteria that are currently existing?

DR. SHAUB: Well, yes, I -- what we try to do basically is if we know what the general source water occurrence is, basically our whole scheme is to define the treatment requirements that would reduce that down to a level where we would have no more than that one in 10,000 yearly risk of infection.

So, basically, the treatment level is going to be geared to the source water concentration levels. In other words, we have a 10^3 level of source water. And then maybe we only need to remove maybe two orders of magnitude of that to maybe be protected. If you have a 10^5 level of material in source water, then you would have to boost your treatment

up two orders of magnitude to give that same level of protection.

DR. STERNER: In the years that I've had as a speaker, my worst nightmare is to wake up far past my appointed time to go ahead and speak. And I am at a point as a moderator of embarrassment in that we do not have Mike Bolger having shown up or nor do I have a bio. Mike, you wouldn't happen to be in the audience, would you? Seeing no favorable response, we will move to the next speaker. And I guess that unfortunately will -- well, fortunately will keep us well on schedule here and on task.

Addressing pathogens on meat will be Kenneth Petersen. He is a Senior Epidemiologist with the Food Safety and Inspection Service, FSIS. And he will present the USDA activities regarding risk assessment. Kenneth.

ASSESSMENT OF RISK: PATHOGENS

Kenneth Petersen, Ph.D.

DR. PETERSEN: Thank you and good morning. It is a pleasure to be here to present some of the risk assessment activities within the Food Safety and Inspection Service. For those of you who are not familiar with us, basically we regulate the meat, poultry and egg products industries.

So to return to this issue of food safety, because it is an issue that unites all of us whether we produce food, regulate its safety, or simply consume it, for all of

us, food safety has become increasingly complex.

Not only do we have more issues to debate, technology, irradiation and microbes just to name a few, but these issues are being debated in public forums as never before. Just look at the attention paid to food safety by the media during the past decade.

The globalization of food trade has presented new and difficult challenges in minimizing food-borne diseases. Although the globalization of food trade has made public debate more contentious, it has not been easy for the public to separate fact from fiction.

So how exactly do we base food safety decisions on science? In countries worldwide, we need to make these decisions. We need a structured way of organizing and analyzing the scientific information that exists, as well as that to be developed in the future. To support major policy-making within USDA, we employ a quantitative farm-to-table approach.

Although our regulatory activities primarily target the post-harvest rather than the on-farm end of the spectrum, we identify whenever possible the best point or points in the food production chain in which to control risks. The scope of our risk assessments and the scientific data utilized is transparent to all interested parties. We emphasize a public process.

The concept of risk analysis is certainly not limited to the food safety arena. In fact, the structure is universal. And its value lies in the fact that it is a fluid process. As new scientific information becomes available, it can be applied in the risk assessment and strategies can be re-evaluated.

In fact, risk assessment is a good way of determining what gaps exist so that we can target needed research. So it also provides a feedback loop to enable the risk to be better defined as new information comes along.

Risk analyses play an important role in managing health hazards in food and, thus, improving food safety. Once hazards are identified, the risk managers can weigh options to address these hazards. Options may include decisions by food companies to modify their process controls or regulatory action when necessary.

A broad range of voluntary options also exist such as activities on the part of industry to modify production, processing or labeling approaches. So there is much support for using risk analysis as a means of making science-based food safety decisions. Risk assessment supported by quantitative data has been used for many years in evaluating the safety of chemicals as we heard already this morning.

But we are significantly lacking in similar data related to food-borne pathogens. In our risk assessments,

we assume that high levels of uncertainty are the rule, not the exception. Part of the challenge relates to the fact that biological population dynamics may be unpredictable.

We must consider survival, growth and decline of microbial populations throughout the farm-to-table continuum. We must assess both the potential for human illness resulting from consumption of food, as well as illness resulting from cross-contamination.

We acknowledge evolutionary changes in pathogens, for example, virulence acquisition. Another challenge relates to the many data gaps that limit the precision of risk assessments. The final assessment is only as good as the data that is currently available.

But despite these methodologic challenges, we have made some progress in conducting risk assessments. Our microbiological risk assessments incorporate the previously mentioned steps of hazard identification, exposure assessment, dose response assessment and risk characterization.

USDA has completed a risk assessment on Salmonella enteritidis in eggs and egg products which was our first farm-to-table quantitative microbial risk assessment. This was completed in June of 1998.

The risk assessment is being used to develop a strategy to address egg safety. In fact, the President's

Food Safety Council, which is conducting strategic planning for food safety, will soon release an action plan to improve food safety in the United States.

We are also conducting a risk assessment for E. coli 0157:H7 in ground beef and carcass trimmings. Consistent with the farm-to-table approach, the exposure assessment addresses on-farm production to include transportation, slaughter inputs from hide removal to carcass chilling, and product preparation from grinding to consumption.

We have also entered into a cooperative agreement with Harvard University for a risk analysis of bovine spongeiform encephalopathy, or BSE. And FDA and FSIS are jointly carrying out a risk assessment for Listeria monocytogenes in a variety of ready-to-eat foods.

So although we prefer to the extent possible quantitative risk assessments, we also believe in risk assessment in the right proportions. That is, the level of detail considered in a risk assessment and included in a risk characterization should be commensurate with the importance of the problem. Salmonella enteritidis, E. coli 0157, Listeria and concerns relating to BSE all reflect important problems.

We also utilize risk analysis to deploy our valuable inspection resources based on food safety risks.

This risk base deployment forms the basis for the HACCP-based inspection models project. For this project, in volunteer plants that slaughter young, healthy classes of animals, industry conducts on-line carcass sorting activities under FSIS oversight and verification. These new inspection activities enable us to concentrate on food safety risks, whether they be visual or microbial.

Beyond the formal risk assessments for major policy decisions, we have also made progress in implementing various risk management strategies. When quantitative data do not exist, we then base our regulatory management strategies on qualitative data.

HACCP, the Hazard Analysis and Critical Control Point Systems, are a risk management tool because they enable the user to identify hazards that are reasonably likely to occur and to develop a plan to prevent or control the hazard. As more quantitative risk assessments are conducted and hazards become more accurately characterized, HACCP plans become more effective.

Right now, we are in the final stages of implementing HACCP in meat and poultry plants. And HACCP is being implemented in other commodities, as well, such as seafood. Performance standards for pathogen reduction are another risk management tool that we use today.

Along with mandatory HACCP, we have in place

pathogen reduction performance standards for Salmonella that slaughter plants much meet. And we test products to ensure that these standards are, in fact, met.

Such standards provide a basis for plants to calibrate their process control measures. So far, testing indicates that plants are meeting the challenges, significantly reducing the prevalence of Salmonella in many raw products. Thus, this risk management tool is working to improve food safety.

And for the future, we will consider establishing pathogen reduction performance standards for other pathogens of public health concern. An additional non-regulatory tool is food safety education. For consumers, we have the "Fight Bac" campaign, the result of a public-private partnership for food safety education begun as the result of the President's Food Safety Initiative.

Food safety education is an important risk management tool because everyone has a responsibility for food safety. And consumers have an important role in handling, preparing and storing food properly to reduce the risk of food-borne illness. In fact, education is needed all along the farm-to-table chain.

The recent public health education activities include communicating the recommended hamburger cooking temperature of 160 degrees Fahrenheit and identification of

meat color as an unreliable indicator of doneness.

So in closing, there are tangible benefits to including food safety standards based on risk assessment. Among the many long-term benefits are improving food safety, maintaining and improving consumer confidence in the safety of the food supply, and facilitating trade. We would like to see more involvement by the industry, consumer groups and others interested in food safety risk assessment to achieve science-based food safety systems both here and abroad.

To maintain confidence in the safety of the food supply and avoid the chaos that would result if we did not, we must see that science wins out of rhetoric; that science guides our food safety policies. By doing so, the consumer will benefit from the food supply that is as safe as possible. It will also facilitate the harmonization of food safety standards and will in turn facilitate trade between nations. Thank you very much.

(Applause.)

DR. STERNER: Questions for Dr. Petersen? We are scheduled for a break due to the absence of Dr. Bolger. We will break for 15 minutes and reconvene in 15.

(Whereupon, a brief recess was taken.)

DR. STERNER: They say in sporting circles you can't start the program without the players. And Dr. Angulo was missing, but we have located him and he is ready to

speak. Fred is well known in veterinary circles for the role that he plays at the CDC and investigating clinical outbreaks of microbial disease that affect humans.

Fred, I am not going to belabor your background or your history since we don't have much of the room. If you will go ahead and get us started, we will stay on time.

HUMAN HEALTH IMPACT FROM FOOD-BORNE DISEASE

Dr. Fred Angulo

(Slide.)

DR. ANGULO: As most of you saw in the risk assessments, much of the data that was provided in the risk assessment is through a new project that has been established at CDC which is called the Food-borne Disease Active Surveillance Network or FoodNet.

FoodNet is the primary food-borne disease component of CDC's emerging infections program. It was established in 1995 within the EIP sites. And it is a collaborative effort between the participating state health departments, U.S. Department of Agriculture Food Safety Inspection Service and FDA.

(Slide.)

Oh, if you would like more information including the annual summaries and descriptions about FoodNet, there is a website that is available and we are happy to -- please let us know and we could provide the website to you at the

end of the talk, also.

In 1999, the FoodNet population catchment area is 28 million. We are happy to announce that we are adding a ninth site. The ninth site will be in the west. And the actual site will be announced tomorrow and will bring our population up to over 30 million persons within the population catchment area.

(Slide.)

The primary objectives of FoodNet are to determine more precisely and to monitor better the burden of food-borne diseases and to determine -- secondarily, determine the proportion of food-borne diseases which are attributable to specific foods. We, therefore, see and are pleased to play a role in risk assessments because we see the data generated within FoodNet as being data essential to doing precise risk assessments.

Equally important, we see FoodNet as a platform to monitor the reduction of food-borne illness that might occur when interventions have been put in place. We work very closely with the USDA FSIS to monitor the pathogen -- monitor success through the pathogen reduction and HACCP plan.

(Slide.)

FoodNet conducts active surveillance on seven bacterial pathogens, one of which is Campylobacter. This

active surveillance for Campylobacter is conducted by visiting at least monthly, but in most cases, weekly each of the clinical laboratories within the population catchment area.

Presently, there is about 350 clinical laboratories. These laboratories receive a stool sample from a person who is ill enough to seek care, a physician concerned enough to gather a stool sample and send it to the clinical laboratory, laboratory test, and then we ascertain the cases actively from those clinical laboratories.

(Slide.)

This just shows the type of data that is available. This is from the annual report which is on the web. And it shows the seasonal distribution of culture-confirmed cases for the foremost commonly identified bacterial pathogens, Campylobacter being the most commonly identified culture-confirmed illness each month of the year. And you also see the marked seasonal distribution of Campylobacter which has been discussed.

(Slide.)

Since FoodNet has been in place since 1996, we can begin to assess trends in food-borne illness. And this is some of the exciting data that we published in March of this year in the MMWR, and also we published in collaboration with FSIS and report to Congress.

And it is very subtle. You see the Salmonella in the second bar there declined a very small proportion from 1996 through 1998. But because we have serotype-specific data, we can explore within specific serotypes declines. And to show you the amount of precision that is within FoodNet, that small decline of Salmonella which we detected in the first three years of the project we believe is -- and particularly when considering the reduction in Salmonella that is present in the slaughter sampling through the pathogen reduction plan, they correlate -- those declines of Salmonella correlate so closely that we believe this decline in Salmonella is attributed to the -- in large part to improved safety of meat and poultry.

(Slide.)

Equally exciting is a remarkable decline in Campylobacter and poultry-confirmed illness, most prevalent in California. This points out that had the risk assessment been done based on 1997 data, there would have been 25 percent more illness. It also suggests that in 1999, because this trend is appearing to continue into 1999, the primary report of that trend will be published in the March 2000 MMWR.

But the trend appears to be continuing in 1999. And had the risk assessment been done on 1999 data, there would have been probably an order of that magnitude

decline in the outcome identified in the risk assessment.

(Slide.)

Besides ascertaining culture-confirmed cases, we ascertain -- the FoodNet personnel ascertain outcomes of those patients which include whether the patients were hospitalized or not. And there has been some misstatements at the meeting that Campylobacter does not frequently result in hospitalization.

In fact about ten percent -- there is actually 12 percent of persons with culture-confirmed Campylobacter infections are hospitalized. So relatively a large burden of illness. We also ascertain deaths.

But all that -- this active case finding within FoodNet is -- although giving enough precision to monitor trends over time which is quite exciting, the enhancements to the FoodNet are really what are novel. And these enhancements are the recognition that the burden of illness caused by food-borne diseases, that the numbers of people that are sick in the community, illness in the general community is a reflection.

When we do surveillance only based upon culture-confirmed cases at the top of the pyramid, we miss all the people who may be seeking care, but don't get a culture collected or they get a culture collected, but it is not tested for the pathogen that caused their illness, etcetera.

Any break in the chain of these events will cause the person to not be culture-confirmed.

Well, the beauty of FoodNet is that we are doing surveys and studies in all of these chains of events to identify what the loss in reporting is of each of the steps and that these surveys are very robust relatively. In terms of, for instance -- it's on the next slide.

(Slide.)

For instance, we are doing a population survey. The population survey is in its third cycle. In each of the cycles, there has been almost 10,000 persons interviewed. We are interviewing 150 people per month in each of the sites and with nine sites coming on-line. Over 1,000 people are interviewed a month.

Those people are interviewed and asked had they had diarrhea in the last week -- excuse me, in the last month. If they had diarrhea, they are asked if they submitted a stool sample, etcetera. So we begin to get information about the prevalence of diarrhea in the population and people seeking care, etcetera, and to begin to understand what is happening at the bottom of the pyramid.

Equally robust is a survey of physicians that we did. We surveyed 5,000 physicians in the FoodNet sites which was close to one-third of all physicians in private --

that handled patients that see -- that see patients with a diarrheal illness. And although the response rate from the physicians survey was only 67 percent, it is a remarkably high response rate for a physician survey. And we have information from the physician survey about how frequently physicians culture patients who seek care.

(Slide.)

And we also survey on an annual basis, but in detail, every two years each of the laboratories within the FoodNet sites to see whether their culture practices are changing from year-to-year.

(Slide.)

The exciting piece of this, besides the FoodNet being used as a platform to monitor -- actively monitor in a consistent and comprehensive manner culture-confirmed illness, we can estimate what is happening at the bottom of the pyramid. And this was published in September of 1999 -- the first author is Paul Meade -- in CDC's Emerging Infectious Disease Journal which is available on-line and copies of which of this article I have at the table at the back.

These are the new estimates and we believe the most precise, to-date estimates of food-borne illness in the United States. We believe that there are 76 million infections each year in food-borne illnesses. These are

infections due to contaminated foods.

And so previous statements of a one in a ten risk of food-borne illness appeared to be -- well, we don't -- we perceive a greater risk than had previously stated. And it also points out the numbers of hospitalizations. This is not all mild illness, although much of it is self-limiting illness, and the numbers of deaths that we attribute to food.

And these estimates actually demonstrate that the risk of cases is somewhat higher than previous risks, but the number of deaths are lower than previous risks -- previous estimates.

(Slide.)

This is itemized in the paper that I mentioned that is available at the back. But these are the numbers of -- these are the most common food-borne illnesses with a known etiology. So the estimate of 76 million includes even an estimate for, we believe, food-borne illness that we have -- public health has not even identified the pathogen yet. So about two-thirds of the 76 million infections are actually unidentified pathogens.

But then amongst the known pathogens, these are the ten -- these are the most common known pathogens just to point out that in terms of illness amongst the known pathogens, Campylobacter causes 14 percent of the food-borne

illness amongst the known pathogens. Salmonella accounts for less, ten percent.

But then as you look at the number of deaths to point out the -- to reiterate the severity of Salmonella infections, Salmonella accounts for 30 percent of the deaths associated with food-borne diseases. And Campylobacter, although not an insignificant number -- 100 deaths are attributed to Campylobacter each year, 99 deaths. That is only five percent of the total deaths.

(Slide.)

Also interesting, just an aside, is these are the most commonly identified food-borne pathogens. And so germane to our discussion here is you can begin to say, well, which of these pathogens can carry resistant determinants through the food supply. And, therefore, it points out the need to focus on Campylobacter and Salmonella in particular, and also perhaps some other pathogens.

But Salmonella and Campylobacter are clearly the ones to monitor closely for the transmission of resistant determinants through the food supply because we believe that Campylobacter and Salmonella is seldom transmitted person to person and is largely transmitted through the food supply.

So if anybody would like additional information about FoodNet, the web page is available. And please take a moment, if you like, to pick up the article published in the

Emerging Infectious Diseases which provides the estimates of food-borne illness in the United States.

(Applause.)

DR. STERNER: Are there questions for Dr. Angulo? Thank you, Fred. Our next presenter is going to deal with food-borne resistant pathogens. Dr. Glenn Morris graduated from Rice University in Houston, Texas with a bachelor of arts in 1973. He received his M.D. degree, magna cum laude in 1997.

And from 1989 until the present, he has been employed at the University of Maryland Medical School where he currently serves as the Chief of the Infectious Diseases Service and is the head of the Department of Epidemiology and Medicine. Dr. Morris.

HUMAN HEALTH IMPACT OF RESISTANT FOOD-BORNE DISEASE

J. Glenn Morris, Jr., M.D.

DR. MORRIS: Thank you. It is a pleasure to be here. And if I can make the contraption up here work, I should be in business. I am going to need your help.

(Slide.)

I just sort of wanted to follow up on what Fred presented. Basically, Fred gave the overall data on incidence of food-borne disease in the country based on the FoodNet estimates. And I would emphasize, the FoodNet database is really a fabulous database which has moved us

forward substantively in our understanding of the occurrence of food-borne disease within this country.

I sort of saw my role as trying to look specifically at the issue of resistant pathogens and sort of asking the question, what happens -- what is the human health impact if you are dealing with a resistant microorganism as opposed to one that is sensitive to the standard complement of antibiotics.

(Slide.)

The primary areas of concern are two-fold. First of all, there are concerns related to the direct transmission of resistant pathogenic microorganisms to humans. In other words, resistant Campylobacter, resistant Salmonella. And, again, I would focus on those two based on the data that Fred has shown and other data from a variety of sources suggesting that those are the major causes of human health problems associated with food-borne disease.

This is not to say that there are not substantive problems with other pathogens. But at least as an initial point of focus, these two appear to be a not unreasonable starting point.

I would emphasize, however, that there is also a second issue which relates to the transmission of genetic material or resistance chains to colonizing microbial flora. The concept here is that rather than -- or, you know, in

the first instance, you are talking about a pathogen that can directly cause illness in humans.

In the second instance, you are talking about a microorganism which may carry a resistance chain which in and of itself may not cause illness in the patient at that point in time, but has the potential of introducing that resistance chain into the microbial flora of the patient.

And, again, keep in mind that we as humans are covered with, filled with bacteria. We have a very intricate microbial flora. And this microbial flora becomes extremely important when you begin to talk about immunosuppressed patients and particularly patients who undergo transplants, organ transplants, bone marrow transplants or intensive chemotherapy.

What you become infected with when you are immunosuppressed as a patient is what you are colonized with. And so consequently, you are colonizing flora. And the resistance status of your colonizing flora becomes an extremely important element in terms of your risk when undergoing subsequent procedures designed to cause immunosuppression.

And I think the two microorganisms that have been the focus of concern in this category would be the enterococci. And there are potential concerns really to E. coli and other enterobacteria. E. c. -- again, the data in

these areas are very poor, actually virtually non-existent. But I think these are areas that need to be kept in mind, particularly in the context of the increasing levels of antimicrobial resistance we are seeing in hospitals throughout the United States.

(Slide.)

If we focus specifically on Salmonella and Campylobacter, the problems of antimicrobial resistance are initially related to failure of therapy. In other words, if you have a serious infection and, as Fred has pointed out, serious infections with these microorganisms do occur, particularly with Salmonella, and you have a resistant organism or multi-resistant organism, then that organism is not going to respond to therapy.

DT104s have attracted a great deal of attention as you all are well aware. These basically are strains that combine resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline. And there are suggestions of increased morbidity and mortality associated with infections of these strains.

Again, some of these data are difficult to interpret because it is hard to sort out cause and effect relationships. But nonetheless, there are data suggesting that these strains do cause more severe illness or have the potential for being associated with higher levels of

morbidity and mortality.

I think from a straight clinical standpoint -- and, again, speaking as a clinician who sees patients on a regular basis -- the suggestions of decreased quinolone susceptibility are probably of even greater concern. And, again, I would hope that many of you have seen the recent article that appeared in the New England Journal of Medicine on November 4th relating to the Danish outbreak of strains which showed a decreased quinolone susceptibility.

And their comment that these -- the patients who were infected with these strains, despite the fact that these strains were technically susceptible to Ciprofloxacin, that there was a "lack of clinical effect" of the quinolones.

I would emphasize the importance of this because, again, from a clinical standpoint, the quinolones are our primary drug in terms of management of Salmonella. Salmonella is -- can be a very devastating infection, particularly in the very young and the very old. It frequently infects endothelial surfaces.

The quinolones have in many ways been miracle drugs with Salmonella. They show excellent cure rates. They penetrate into areas where you don't get good penetration with other drugs. And clearly the drug of choice for disseminated Salmonellosis are the quinolones.

In that sense, the DT104s are of concern. But you are not necessarily dealing with the drug of choice. When you begin to deal with decreased quinolone susceptibility, particularly when combined with strains that carry the DT104 resistance pattern, you have a very significant clinical problem because you are beginning to lose your drug of choice. And, again, Salmonella infections can be very severe and life-threatening.

(Slide.)

In terms of Campylobacter, again, quinolone resistance, I think at this point there is good documentation that there are increasing problems with quinolone resistance in Campylobacter. Available data suggests that quinolone-resistant strains result in a longer duration of diarrhea. Data out of Minnesota, some of the FoodNet data, you do get several days of increased diarrheal illness.

However, we really don't have a good handle on some of the other health impacts. As Fred has pointed out, Campylobacter is not always an innocuous disease. And, again, our reporting systems are probably skewed to the more severe end of the spectrum. But nonetheless, you do see a substantive hospitalization rate.

And there are good data suggesting that an immunocompromised host, particularly patients with AIDS,

Campylobacter can be a very severe illness. And in those patients, loss of the quinolones may become a very important factor. Again, speaking to someone who sees AIDS patients, I am very concerned about this ongoing difficulty and the specter of decreasing availability of quinolones as a first-line therapy for patients with disseminated Campylobacter infections.

I would also raise the question about the Guillain Barre syndrome rates. As you are aware, the predominant long-term sequelae and by far the most serious long-term sequelae of Campylobacter infections is Guillain Barre syndrome. And at this point in time, we don't have a good feel for what is going to happen if we lose our primary therapeutic agent against Campylobacter in terms of ongoing rates of GBS.

So we really don't have any data on these other health impacts. But I think that these are clearly areas that need to be looked at because they may make a profound difference in the way in which we deal with these data.

(Slide.)

Other issues, there are suggestions that resistant strains may have increased virulence. Again, it is difficult to tease out the effect of increased virulence, increased numbers of hospitalization versus various types of reporting bias. But this had been suggested.

There are also issues relating to increased transmissibility of these agents, particularly in association with prior antimicrobial use. And it is very clear that if you perturb someone's colonic flora with prior antibiotics, it, you know, sets them up for infection with a multi-resistant strain.

And there are even suggestions that the infectious dose may be dropped, again, in the setting of prior perturbation of the colonic flora with antimicrobial agents which is not an uncommon circumstance these days. If you go to your physician, you may well get an antibiotic for something and that may well set you up for subsequent infection.

(Slide.)

In terms of introduction of resistance chains, I think most of the focus there has been on the enterococci, particularly on the resistance to vancomycin, VRE, vancomycin resistant enterococci. I would emphasize the concept that I mentioned earlier is that the colonizing strains, the strains with which you were colonized in your intestinal tract are the strains with which you become subsequently infected.

And, again, we have shown this in several studies, following patients longitudinally. Once you are infected with a VRE strain, you basically are infected with that

strain for life. The numbers may drop to low detectable levels. But if you are subjected to antibiotics or chemotherapy, that strain will re-emerge.

And if in turn you were at a severely immunocompromised state, that strain which may be untreatable with currently available antibiotics may well be the cause of your demise. So you really don't want to introduce resistance chains into the colonizing flora in patients.

I would also note that there have now been several studies pointing out the significant cost associated with vancomycin-resistant enterococci versus vancomycin-sensitive enterococci. Estimates vary widely, anywhere from several thousand dollars up to $90,000.00 or $100,000.00 per case. So vancomycin-resistant enterococci is a substantive concern.

(Slide.)

Now, I will say that in this country, we have had substantive problems with vancomycin-resistant enterococci. This happens to be our own home-grown problem in University Hospital in Baltimore. And it is a substantive problem with deaths associated.

Now, of course, the thing in the United States is that we have not used the vancomycin analogues in animal feeds. And so consequently, this appears to be, speaking as

a physician, of our own doing associated with our heavy use of vancomycin in the hospital setting.

Nonetheless, I think there are increasingly convincing data coming out of Europe that there can indeed be introduction of vancomycin resistance chains through the food supply and, again, demonstrating that these are possible transmission routes.

I think the other point that I would make with these is, again, the concept of endemicity. What has happened in the United States is that VRE has become endemic in patient populations. We are finding that 20 to 25 percent of all hospitalized patients carry VRE in their intestinal tract.

Again, for most of these patients, these are innocuous colonizations. They don't cause any problem. But, again, if you have got a patient with VRE who you subsequently try to do a bone marrow transplant on, they are at substantive risk that they will develop VRE bacteremia.

You get to the concept of thresholds on this. And my sense in watching the VRE epidemic progress -- and, again, it truly has been an epidemic which has progressed over the past decade -- is that it is very difficult to set a lower threshold; that once you begin to see the genes introduced into human populations, these will be amplified by use of drugs in humans.

And so the key factor is not introducing the gene into human populations in the first place because, again, I can tell you that we as physicians will be using these drugs when we have to. And when we do, then we will get amplification and we will end up with the type of situation that we currently have with vancomycin-resistant enterococci in this country.

(Slide.)

The resistance to quinupristin and dalfopristin I think is probably one of the major concerns right at the moment. Again, as you are aware, this is a drug, analogues of which have been widely used in agriculture. There is a high rate of resistance in agricultural isolates. We have found a low rate of resistance in humans. Actually, there have been several studies which have documented this.

And I think the real question, and it is going to be an interesting natural experiment if you will, will be to see with the current introduction of Sinersid as a drug for human use within the past several weeks, whether we will see an amplification cycle in people of these genes and of these resistant strains that we are finding at very low levels in terms of colonization in humans at the present time.

I can tell you, there has been very aggressive promoting of Sinersid as a drug in this country. And so there is likely to be fairly heavy clinical use. And,

again, I think this -- at least on the part of the physicians. And I think, again, it is going to be interesting to see what happens given the low level of resistance that we know is already present in the human population.

The gram negative microorganisms, again, as I said, there are no data. These are obviously areas of concern. Again, I can tell you, since I spend a fair amount of time watching levels of resistance within hospitals, there are substantive increases in resistance levels in gram negative microorganisms within hospitals.

Probably most of this is driven by physician use of antimicrobial agents. But I think there needs to be some awareness that there may also be some transfer of genes between animal and human populations which at least need to be thought of or looked at more closely.

(Slide.)

So to summarize, in terms of the impact of resistant microorganisms, there are two routes that would appear to be a major concern: the direct transmission of resistant pathogenic microorganisms and, secondly, the transmission of genetic material or resistance genes to colonizing microbial flora.

There is a clear health impact associated with resistant strains. But at the same time, as has been

repeatedly said, there are substantive data gaps and there is a clear need for further quantitative data and further modeling in these areas. Thank you.

(Applause.)

DR. STERNER: Questions for Dr. Morris? Please go to the microphone.

MR. : Just a couple of points. Do you think -- you gave nice examples of the physician-driven vancomycin resistance. Right? And I just wonder if another illustration of that might be if you look around at different countries in the world who don't use vancomycin as much as here, who don't use treatment of Campylobacter early on, they have much less resistance problem. And I think we have to be careful not to blame the animals too much or put the blame on our own doorstep.

For example, the use of gentamicin for 30 years in animals has produced no resistant strains in man at all that we have found at present, although the use again may select for those resistant strains later on. So I just wondered if you look around geographically, if you think it confirms the hypothesis that physicians do have quite a lot to do with this.

DR. MORRIS: I think there is absolutely no question speaking as a physician that physicians play a very substantive role in development of antimicrobial use in

human populations. I think, however, there is the issue both of the ongoing physician use of these drugs and the potential introduction of resistance chains in the human populations where within which there can then be subsequent amplification.

There is no question that physicians in this country through their antimicrobial use practices amplify resistance. The question is can we change that. I can tell you, having been very active with CDC programs related to judicious use of antimicrobials, being very active in our hospital in trying to restrict antimicrobial use, I would love to tell you that we are going to be able to successfully change the prescribing practices of physicians in this country. But I can't.

I can tell you that all of the efforts we've made to date to try to make a substantive impact in the prescribing practices of physicians have not worked that well. And so I think there needs to be a recognition that while, you know, we may not like it, there is, indeed, going to be amplification once genes are present in the human population. And that amplification is clearly going to be driven by human use of antimicrobial agents.

But I think that -- when you are talking about risk assessment and about threshold levels, I think it has to be recognized that there will be that amplification

pattern.

MR. : Could you explain further your concern for Guillain Barre and fluoroquinolone resistance, what that connection might be?

DR. MORRIS: As I said, this is extremely -- you know, these things are extremely speculative in that one of the -- Guillain Barre appears to be basically an immunologically mediated response to infection with specific strains of Campylobacter. The question is whether early treatment of Campylobacter might in some way abort that response or might have some impact on Guillain Barre.

This is entirely, completely speculative. I have no idea. But I think again, if you were beginning to look at health impacts to design risk assessment models, I think there needs to be a recognition that the lack of an effective first-line drug against Campylobacter may have an impact further downstream on long-term sequelae.

And I think, again, if you look at the medical impact of Campylobacter, by far the greatest costs are associated with Guillain Barre as opposed to the acute diarrheal episodes. I am not saying there is any association. I am simply saying if you think about what needs to go into a modeling process, that don't forget the downstream sequelae and the possible impact of the lack of an immediate, effective, first-line drug.

Now, again, erythromycin is available. But the quinolones have been awfully nice. And at least at this point in time, I would say that by far the standard practice pattern is to use the quinolones.

DR. STERNER: David?

MR. : Glenn, that was a very nice talk. I would just like to provide some follow-up on your comment that our efforts to influence human physician prescribing practices haven't worked that well. See, this is actually a very complicated area as you may know. There is out-patient and in-patient and different specialties. It is kind of like saying drugs on the farm. You know, I mean, there is just such great variation.

We have had challenges particularly in the hospital prescribing practices. But we are in the process of learning how to influence the primary care prescribing practices. And we have a number of intervention projects that are starting to show benefit. We had a workshop of these projects -- well, primary investigators of these projects in June. And a report of this workshop is going to appear in the American Journal of Public Health.

So this is difficult. It involves patient education, behavior of the physicians and other parameters. But we are actually starting to learn how to do it.

DR. MORRIS: I concur. And, again, there is some

beautiful work being done in trying to change physician practices. Nonetheless, if you are talking about a risk assessment model for today, I think it has to be recognized that there is an inevitable physician amplification component of it.

I sincerely hope that ten years from now, the impact of that physician amplification will be substantively less. And, again, we are actively working on that and I know a number of centers are. But for right now and probably for the next three to four to five years, it must be recognized that the physician amplification component is unfortunately, and I emphasize unfortunately, an inevitable component of any type of modeling that you do.

DR. STERNER: Thank you, Dr. Morris. It is always reassuring as a veterinarian to hear the words to the effect of, "Physician, heal thyself."

Our next speaker it might said has a history of professional parapetic peregrination, or more properly interpreted, that means that his resume looks as if he wasn't able to hold a steady professional job.

(Laughter.)

Will Heuston is a veterinary epidemiologist experienced in risk assessment, risk management, risk communication in industry, government and academia. And I might add on a personal note for those of you who have

concerns over the transmissible spongeiform encephalopathies, that he was one of the visionary people who probably 12 years ago now was on a committee that saw fit to keep that problem from rearing its ugly head here in the United States and the devastating impact that it would have had on the cattle business in the United States and Canada. With that, Will, I will introduce you to talk about risk assessment. Put it all together.

INTERPRETING AND WEIGHING RISK

Will Hueston, D.V.M.

DR. HUESTON: My challenge, I would like you to note first my challenge is to talk about risk management. And I am going to speak to you, in fact, as an ex-risk manager. So I have donned the appropriate apparel. I have my dark suit, white shirt and power tie.

(Laughter.)

The challenge is that I am going to try to put myself in the position, in fact -- I use Steve Sundlof as an example -- as the risk manager that must consider the information that is put forward and and make the decisions or recommendations for regulatory action.

I would like to start by giving you a little clarification, Politics 101. Now, there are actually two types of risk assessments that are ongoing for every decision or every regulatory issue. There is a scientific

risk assessment and then there is a politic risk assessment.

So what happens is the lower down you get into an organization, the more science becomes important and touted. The higher you get into an organization, the more important politics. So in the United States at our top tier are all political appointees. And don't ever kid yourself that politics aren't taken into the equation for making decisions.

At the same time, the government has excellent scientists. And the scientists at the other end of the spectrum are doing some very good and some very clear science. Now, in the middle rests the position of the risk manager who must manage both the political risks and the scientific risks.

I want to give you then ten or 12 points or bullets to take away about the challenge of risk management. And these are Will Hueston's personal opinions based on my personal experience and please take them as such.

Number one, the risk manager must balance science and politics. Let's start with the science part. I think it is very -- it is noble. It is appropriate to say that policy making must be science-based. Do not kid yourself for one moment that there are not politics in science.

If we take the same set of data and ten scientists, we are very likely to get multiple, if not ten,

different interpretations of the data. I think it was pointed out yesterday, this is one of the advantages and benefits of the scientific method, the conjecture and refutation, the argumentation that ultimately we hope leads to the best conclusion.

Secondly, this concept of mixing in the politics is all about who stands to win and who stands to lose, and recognize that wherever two or more people are gathered together, there are politics. And decisions in the end are not necessarily predicated on their relative importance in terms of risk to the United States. And I need not go very far with discussing cigarettes and human health to make that point in terms of regulatory decision-making.

We add for the risk manager the challenging of adding a modicum of common sense which is practicality in economics. The most scientifically sound risk management strategy is worthless if compliance is low, a lesson painfully learned in some of our recent public health issues.

Point number two, risk analysis is a tool. And i firmly believe that risk analysis is a tool to support rational decision-making in the face of uncertainty. Now, this risk analysis tool incorporates hazard identification, risk assessment, risk management and risk communication.

The critical first step as emphasized I think

yesterday by Louise Kelly, the critical first step is clarifying the question. Often overlooked is the importance of clarifying the question. The interpretations of the results can only be done in the context of the question that was asked.

Now, nextly -- next, the question itself may limit the need for the implementation of this risk analysis paradigm. We may, in fact, ask what are the hazards alone or ask in the case -- part of the case of the situation we are currently describing what are the consequences.

As well, and just a reality check for you, because of the involvement of politics and risk analysis, there are occasions in which political decisions are made. And the risk analysts are asked to put together a risk assessment to justify a political decision that has already been made.

Now, I am not trying to say in any way, shape or form that the scientists that are involved in these agencies are biased. I am just giving you a reality check on what actually happens at times.

Point number three, the risk assessment or risk analysis process is far more important than the final output, probability or numbers. So the beauty of this concept or this paradigm is the process. It is a logical approach to organizing data, available information to taking inputs through processes to outcomes in a systematic way.

And the many benefits of risk analysis include identification of data gaps, detailing of assumptions, the redistribution of resources in terms of risk management potentially, and the targeting of educational priorities.

Point number four, risk communication is far more than simply sharing the results. Risk communication means at its heart the involvement of all of those potentially affected parties in the entire risk analysis process.

Now, I would like to clarify some points that were maybe perhaps miscommunicated yesterday from my personal perspective. The risk analyst must solicit information from both the scientists and the stakeholders.

And I think one of the great advantages of risk analysis, in fact, is that as one begins to clarify the hazards, hazard identification in and of itself is one area in which we have the greatest amount of expertise and the widest population. In other words, every American considers himself an expert in hazard identification.

At the same time, if we involve the stakeholders, as well as the scientists, in the process of hazard identification, model development, identification of data sets, they gain greater buy-in and the ultimate product or process of risk assessment gains additional credibility.

At the end, we need most to avoid what I have heard called the "dad fallacy." And that is you do your

analysis in private, in secret. You decide on your regulatory approach or your risk management approach. You announce your approach and you hold up the risk assessment as your justification. To me, that is an abuse of the process.

Point number five, a systems approach or a pathway analysis supports risk management. So as a former risk manager, it was very critical for me to be able to differentiate between the options and a pathway analysis that allows then not only an evaluation of the magnitude of various impacts -- of various inputs, but also allows the evaluation of their effect on the outcome of concern.

As was presented in this risk assessment, a very interesting use of these spider diagrams, sensitivity analysis, and that can be used very effectively from a risk manager's point of view to look at the relative impact of different strategies of risk management on the final outcome.

At the same time, risk analysis can help us to identify the attributable fraction. In other words, that part of the risk that can be attributed to specific practices. Our ultimate decision may want to incorporate that because we may want to target those behaviors or those actions that have the greatest contribution.

At the same time, the reality check is as just was

eloquently presented and discussed by Glenn. And that is the challenge that some of the risk management procedures that one might -- options that one might lay out in the idea situation may not be available to us because the population and the risk -- the change in risk behaviors cannot be accomplished.

Point number six, evaluation of one risk cannot be accomplished in a vacuum. We need to develop holistic approaches. Back when I was studying physics, about the only thing I remember from physics is a concept that says for every action, there is an equal but opposite reaction. And an actual fact in the world in which we live and the ecology of the world in which we live, to take an action has implications in other areas.

And one of our challenges in doing -- as risk analysts is to begin to incorporate this into a holistic approach to risk analysis. We must consider the impacts of proposed risk management on other risks.

An interesting example, the DPT vaccine. Corporate America made a risk -- an economic risk assessment that said that the risk of a lawsuit for the sequelae to DPT vaccine was greater than the benefit, the profit that they made from selling the vaccine. It led to in a sense at one point if I understand it correctly the lack of a company to produce the vaccine. We ended up coming with a risk

management strategy to address those concerns to get the vaccine back into place to meet the public health need.

Point number seven, effective risk management must consider economics, cost effectiveness and practicality. Now, I realize -- and this morning was presented I think some very important concepts. If you follow the legislation, it is very clearly stated in the legislation as it regards the evaluation of some risks, that benefits cannot be considered.

I also recognize that one area of -- let's see, I won't use the word, "friction" -- of difference between the way in which the U.S. Department of Agriculture evaluates risks or implements risk analysis and the way in which the human health services has implemented risk analysis is the question of whether or not economics are incorporated in the risk analysis.

In the human health side, the public health side, we tend to shy away and say that we cannot put a value on a human life. We cannot translate a human life into a value. I would contend that, in fact, we do that on a daily basis. We may feel more comfortable to suggest or to say let's look at the public health measures that have the greatest impact in reducing illness or length of illness or number of deaths. But much of that translates very clearly into economics.

We have finite resources for public health. Therefore, we must look at the opportunity cost. In other words, what are we not doing if we put more money into a risk management strategy.

At the same time, we need to reiterate that the most logical and ideal solution may not be the most effective. Again, we can't rely, if you will, on scientists alone. We have the issues of sociology, of behavior. Now, a lesson that I learned quite painfully is that regulation alone does not accomplish risk mitigation.

If you would like proof for that, then drive home with me tonight on the Beltway at 4:30, a beltway on which the speed limit is 55 miles an hour. And I would argue, and anyone who lives in the D.C. area, that if you drive 55 miles per hour, I think that you are probably at a greater risk than if you drive somewhere between 65 and 70.

I would like also to end this risk management -- in the challenge of risk management to point out and to emphasize the very difficult position in which the Food and Drug Administration finds itself. I have great empathy.

I think of all the federal agencies with which I have had experience, the Food and Drug Administration is in the unique position of having the greatest numbers of unfunded mandates and the least increase in terms of their budget while at the same time carrying with them the

greatest impression of being the bad guys. So it is a real challenge for my colleagues in FDA I think.

Point number eight, reasonable and acceptable risk are fluid concepts and they vary according to a couple of -- a number of factors. So we have already established or we discussed the challenge of defining safe. Safe is a subjective term. I would not get concurrence in this room on a definition of safety. Safe is a subjective term.

At the same time, zero risk is unachievable. There is no zero risk. We face the challenge that we have prostulitized, if you will, that zero risk is achievable when, in fact, it is not. So the concept of safety and the reasonable or acceptable or tolerable risk are as much tied to a number of very human concerns like the outrage factor, the fear of the unknown, the question of whether or not a consumer has a choice.

Now, it also cannot -- risk cannot totally be defined as a mathematical entity. And I just want to share one small anecdote that impressed me with this. I was in a meeting in Paris, an international meeting in which we were talking about food safety at the farm level. And there were several presentations from the U.S. about farm-to-table risk assessment and the impact of the farm and the discussion of the potential carry-over risks of microbiological contamination.

During the discussion period, a Frenchman stood up and very impassionately said, "You Americans have forgotten what the jois de vie is all about. I want to eat my raw cheese. I want to drink unpasteurized milk. And I am willing to take the additional risk so that I may enjoy life."

We need to be very careful to recognize, in fact, that different cultures and different backgrounds and different personalities define safety differently. The challenge then of the risk manager, not to discriminate.

Point number nine, risk analysis is a dynamic process. It is not static. It is forever changing with new data. In fact, the document that was presented to you two, three, what, less than a week ago has already changed because this meeting will stimulate new data. And new ideas are coming to the people participating in this meeting. It is not a static situation.

If the risk management is successful, then -- in dealing with one of the contributors to risk, then something else will become more important.

Now, point number ten, the key to credible and effective risk analysis is trust, T-R-U-S-T, trust. And trust is built over time. And trust depends on openness and involvement. And trust is built first and foremost on the ability to listen.

It is interesting -- it can be very interesting that -- it is interesting to note that a good risk analysis in and of itself reduces risk. It reduces risk because of the increased education. In fact, some of the greatest risk management successes I experienced were situations in which we had sufficiently analyzed risks and involved stakeholders, that the stakeholders took actions without the necessitating for regulation.

Regulatory action is a very expensive, a very slow and a not very effective means for managing risk. We do not have a compliance force large enough in the United States to ensure 100 percent compliance with any regulation. So if one can achieve buy-in and trust and participation, then one may often accomplish greater risk management, in fact, simply in the process of doing risk analysis.

Point number 11, risk analysis presents -- risk analysis in the microbial field presents some new challenges. One cannot automatically take our toxicologic risk analysis and other risk analysis models and simply transpose those onto microbiological risk assessment.

I think as Dick Whiting pointed out very nicely, this microbiological risk assessment is a brand new and interesting area. It is also an area in which we are going to have to struggle with challenges that what is the risk manager's role in factoring in the -- for instance, the

temperature abuse of the consumer. So what does -- where does the government's responsibility and industry's responsibility and the consumer's responsibility begin? A very difficult question.

Well, lastly -- or just before I reiterate in some of my points, I would like to make one other. I would like to make a plea. And this is a plea for a unified approach. Interestingly enough, I believe that down deep, we all share the same goal. We are all consumers. I don't believe that there is industry out there or businessmen out there that consciously want to produce a product that harms human health.

I would also like to extend this plea in terms of the public health community. I am a veterinarian. I firmly believe that everything I do as a veterinarian I do because of public health. And there are great opportunities I believe for increased collaboration. There is no place in risk analysis for differentiating between good guys and bad guys, for incorporating finger-pointing and for demeaning our colleagues. That isn't going to help us achieve credible risk analyses.

All right. Let me reinforce then the points. Point number one, the risk manager must balance science and politics. Point number two, risk analysis is a tool. It supports rational decision-making in the face of

uncertainty. Point number three, risk assessment and risk analysis are a process. The process is more important than the final output, probabilities or number.

Point number four, risk communication is far more than simply sharing the results. It means and requires the involvement of stakeholders in the entire process. Point number five, a systems approach, a pathways analysis supports the risk manager and risk management decisions.

Point number six, evaluation of one risk cannot be accomplished in an absolute and total vacuum. We must look to bring about or incorporate more holistic approaches. Point number seven, effective risk management must consider economics, cost effectiveness and practicality.

Point number eight, reasonable and acceptable risks are fluid concepts. Reasonable and acceptable risks are fluid concepts. Point number nine, risk analysis in and of itself is a dynamic process, not static. Therefore, the analysis itself will be continually changing.

Point number ten, the key to credible and effective risk analysis is trust. And last point, number 11, microbial risk analysis presents us with some new challenges.

I would like then to finish by sharing two things that I learned in my time as a risk manager that continue to be reinforced. Number one, there are some questions that

the American public feel are too important to be left to scientists. We should all be humbled by that occasion.

There are some questions that the American public feel are too important to be left to scientists.

And number two, the joy and benefit of being a risk manager, here is the interest paradox. If, in fact, we can successfully prevent disease, then we will be criticized for wasting resources on a problem that doesn't exist. If, on the other hand, we do not prevent disease, we will be criticized for not having taken sufficient action.

So I stand before you ready to be criticized. Thank you very much.

(Applause.)

DR. STERNER: You will notice that Dr. Hueston left time to answer questions. I told him to try and be controversial. I am not sure that I saw anything but heads nodding yes, yes, yes here. That's leading the cheer here I think. Anybody who has a question, please go to the microphone.

MR. : Thank you, Will. I was one of those nodding my heads through most of that. I do want to make a comment in defense of the risk assessors and the risk managers, at least that USDA which I am most familiar with. Not too many years ago, decisions were made, you know, behind the rooms, you know, behind the closed doors of the

administrators and such. And then we came to the point where there were decisions made. And then when we got risk assessors, then we were given the challenge of providing assessment to support the decision.

I think at USDA, which I can speak most closely about, that has changed greatly in the last five years. And I think with the E. coli 0157 risk assessment that is being presented this afternoon downtown and such things, and the S. e. risk assessment, that it shows that we have had a change. And so the world has changed.

DR. HUESTON: I agree wholeheartedly. And I think the openness and sharing the openness is a very important point. And I think there has been progress. And I certainly don't want to demean that in any, shape or form. Yes, sir.

MR. : I would like to ask a question on risk communication. In Europe in the food area, we got a reaction in our consumers which is quite dramatically different from that in the U.S. with regard to, if you like, hormones in beef, antibiotics as growth promoters and recently and most dramatically, genetically modified food.

We got it wrong. Have you got it right? How have we managed to communicate an element of hysteria rather than perhaps a rational thought?

DR. HUESTON: Well, as you may or may not -- that

is a superb question. I will try -- I will share some of my thoughts. As you may or may not know, I have served -- I just finished serving six years as a member of the Spongeiform Encephalopathy Advisory Committee in the U.K.

Some interesting differences -- there are lots of differences between Europe and the U.S. For all of those -- those of you who have had the pleasure of living in Europe, it is a considerably different environment. And I certainly found in the U.K. -- and that is the area in which I have the most experience -- a couple of interesting things.

One, risk analyses are done in the U.K. in the spirit of secrecy. And one has the official Secrets Act which one can hold up and say this is a secret. And you are legally precluded -- the newspapers, in fact, are legally precluded from publishing that secret. If they publish, they close the newspaper and haul the publisher off to jail.

Number two -- and we are struggling. You know, in six years of SEAC, you have watched -- it has been interesting in the last six years to watch the whole evolution. Public meetings -- I have never attended a public meeting like this, that involved SEAC.

I served for a short time on the Spongeiform Encephalopathy Advisory Group -- the Transmissible Spongeiform Encephalopathy Advisor Group for the United States. All the meetings were held in public. They were

all open. Anyone that wants to attend sits in the back. Everyone has a chance to comment. All of the SEAC meetings are held in private.

There have over the years, therefore, built up some public feelings about the role of the government and about what is going on. And they are a little different than what happens in the United States. Now, that is one thing.

I think as well that there are cultural differences. I mean, certainly within the European community itself on some of the very issues you mentioned, huge cultural differences in terms of people's willingness to look to the future of GMOs.

So all I am saying in the end is I don't think there is a right answer. What may be the right answer for the United States today may not be the right answer for Nigeria.

If you have heard or read or followed the WTO discussions in Seattle, as well as some of the other discussions that have gone on, even CODEX meetings, a number of the developing countries have stood up and said, "Do not" -- "It is not appropriate for you developed countries to set a standard that determines food safety in our countries. We are still concerned about food security, the provision of an adequate food supply."

So I think it has to be looked at very carefully and in the context of each individual country.

MR. : If I could just comment, I think one overriding reason that -- from our side is that we don't have anything equivalent in terms of respect, authority of the FDA and the CVM. And I think rather late in the day, countries are now feverishly trying to establish food safety agencies along the lines of the FDA which will have that respect. I wait with interest and I rather doubt they will have it when it comes. Thank you.

DR. HUESTON: Good point. Interesting to watch.

DR. STERNER: Further questions for Dr. Hueston? Thank you, Will.

(Applause.)

DR. STERNER: Our final speaker this morning hails from CVM. Dr. Linda Tollefson is the Director of the Office of Surveillance and Compliance at the Center for Veterinary Medicine. Her D.V.M. degree is from the University of Illinois and her master's in public Health is from Johns Hopkins University.

Dr. Tollefson was one of the developers of the National Antimicrobial Resistance Monitoring System, known as NARMS. For those of you who are TLA challenged as I am, that is three-letter acronym challenged, the FFDCA stands for Federal Food, Drug and Cosmetic Act. I actually had to

go ask Linda.

EVALUATING RISK FROM RESISTANT PATHOGENS UNDER FFDCA

Linda Tollefson, D.V.M.

DR. TOLLEFSON: We are moving from jois de vie to Food, Drug and Cosmetic Act. And I think there is quite a bit of difference between those two. You can't time me now until I get this.

DR. STERNER: It's coming now, Linda.

DR. TOLLEFSON: It's okay.

(Slide.)

This afternoon after lunch, we have asked several experts to discuss in a panel format how FDA should evaluate the human health risk attributable to resistant pathogens. And as Dr. Hueston pointed out, this is a very difficult topic because it does encompass both science and public policy.

Now, the purpose of my presentation, what I would like to do is lay out what FDA is thinking on this issue as we develop what is now generally referred to as the Framework Document and then more recently, our analysis of the comments on the Framework Document. And the analysis of the comments is available out at the registration desk if you haven't gotten that yet.

(Slide.)

FDA operates under the Food, Drug and Cosmetic Act

and the regulations adopted under it. You heard a lot about it this morning. Section 512 is one of the safety standards that establishes conditions of approval for new animal drugs. And in that section, it requires that the drugs be proven to be safe.

Now, prior to the addition of this section to the Act by the Animal Drug Amendments of 1968, animal drugs were regulated under several sections of the Act. And Dr. Rulis mentioned the Section 409 which is the food additive provisions. Substances formed in or on food due to the use of animal drugs were regulated under the food additive provisions in this Section 409.

Dr. Rulis also pointed out that neither Section 512 nor 409 provides a definition of safe. However, the legislative history of Section 409, the food additive amendments -- again, Dr. Rulis covered this briefly -- states that safety requires proof of a reasonable certainty that no harm will result from the proposed used of the additive. Okay?

(Slide.)

A similar definition of safety in the context of food additives has been established by regulation. And that statement is very similar. It states that there is a -- safety means that there is a reasonable safety in the minds of competent scientists that the substance is not harmful

under the intended conventions of use.

The regulation goes further and states, as the legislative history does also, that this does not mean that we can establish with complete certainly the absolute harmlessness of the use of any substance. Also, that safety may be determined by scientific procedures or by general recognition of safety in some instances.

And in determining safety, the follow factors shall be considered: the probable consumption of the substance and of any substance formed in or on food because of its use, the cumulative effect of the substance in the diet, considering any chemically or pharmacologically-related substance or substances in that diet, and then safety factors which in the opinion of experts who are qualified to assess this are generally recognized as appropriate. So that it is a whole paradigm rather than a strict definition of safety.

Now, the Agency has consistently applied the reasonable certainty of no harm standard in determining the safety of substances formed in or on food as the result of the use of an animal drug. Dr. Kevin Greenlees earlier this morning provided an overview of how the Agency applies that standard to animal drug residues.

It is clear, however, that there is a significant difference between the traditional residue-based

determination of the safety of animal drugs intended for food animal use and the determination of safety in the context of antimicrobial resistance of resistant pathogens.

(Slide.)

The former involves the risk of consumption of the chemical substance formed in or on the food as the residues of the drug. This risk is not anticipated that it will change appreciably over time. Safety in the context of antimicrobial resistance involves assessment of the risk of a substance, in this case resistant microbes, which may increase in prevalence over time as a result of the use of the drug in animals.

Now, FDA recognized the difficulties associated with managing this nontraditional risk. We have been attempting to do this now for a few years. And we outlined a mechanism to deal with it. Late last year, the Guidance for Industry and the Framework Document.

In November of 1998, FDA issued guidance for industry that stated the regulatory system for assessing the safety of antimicrobial drugs intended for use in food-producing animals should be modified to address microbial safety concerns, in addition to the toxicological safety concerns that we had always addressed. We emphasize that this included all uses of all classes of antimicrobial and new animal drugs for use in food-producing animals.

(Slide.)

Then in December of 1998, we issued a discussion document which laid out a conceptual risk-based framework for evaluating microbial safety of antimicrobials intended for food animals. Implicit in the Framework Document is the application of the safety standard in a manner that ensures protection of public health by preserving the effectiveness of antimicrobial drugs for treating diseases of humans, that is by assuring that the ability to treat significant microbial diseases of humans is not lost.

Now, in developing this Framework Document, we did recognize that having a resistant infection in and of itself may affect human health, even when alternative antimicrobial therapies are available. And it may be appropriate to initiate mitigation efforts on the basis of those effects.

(Slide.)

However, in order to permit the graded level of regulatory response to the development of resistance that was outlined or proposed in the Framework Document, we viewed harm associated with the use of an antimicrobial drug in food-producing animals as loss of the long-term availability of safe and effective antimicrobial drugs to treat human disease.

We were pretty explicit about that. Also, I thought it was interesting this morning that EPA developed a

similar definition of harm in their review of the gentamicin for pesticide use.

Now, inherent in this definition is an assessment of alternative therapies available to treat a particular disease, alternative therapies to humans. What we did was make an for assessment of microbial risk through an initial categorization process which considers the importance of various drugs or drug classes to the treatment of microbial disease in humans.

FDA felt that it was crucial to first determine the drug's importance to humans before determining what effect the development of resistance to that drug from animal use will have in human health. We fully intend to expend most of our regulation oversight then on the drugs of most importance to human health.

(Slide.)

FDA proposed three categories based on importance of the produce in human medical therapy. Drugs in Category 1 represent those of highest public health concern. And that is the only category I am going to mention this morning.

For these drugs, FDA believes that human exposure to resistant bacteria from animals must be avoided or extensively minimized to assure that these drugs remain effective for human medical therapy.

Drugs would be placed in Category 1 if they meet any of the following criteria: if they are essential for treatment of a serious or life-threatening disease in humans for which there is no satisfactory alternative therapy, or important for the treatment of food-borne disease in humans where resistance to alternative antimicrobial drugs may limit the therapeutic options, or members of a class of drugs for which the mechanism of action or the nature of resistance induction is unique.

Resistance to the drug is rare among the human pathogens and the drug holds potential for long-term therapy in human medicine.

Now, the Agency anticipated that drugs in this class, in this Category 1 class, could be used for food-producing animals if controls could be put in place to ensure little or no resistance transfer from the treated animals to humans with respect to the human diseases of concern.

And we actually went a bit further and provided specific examples in the Framework Document to further illustrate our thinking on the categorization of drugs. For the quinolones, we considered that was very important for serious infections caused by multi-drug resistant Salmonella species where it is resistant to Category 2 drugs or perhaps another Category 1 drug.

At this point in time, we still are not certain which drugs are going to be in which category. That is still open for public comment and further work.

Quinolones are frequently the primary treatment for Salmonellosis. And quinolones are also the drugs of choice in alternative therapies for many life-threatening resistant gram negative infections.

For vancomycin, we considered serious infections caused by methicillin-resistant Staph. aureus and ampicillin-resistant enterococci. Vancomycin is really the only well proven treatment available to treat serious infections with these organisms.

Now, there is quinupristin, dalfopristin or vancomycin-resistant enterococci. The human drug, Sinersid, was just recently approved for this use. And Sinersid also has the unique mechanism of action. So it meets more than one criteria. Many of these drugs do meet more than one criteria. And then third generation cephalosporins for food-borne infections, for example, ceftriaxone for Salmonella infections in children.

(Slide.)

We received several comments questioning what safety standard is relevant to the evaluation of risk from the resistant microorganisms and we hope to receive additional input on the issue via the expert panel

discussion and also the public comment period this afternoon.

What I have described is our effort to evaluate risks from the recent pathogens under the Food, Drug, and Cosmetic Act. And we have been struggling with this issue for a while. Later in the afternoon, Dr. Thompson will discuss more how to implement this through the development of thresholds or other means. But we definitely appreciate any help that the panel or others could give us.

(Applause.)

DR. STERNER: I think one more round of applause for all of our speakers for getting us done ahead of time is called for.

(Applause.)

DR. STERNER: Questions for Dr. Tollefson? Yes?

DR. CONDON: Linda, this is Robert Condon.

DR. TOLLEFSON: Yes, I know.

DR. CONDON: Well, I don't know whether you need it for the record or not. Unless they have changed in the last couple of years, in case somebody wants to go back and look at the legislative history, are not antibiotics in CVM regulated under 512?

DR. TOLLEFSON: Yes.

DR. CONDON: Rather than 409?

DR. TOLLEFSON: Yes, that's what I said.

DR. CONDON: And the standards are a little bit different. And I think one of the main things is that those 512 are safe by all reasonable tests that are applicable.

DR. TOLLEFSON: Right, that's fine. I mean, there is really no definition of safety. Safety is under the legislative history and the 409 regulations.

DR. STERNER: Other questions for Dr. Tollefson? Well, you are going to get yourself an extended noon hour. We will begin promptly at 1:00. Thank you for your attention this morning.

(Whereupon, a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

PANEL DISCUSSION: HOW SHOULD CVM EVALUATE RISK FROM RESISTANT PATHOGENS

DR. STERNER: We will begin with the session's introductions while people will filter into the room. I tried reading biographical sketches this morning and find those dreadfully boring and they don't really add a whole lot. What I have a lot more fun with is hearing people tell who they are and where they are from.

And I would challenge each of you to tell us one thing about yourself in addition to your professional interests that nobody might have ever guessed about you, just in case somebody wants to strike up a conversation after the panel discussion is over. So we will start with A) Dr. Apley on the end. Would you introduce yourself and give us a small biographical sketch.

DR. APLEY: I am Mike Apley. I am Assistant Professor of Beef-production Medicine, Iowa State University. My advanced training is in clinical pharmacology with my Ph.D. in boards. My interests are risk assessment. I work primarily in feed lot, clinical pharmacology and other animal species. And something nobody knew, semi-serious truck puller.

DR. LIEBERMAN: Well, I think this part has me

more intimidated than my comments now. I am Patty Lieberman from the Center for Science in the Public Interest. I have been there as a staff scientist for about three years.

What people might not know about me is that my grandpa was a cattle dealer. And my father's biggest client was a pork producer/processor people. So I think people would probably not expect that I have some -- although nothing immediate in my life is revolving in agricultures at my work, but that I have some background in and appreciate for it.

DR. McCLURE: Hi. My name is Kent McClure. I am with the Animal Health Institute. I am both a veterinarian and a lawyer. I practice both veterinary medicine and law. And I practice law in a regulatory context. As far as something that someone might not know about me, I enjoy brewing beer at home.

DR. ANGULO: Hi. My name is Fred Angulo. I am the Chief of the FoodNet and the NARMS activities in the Food-borne and Diarrheal Diseases Branch at CDC, where I have been since 1993. And I am the proud father of three children. And I think that is the thing I am most proud of.

DR. MORRIS: I am Glenn Morris. I am on the faculty as a professor at the University of Maryland School of Medicine. I am a physician/epidemiologist. I was at CDC. I spent several years with FSIS with Mike Taylor.

And I am now happily back at the university working primarily in the area of emerging pathogens, with a particular focus on emergence of multi-resistant pathogens within a variety of environments. I will follow up with Fred. I am the father of three daughters. And that alone I am sure has had a major impact on my psyche, probably more than anything else in my life.

DR. CRAWFORD: Thanks. I am Les Crawford. I am Director of the Center for Food and Nutrition Policy at Georgetown University. I used to be at FDA, University of Georgia and also FSIS and about 12 other places. And I enjoy drinking beer at home.

(Laughter.)

DR. McEWEN: I am Scott McEwen and I knew that sitting beside Lester Crawford was going to be a problem, trying to follow that act. I am a professor at the University of Guelph in epidemiology, focusing on food safety. I have two boys and I like woodworking. I make Windsor chairs. And like all Canadians, I have built a log cabin.

(Laughter.)

DR. STERNER: Kenneth Petersen is not here yet. When he comes, we will go ahead and pin him with the same task that the rest of the panel has. I am Keith Sterner, moderator for the first part of this afternoon's session.

I am a graduate of Michigan State University in 1969. After that, I did two years on active duty in the United States Army Veterinary Corps, served in Seattle, Washington and Pouson, Korea. And I got an in-country discharge. And I found that if you go far enough in that direction, you will come back in that direction.

And I took about six months to go around the world. And due to the vagueness of my discharge papers, they entitled me to trans-oceanic transportation within one year of discharge. They failed to specify which ocean. And it is amazing when you show up at duty stations late enough on a Friday afternoon what you can get done and hopping military hops.

(Laughter.)

I am a co-owner of a ten-person mixed practice veterinary clinic in the central part of Michigan. We do all creatures except for horses and have -- and in the practice that my father started 52 years ago this month as a matter of fact.

And I have been active in organized veterinary medicine, having served as an Officer in the American Association of Bovine Practitioners. And I have been active in the National Mastitis Council and I am the past president of it, as well.

I am currently the Chair of the American

Veterinary Medical Association's Council on Education. And I think I am here because Sharon has a grudge against me. I serve as the current Chair of VMAC, as well.

With those introductions, I would like to go ahead. And I am going to randomly move through the panel and ask them to address the questions here. And because Glenn Morris reminded me that he has real patients to see this afternoon and may have to leave as the discussion begins to wind down a bit, he has the prerogative of speaking first and trying to address these questions that the panel has been posed. So, Glenn, the floor is yours.

J. Glenn Morris, Jr., M.D.

DR. MORRIS: I am not sure that this is the appropriate award here because I am not sure I can necessarily completely answer these questions. It would have nice to hear somebody else first. However, I may slip out here in a minute. It's nothing personal. It's just unfortunately because of my scheduling. I have attending responsibilities this month and have patients waiting for me. So I am going to slip out in a little while.

But to deal with the issues that are raised here -- and, again, as I said, I will admit as to some uncertainty as to how to address these. The question first is what is an appropriate risk standard to apply to resistant pathogens.

And I guess as a physician, I struggle with trying to understand the concept of standards with regard to resistant pathogens. I am not overly fond of resistant pathogens. And I would prefer to see the numbers minimized.

I recognize from a regulatory standpoint, there is a need to try to put this in a, you know, better framework.

I think if you begin to look at some of the impacts associated -- human health impacts associated with resistant pathogens, one of the things that has been mentioned for Campylobacter resistant to quinolones has been prolongation of diarrheal illness. I realize that there is probably of a sense of, oh, okay, so they have a few more days of diarrhea, so what.

I can tell you as a physician who has seen a lot of patients with Campylobacter infections that a couple of extra days of diarrhea is not a so what. If you had Campylobacter, it is a really -- you are pretty sick. Actually, the sickest patients I see in terms of occurrence of diarrheal disease are those with Campylobacter. It makes young adults really sick. And those couple of extra days of diarrhea are not trivial.

Nonetheless, I think there should also be a recognition that the approach that has been taken in this risk assessment has not really looked carefully at specific population breakdowns. And, again, this sort of gets into

the question number two.

As an epidemiologist, clearly I think what happens with these types of data is that you are skewed more towards the high risk populations. Those are the people who come to see doctors. Those are the people who seek medical therapy. And it is the high risk populations that are at greatest risk for serious illness.

And, again, particularly from my vantage point in a, you know, large university medical center, the population that comes to mind most often is the HIV positive patients. Those patients are at clear risk for significant Campylobacter infections. For those patients, if they come in with serious illness, we need to be able to use medication empirically. We need to have a high degree of confidence that the drug we are using is going to be efficacious.

With the rising rates of resistance to quinolones of Campylobacter, suddenly what is our first-line drug? We are beginning to have doubts about it. And so I realize that this doesn't give a quantitative level, but I will tell you from a clinical practice standpoint, the fact that we are beginning to have questions about the ability to use certain drugs empirically is a fairly significant problem.

I think that a second concern that arises in looking at this is that this model is, if you will, a static

model. It recognizes things at one point in time in 1998. And unfortunately, this is not a static process. And I think what we are seeing is very much the dynamism of it which are rising rates of quinolone resistance to Campylobacter.

And I would like somehow to be able to see this concept of the dynamism of the process incorporated into the model, both in terms of the dynamism that reflects physician responses and physician use of drugs which I talked about earlier, but also the dynamism of, you know, potential amplification of resistant organisms within animal populations. It is a dynamic process.

So although you are talking about -- I believe the number was three percent in general population numbers, my understanding is that those numbers actually probably are fairly low compared to what is happening in 1999. And so the dynamic element of this is something that I think has to be taken into account.

And, again, I think there needs to be an ability to deal with the concept of amplification, that things tend to get worse fairly rapidly. And my concern in a hospital setting is that I am seeing things get worse fairly rapidly with multiple pathogens. And it is very clear to us when we are dealing with this on the front lines of medicine that we have a substantive problem across the board with rising

resistance rates to all of our pathogens.

As has already been noted, there are multiple factors that drive that process. But I think that dynamic element needs to be considered when you look at the standards and the establishments of standards. And I think I will stop there.

DR. STERNER: Dr. Lieberman.

Patricia Lieberman, Ph.D.

DR. LIEBERMAN: Well, I think I jumped the gun yesterday and stated some of my views. So some of this is going to be a little repetitive. I would have to say that consumers feel that the only legal or scientific standards acceptable is the standard of reasonable certainty of no harm. And I guess I would have to express some concern about these -- looking into what other standards are with the thought that it is possible that CVM is considering trying to change these standards and how they would go about doing it.

It seems to us that a discussion of it or a guidance document or the discretion of the FDA Commissioner would not be an acceptable way to do that if that is what is going to happen and that that would have to be done either by rule-making or by Congress.

As to the appropriate populations on which to base the standards, I think we need to take into account the most

susceptible members of the population, not the entire population of the United States, but thinking about children, the elderly and immunocompromised people for whom the disease is more likely to be harmful and, in fact, is more likely. And I think Dr. Morris already spoke to that.

With the issue of children, it seems like at this point, treatment with fluoroquinolone -- that the risk assessment undertaken by CVM which looks at fluoroquinolones wouldn't consider children at higher risk. But I think we need to keep in mind what I don't remember who said about how it seems likely that fluoroquinolones will be used in children whether or not they are approved for use and if they will in the future be approved for use in children.

I think it is very important that the threshold should be set to identify problems before people have been harmed, preferably looking at resistance in the livestock and also taking into account not just full-blown resistance, but decreases in susceptibility. And those should be dealt with as the early warnings which would necessitate mitigation strategies.

I have a few other comments that I guess I will make now. I guess they could also be done during the public comments. But about the issue of if this process is supposed to be transparent, what does that mean. What is the impact of having a public meeting when we have no real

sense of how this information is going to be used and how the people who are the decision-makers -- you know, whether it is just so that we can vent our feelings to you and so you can say, "We listened", or whether or not these -- our input is shaping the decisions that are going to be made.

In other words, have we gotten riled up for nothing? And I have only been in this field for a little while. But I feel like I have done this a lot already which is okay I guess. But it is hard to tell the impact of it.

And with this particular risk assessment on fluoroquinolones, now that there has been this risk assessment that shows there has been harm to humans, what is going to be done about? How can the use remain permissible?

And looking at how other regulators look at risk, seeing how the people who regulate food additives, if they had a food additive that harmed about 5,000 people a year, would they feel that they had to take action? And how does the situation differ from that of a food additive because the prevalence of resistant Campylobacter is likely to increase and fluoroquinolone-resistant Salmonella are beginning to emerge?

So those are some things that have me concerned about the process. And I guess I will stop.

DR. STERNER: Dr. Crawford.

Dr. Lester Crawford

DR. CRAWFORD: Thank you. I am going to address most of my remarks -- I will cover these three subjects. But the framework I will use will be the concept of threshold. As one who was involved in earlier initiatives with respect to antibiotic resistance at CVM and elsewhere, I think this is a concept that we could certainly have used in dealing with those problems. And am thinking primarily of penicillin and tetracycline.

I believe that the risk assessment is obviously well done and it is an enormously good tool for dealing with this. And it leads then naturally into what I will say about thresholds.

I believe they must be based in regulation and not in a gentlemen's agreement. I mentioned earlier the Regulatory Improvement Act of 1999. And when I testified on that, I mentioned this particular aspect.

The second thing is that products that are known to rapidly engender resistance or that are known to have dangerous cross-resistance profiles should not be eligible for approval. And I believe the Framework Document addresses that quite adequately.

Presumably, these would wash-out in the pre-approval risk assessment process. And whoever made the comment earlier about pre-approval risk assessment I think was right on target.

Thirdly, I think that post-approval monitoring should be performed for all approved antibiotics from animal isolates. I recognize that human isolates would help to some extent. But animal isolates are primarily within CVM's purview. And so that should be sufficient.

I think they should be tailored, the thresholds, for each antibiotic, but consistent in magnitude and based on the minimum inhibitory concentration of the target organisms. For example, when ten percent of isolates from human and veterinary isolates require a significant concentration increase over the pre-approval level, action should be taken. The question is what is the action. And that is the $64,000.00 question. Something like a moratorium with the approval still in place might be a good idea.

We were -- we actually did discuss this in the London Conference on Antibiotic Resistance in 1981 where we presented university figures from the University of Georgia which show that over the many years of use in the veterinary teaching hospital there, that we had a natural selection process for antibiotics because when an antibiotic -- when bacteria became so resistant to certain antibiotics that clinicians stopped ordering those from the pharmacy.

So over a period of time, their resistance profiles declined and susceptibility improved. And I

thought it was a very powerful testimony based on fact and based on thousands and thousands of isolates. Unfortunately, we did not translate that into regulatory action. But it was nonetheless interesting.

And I think that if a moratorium or some sort of ameliorating action is initiated, I think that monitoring should continue. And if there is no improvement, then perhaps the moratorium or whatever the remedial action is should continue.

And I also think that you have to be very careful -- and I notice you've got a legal question here which I am not qualified to answer. But I think you have to be very careful about due process. And you need to have a carefully articulated position on what happens to administrative hearings, whether these would be truncated, abbreviated or obviated. And I would recommend some of all three in closing.

DR. STERNER: Thank you, Lester. Kent McClure.

Kent McClure, Esquire, D.V.M.

DR. McCLURE: Thank you. First of all, I want to say that I am very happy to be here today. I believe antibiotic resistance is an important issue that needs addressing. And we are happy to have input on the process with respect to this panel. We have had frankly little time to review the risk assessment. And we intend to comment on

it, analyze it and do that in detail. And we will provide further comments later.

But I do want to say that one thing that I think has been missed from looking through the -- just a preliminary look through the document was everything was stated in a negative sense. And if you flip it around, one thing that struck me was that you can say that for the average U.S. citizen, there was greater than a 99.99 percent probability that they would be unaffected by a resistant Campylobacteriosis. And I think that has to be kept in mind when you discuss what standards should apply and how we should implement them.

I am going to try to talk just a second about the legal standard. It is impossible in this context in this time period to have a thorough analysis of it. But I do want to kind of just give a few thoughts on it. One is -- and I will do a nutshell answer first. And that is that the Federal Food, Drug and Cosmetic Act in this context does not mandate any standard other than safe.

The statute requires that a new animal drug be shown to be safe. Safe is defined as referring to the health of animal or man. The statute gives no further guidance on the standard.

The statute does provide some factors that have to be considered. But it doesn't give you a standard to weigh

those factors against. And there is a big difference in articulating factors to consider and then articulating the standard that you weigh them against. They are not the same thing.

In this context, the regulations promulgated by the FDA parallel the statute. They provide factors to consider, but no standard. In court cases in which the FDA has been a party in this context -- and that is, this context is the approval of new animal drugs in a food-producing species -- the FDA has not argued that any regulation they have promulgated sets a safety standard.

The Federal Courts that have then tried to determine what is the safety standard that applies have held that there is not one. A quote from one of the Courts that considered it is that, "The Food, Drug and Cosmetic Act does not indicate the standard an applicant must meet to demonstrate a new drug safety or the evidence upon which the FDA must base its safety determination." That was a new animal drug in a food-producing species -- that case involved that.

There are several other points that Federal Courts have made that are of interest to this discussion. One of them is that the D.C. Court of Appeals has at least twice rejected the Agency's argument that the legislative history behind the Animal Drug Amendments of 1968 set the particular

standard that must be used to evaluate the safety of new animal drug in a food-producing species.

The D.C. Court of Appeals has also held that a risk benefit analysis is inherent in the process of safety evaluation in new animal drugs for food-producing species. Now, we have heard some talk today about how you can have only a risk-oriented standard.

The D.C. Court of Appeals has remanded cases back to the Agency for further consideration when that standard has been applied. That is not one that should pass the D.C. Court of Appeals.

And finally, I would say that one thing that is evident when you gather the court cases that deal with safety standards in this context, conspicuously absent from those decisions is a discussion of reasonable certain of no harm. You will not find it mentioned in any of them.

The take-away message from that is that the Agency has flexibility. They have the flexibility to craft a solution that is to a unique situation, that is workable, reasonable and protects public health.

Like I said, there is a whole lot more to that analysis than what I just articulated. But for the sake of time, I am going to move on. The -- I want to say that we agree with CVM that there are significant differences between residue-based issues and resistant-based issues.

Attempting to regulate resistance in the context of residues is like trying to put a square peg in a round hole. And that is part of the reason why we have had so much discussion over this and why CVM has had to struggle with this.

The USDA and the FDA both have standards -- or not standards, but regulations that deal with pathogens or can be interpreted to cover them. And it is imperative that they be the same. The USDA standard we believe is the most appropriate. It takes into account the HACCP Program of pathogen reduction and the fact that raw meat and poultry is intended to be cooked prior to consumption. As discussed earlier, food packaging and labeling includes warnings about how to handle food and cooking.

The USDA standard revolves around the quantity of pathogen that is present. The Poultry Inspection Act and the Meat Inspection Acts do not consider a pathogen, resistant or otherwise, to make a carcass adulterated if the quantity does not ordinarily render it injurious to health. And this standard needs to be explored by the FDA in cooperation with the USDA. And there is a huge reason for that.

And that is that you have almost identical language -- and if I had it before me to compare, I might say it was identical, but I would have to have it before me

to do it -- on that particular standard. And what I am talking about is whether or not you consider a resistant pathogen to be an added substance or a -- or just a substance.

And you can't have identical language in two different regulations in the Code of Federal Regulations that is interpreted differently by the Courts, even though it comes from different agencies. A Federal Court does not say in this context, this word means this and in the same context with a different agency, this word in the same sentence means something different. It doesn't happen.

If you define a resistant pathogen to be an added substance, then every carcass that has a resistant pathogen on it is adulterated. And you can't define it one way in one place and a different way in another place in the same regulatory scheme on the same stuff when you use the same language. That won't fly. Legally that won't fly, at least that is my opinion.

The other thing that I think is important to note here is that it is important to ask where in the process is the standard applied. We have heard a lot about the risk assessment and the thresholds and things like that and post-monitoring surveillance. I want to say first of all that AHI has been in favor of risk assessments. We have helped fund one, not this particular one, but another one. And so

we are glad to see them done.

We are also in favor of post-approval monitoring. We have applauded the NARMS program. However, it would be wrong and not legally justified to hold the drug approval process hostage to post-approval activities.

We talk about setting thresholds. You know, if you went back several years in time and you said let's set a threshold for fluoroquinolone with Campylobacter, you wouldn't have even foreseen that as being a problem. I guess my point is that would have never even come into the mix because it wouldn't have been considered.

And so when you sit down with a new drug, it is impossible that you can have all the areas ahead of time to know what you are going to consider. And so to require a manufacture to agree up front to withdraw a product from the market or do whatever simply because some arbitrary threshold is crossed, 1) is not supported by the Act, and 2) doesn't make sense.

The Federal Food, Drug and Cosmetic Act has provisions within for removing products from the market. In fact, most of the time when there is a legitimate problem with products, the manufacture and the Agency work together on a solution. But if they can't come to a solution, then the Act has provisions for removal of product from the marketplace.

It is not -- I guess what the context is, is that it would not be right for the Agency to circumvent the provisions of the Act through the standard, itself. The bottom line is that the standard for regulation has to be coordinated with the USDA. You can't do it in a vacuum as we have heard many times.

The Agency does have tremendous flexibility in dealing with this situation. And we would say that the approval process and post-surveillance monitoring are distinct activities. You can have them both going forward at the same time. You can monitor products and take action on what happens.

And I guess rather than going on and rambling, I will conclude with that. I will just say that we look forward to an ongoing discussion on the topic and working further with CVM. Thank you.

DR. STERNER: Thank you. Fred.

Dr. Fred Angulo

DR. ANGULO: I think, as many of you know, CDC is a non-regulatory agency with the mission of identifying risks and working with partnerships to try to mitigate those risks. And I think it is a matter of public record that CDC identified the potential risk of fluoroquinolone-resistant Campylobacter prior to the approval of fluoroquinolones in poultry. In fact, it is a matter of public record that we

advised against -- or, that's too strong, that we had concerns about such an approval.

Nonetheless, I don't mean to go back there again, but that is in contrast to what Kent just mentioned. Nonetheless, I did want to comment perhaps on some of the questions that were raised. The first question about the appropriate risk standard to apply to resistant pathogens, I think the question really means to ask the appropriate risk standard to apply to resistant pathogens which result from the use of antimicrobials in food animals, or what is the appropriate risk standard to apply to the use of antimicrobials in food animals.

Without commenting on the current statute or policy, the risk of adverse human health consequences due to the risk of antimicrobials in food animals should be managed based on the best available data, for example, the current risk assessment, and should protect the public from harm.

Several governmental agencies manage and regulate the risk of food-borne diseases. In particular, the USDA Food Safety Inspection Service manages the risk of food-borne diseases from meat and poultry. The FDA's Center for Veterinary Medicine manages the incremental risk or the increased risk of food-borne diseases which are resistant to antibiotics as a consequence of antibiotic use in food animals.

Therefore, FSIS manages the risk of Campylobacter infections from poultry and CVM manages the incremental risk of fluoroquinolone-resistant Campylobacter from poultry. Therefore, because FSIS is already managing the risk of a person in the general population getting a Campylobacter infection, the appropriate population on which to manage the risk for -- we would say for FDA CVM is the incremental risk of fluoroquinolone-resistant Campylobacter from poultry as a consequence of fluoroquinolone use in poultry.

And it should be managed -- the appropriate population should be for those persons with Campylobacter infections. However, this risk management should consider all the potential outcomes due to that resistance. For example, the risk assessment should consider all the potential outcomes of fluoroquinolone-resistant Campylobacter which arises as a consequence of fluoroquinolone use in poultry.

This risk assessment only considers the outcome of persons who are ill enough to seek care, receive an antibiotic and are prescribed fluoroquinolone. I am sure many of you recognize the logic error that this is a self-mitigating risk assessment because if resistance to Campylobacter emerges to such an extent, physicians will stop using fluoroquinolones. And so, therefore, when the usage of fluoroquinolones reaches zero, the harm is zero.

So it is a self-mitigating model and will self-mitigate taken to its extreme. So that is a concern with the current model.

But in terms of setting then the population, we would say that the population that should -- that -- on which to base a standard, although I don't mean this to be a legal statement -- but the population to base the standard should be people with Campylobacter as the denominator and people with fluoroquinolone-resistant Campylobacter which arises from the use of fluoroquinolone-resistant -- fluoroquinolone use in poultry as the numerator.

And if your outcome is people who seek care and receive a fluoroquinolone when they seek care, they can be the denominator and the numerator should be amongst those groups, how many of them have a fluoroquinolone-resistant infection as a consequence of fluoroquinolone use in poultry.

Regardless of what population is selected, the public should not be harmed by the use of antibiotics in food animals. Finally, we caution that to prevent this harm in Salmonella infections, conservative thresholds should be established. Even modest harm with Campylobacter, which this risk assessment clearly demonstrates is now occurring in the United States, even modest harm with Campylobacter is a sentinel event indicating the potential for much greater

harm when Salmonella becomes fluoroquinolone-resistant.

DR. STERNER: Does that conclude your comments for now?

DR. ANGULO: It does.

DR. STERNER: Okay. Scott.

Dr. Scott McEwen

DR. McEWEN: Thanks very much. I would just like to say at the outset that I -- as a foreigner, it makes me a little nervous to talk about U.S. regulatory matters. So I would just like to acknowledge that. And the comments I make are made with respect and I hope no one takes offense.

I think in terms of the appropriate risk standard, I think, obviously, that those should be quantitative where possible and using good quantitative risk assessment methods. And the outcome should be public health. That could be sort of -- that could come back to thresholds at an earlier phase in the production cycle if appropriate. But it should relate quantitatively ideally to a public health outcome.

Again, ideally I think it all hinges on the adverse effect in humans attributable to the use of the drug in question in approved species. And I think it should be drug-specific and organism-specific where possible. And I think that should include the treatment and failure issue as well as the issue of pre-existing drug use being a risk

factor for infection, pathogen load in terms of spread within an animal species and the concentration on food products, the altered virulence question that is out there.

And it should include resistant, food-borne pathogens as well as commensals in the treating transfer issue, so the whole thing. Now, I realize that pragmatically, it is probably necessary to back off that and focus on specific aspects. But I think that is a regulatory political sort of decision based on priority setting and that sort of thing.

But they emphasize that it should be the portion attributable to the use of the drug in animals. And for that, I think we could look to some other examples of risks in other food safety applications. And I think we have two main sort of classifications, the naturally-occurring hazards that are already in existence including things like 0157:H7, Salmonella enteritidis, natural sex hormones in a sense.

And for those, we have a kind of background level that is out there. They are already in place to some extent. And we heard this morning in the water area, that EPA is using a one in 10,000 yearly risk of enteric disease, so that sort of background level of pathogen.

And we've got -- the other class is sort of -- well, it would be called the technology-created hazards. It

would be things like antibiotic drugs, hormones, for example. I think I put drug-resistant organisms in that category. So we are in a sense creating these, not to be sort of inflammatory about it. But there is no in a sense natural background level.

Maybe you could argue that there -- just to sort of back off from that, that if the drug has been used already a lot in human medicine and we do have a background degree of resistance. And that could be sort of factored into this. But I guess in the case of food-borne pathogens, Salmonella and Campylobacter, we tend to think that resistance arises from drug use in agriculture. So that's maybe a moot point.

I think we have to consider the adverse effect, both in terms of morbidity and mortality. In the case of mortality, we have examples in carcinogenicity and so on of an estimated risk of one in a million being acceptable. And this is sort of targeting the discussion on acceptable levels.

And I think we could look at translating not to infectious agents. You will recall that National Academy in the '80s looked at this for infectious disease. I forget the number. We would have to ask the statisticians. But it could translate the one in a million to the annual risk of fatality or daily or something of that particular sort.

I think the morbidity question is a lot more problematic. And I think anything -- allowing anything more than one case is in a sense an implicit acknowledgement that we are balancing risks and benefits. I think the unique situation with the microorganisms as opposed to the xenobiotic drugs and so on is we have actual cases. They are kind of interfaced and being diagnosed. And it is not some sort of esoteric theoretical sort of risk calculation.

So I am in favor of balancing risks and benefits. And I think in western democracies, we do that all the time. We should have a mechanism for allowing that.

In terms of setting the allowable levels, we heard from Dick Whiting I think this morning that that is not being done yet in the naturally-occurring organisms. I think it might be naive to suggest it, but maybe it is time for an open symposium to try and nail down some figures for that in terms of acceptable levels of morbidity for food-borne pathogens.

I think this morning I was trying to think of a corollary to the antibiotic-resistant organisms with drug use in animals. But I couldn't think of another example. I think it is very unique in a sense that -- and without being an alarmist, we are almost creating a new type of organism from using a technology in an area that is not primarily intended to enhance public health. And so that creates some

new difficulties.

I think there are figures out there of something like 78,000 people. They put variability on that figure, I think. But people dying as a result of mistakes in the health care system. And I think we would all agree that that is too high.

But, again, some of that is probably a result of treating people, for example, for life-threatening conditions and you are going to acknowledge that there is some risk to that. Again, we are trading off public health risks, not public -- one public health risk and another type of benefit.

I think in terms of looking at morbidity, we also have to scale in different types of morbidity in terms of severity perhaps, transient diarrhea at one level, pain being factored in there, long-term organ dysfunction or failure is another one and so on. So there has to be a kind of weighting of degrees of morbidity.

In terms of the appropriate population, I think obviously we have got to look at both general and high risk groups. And I think whether you go for something that has been used elsewhere and say that to protect a ninety-eighth percentile in either group, I think -- which is again an implicit sort of trade off of risk and benefit, I think we have to -- that would be a function of the costs of having a

high standard.

One form of that cost could be whether or not that new drug approvals actually have taken place. I think look to the residue situation for example. You are going to have a very high standard there of safety.

And one of the reasons we can do that is that it seems that the industry, animal industry, and the drug industries can actually live with that. It is not sort of ruling out drugs that -- maybe it has some, but not too many that I know of. But if we do that for microbial resistance risks, it might be a lot more difficult.

In terms of the legal standard, again, I don't have any real comments on that. And I think it is the same in my country and others, I think that this business of public health agencies being only able to look at harm and safety and not the sort of benefits is a problem that we -- that nations have to get around. We have to be able to weigh in explicitly I think the benefits somehow. Thank you.

DR. STERNER: And last but by no means least, Dr. Apley.

Michael Apley, Ph.D.

DR. APLEY: I think the Chief put me here just so I couldn't have a piece of candy in this whole deal.

(Laughter.)

Well, when this first came up and Lyle Vogel said, "Well, why don't you talk up there?" And I said, "Well, I don't know anything about risk assessments." And I think as someone pointed out, that doesn't stop you from talking about cattle and pharmacology, so why don't you get up there.

But, you know, what that brings up is that I don't think you have to be an risk assessment expert to have a real meaningful part in this whole process. And AVMA would like to commend -- those of here today would like to commend the FDA CVM for the process and bringing people in. And we are glad to be here. And we appreciate the ability to comment.

But you don't have to be an expert in mathematics to have a lot of input onto things. And the comment about the importance of the process, it really dawned on me these last two days is very similar to our decision system as we go around coming up with pharmacokinetic, pharmacodynamic susceptibility data to work on that project. You end up finding a lot of holes that you thought somebody knew that. You thought we were doing something because somebody knew it. And I think we are finding out through a lot of things we didn't.

The AVMA has been involved in animal welfare and human health for about 130 years. Again, we commend the FDA

CVM for the work completed on this risk assessment. And we would like to thank Dr. Sundlof and Dr. Bell and Dr. Sharon Thompson has also attended some, the Steering Committee for Judicious Therapeutic Antimicrobial Use. This dialogue has meant a lot to us on this issue, talking back and forth.

I think one of the things all the stakeholders have to avoid on this is the drunk and the lamp post syndrome where we use the process and the data for support rather than illumination. And I think we are on the way there with the dialogues that we are having.

I think of the groups represented at this meeting, there is a reason so many veterinarians are here. And that is because we are uniquely prepared to address most of these issues. And we are responsible for both human and animal health in our daily activities. And we are the people on the front lines for the antimicrobial use decisions being discussed here and made.

We will be submitting more detailed written comments later, but we wanted to take a shot at addressing the three main questions and a couple of other comments. What is an appropriate risk standard to apply to resistant pathogens? Well, we are concerned that the assessment of fluoroquinolone use in poultry based only on possible adverse effects on human health is incomplete.

There has been significant process on this issue

through the risk assessment presented at this meeting. However, there is a risk not being evaluated. And that is the risk of harm from increased disease and impaired health of animals going to slaughter.

Whether or not you personally believe that an adverse event could occur due to the withdrawal of a drug from food animals doesn't matter at this point. The important concept is that pathogen load of target or other organisms could be either increased or decreased by withdrawal of the drug.

The assumption that only good can result from withdrawal of an antimicrobial from use in food animals is unfounded and is a dangerous precedent on which to proceed. Dr. Shaub this morning represented a refreshing concept in addressing water treatment to control Cryptosporidium. In addressing the Crypto. contamination of drinking water, could another hazard be created and what are the risks associated with that hazard?

I also noted a particularly appropriate statement by Dr. Morris this morning. "Don't forget the long-term, downstream sequelae of the lack of an appropriate first-line therapy." We should remember that enterofloxacin is an effective, improved therapy for colibacillosis in chickens. Removal of this agent would require the extra label use of antimicrobials to address this issue. We would move from a

labeled drug to the uncertainties of extra label use or to no therapy at all.

It should be remembered that there is an economic disincentive to use this compound in chickens which balances any desire that would be present to use it is a precautionary measure. And I would point out that we were HMO before HMO was cool.

We should also keep in mind that in some hospital studies, we see a dramatic decrease in resistance to the drug that is pulled from the formulary or an example of the Danish data with erythromycin with streptococci that after several years, the resistance level declined.

But some of these studies also report -- not necessarily that one, but some of the hospital studies I have reviewed -- an increase in resistance to the drug that was put in its place. So while we may focus on the drug that is taken away, what will happen with others that are then needed to be used in its place.

And Dr. Hueston in his presentation addressed these issues in point number six which was you can't do a risk assessment in a vacuum. And we fully realize the need to narrow down the risk assessment which is valid to as little variation as possible or as little complicating factors. But then we have to put that back into the larger picture.

What is the appropriate population on which to base a standard? Singling out one population or sub-population to me gives the impression that one population provides a more accurate estimate than another which we are not aware of. The percentage of the population that actually consumes poultry products should be taken into account in estimating the affected cases.

And I think an approach that is relevant to this was illustrated, again, by the EPA this morning and the strategy of evaluating the risk of the entire population that could be affected and then also considering groups with special attributes. I think what we come down to is the fact that we are going to look at all these groups and evaluate them individually. So I don't see the need to just say this one is it.

What is the appropriate legal standard to apply to the evaluation of resistance pathogens? I had that exact same thing, all those things fixed up there to refer to and I left them at home.

(Laughter.)

Taken at the expense of Dr. McClure there. I have got about this much on that. We don't believe the food additive standard for reasonable certainty of no harm was conceived with a concept of the complexity of microbial issues in mind. I think we are into a new area that is much

more complex than that was originally conceived to address.

Again, Dr. Shaub from the EPA has recognized -- said they recognize the futility of a zero risk approach in the areas they regulate. And their areas are similar and they involve complex interactions of source, environment, exposure and individual susceptibility.

I would have a couple of other things that I -- that also illustrate some cautions. In looking at attributing all fluoroquinolone resistance in Campylobacter to poultry, it does make the model more convenient and is an assumption that it is based on. In looking at that, one of the things that is said is the assumption that no fluoroquinolones were used in food animals prior to fluoroquinolone approvals in poultry. And that is incorrect.

Until the FDA CVM ban on extra label use in food animals, extra label use of fluoroquinolones in food animals was allowed under Compliance Policy Guideline 712506. And I think I have that number correct. While this does nothing to quantitative the use and does not propose that its use was widespread, it does point out that using the argument that no fluoroquinolones were used in food animals prior to poultry as a support for the assumption that the all resistant Campy comes from poultry is unfounded.

The issue becomes balancing between simplifying a

model and weighing some of those assumptions. So that is just a point I wanted to bring forward on that.

And the other thing I have noticed today, and this comes sitting there looking at it from the angle of a pharmacologist, is hearing speculation on potential links between virulence and susceptibility, I am not aware of concrete links.

And I luckily have a graduate student sitting back at Iowa State, affectionately referred to as the "Web Goddess" who I called up and sicked Virginia on this. And she came up with about 400 articles and searched through. And we found one with some type of link between -- or they thought potentially in an organism between susceptibility states and perhaps its ability to survive out in flora. And then we saw two others that were related to penicillin therapy of pneumococci that showed no correlation on the virulence.

So I am not saying that the data isn't maybe out there being developed. But as we talk about risk communication, I would caution us to some things like that as we speculate on whether or not it is true, or that maybe data gives a preliminary idea that that could be true, that we are very cautious in stating that because that is a -- coming from a pharmacologist's point of view again, to link virulence with changes in susceptibility is a tremendous

leap. And I would like us to have our ducks really in a row before that hit the press.

And I think that is a strategy we should all adhere to because that as we discuss these -- and I think you have been clear in that this is a speculation, but that we are very, very clear because this will be filtered through -- excuse me -- through, in my politically correct part of switching on now, through a scientifically challenged press to the public. So thank you again.

Keith Sterner, D.V.M.

DR. STERNER: I am scheduled to be a panel member, too. But after listening to this discussion, the only thing that I can do is shed darkness where they have attempted to bring light.

I do have one comment. And it stems from my experience in serving our country against all enemies, foreign and domestic. And it was characterized as the Ten Percent Rule. And it is more popularly know or enshrined as the Darwin Award with reference to risk standards and which populations we should look at.

And for those of you unfamiliar with the Darwin Award, these are individuals who have gone above and beyond the normal things that people do to thwart mechanisms that are designed to protect themselves and ensure that their genes do not pass on to future generations.

(Laughter.)

And I think that in all candor when you are looking at your risk model and risk assessment, there comes a point at which there are individuals who will no matter what -- no matter what efforts you make at protecting them from themselves, they will bring great harm to themselves and others around them.

And that gets back to Dr. Hueston's eloquent comments this morning about the need for a cost benefit analysis when you take a look at this. And I would echo Dr. Apley's comments that I always remind veterinary students who ride with us, "You have corrected one problem. And you may have created an entirely worse set of problems as a result of your corrections."

So -- and I realize that there is a limit to which you can do this. You are charged with enforcing the law and I don't envy you the task. You have done a yeoman's job thus far in trying to get us to some point that we all can live with it. With that, the panel is open to questions from the audience. If you would step to the microphone, identify yourself and ask the question, we will do the best we can to respond.

QUESTIONS/COMMENTS TO THE PANEL

DR. STERNER: Bob.

DR. CONDON: Robert Condon again. I am just

amazed sitting here and it just reminds me of a group of blind people grabbing a hold of the elephant, trying to describe what is going on. And I think maybe the best thing CVM can do with this whole process is to sit down and describe what is the legal criteria.

It is not 409. It is not adulteration. It is 512, okay. And 512 is basically all tests reasonably applicable. It is any substance formed in or on food. So the question there is Campylobacter resistance, is that a substance formed on food due to the use of the product.

I am not sure of the legal definition, if a bacteria is a substance. But that is the basis. Unfortunately, the adulteration issue is different between FSIS and FDA. FDA has a very easy standard. The food is deemed, deemed adulterated if it bears or contains an unapproved new animal drug. We don't have to show any harm. We don't have to show anything. Only that the substance is present.

Under adulteration under the food additives in USDA, you have other standards you have to meet. It is different. So that is -- the same thing, adulteration of the food, is different depending on which standard you do it.

And I think to make progress on the risk assessment, we need to define what standards we are working

with and make that clear. Just what do we have control over? What can be regulated? Because it is just everybody has their own idea and everybody is using their own standard.

Is it uncertainty of harm? Is it, you know, if you demonstrated there actually is harm? There are all different kinds of standards for food safety. Unfortunately, CVM can't choose which one it wants to use. These are animal drugs. It is 512. And I think it might be very helpful of CVM would lay that out right up front. Maybe you might have to do a little work on it.

But this is the standard. And then you can start looking to see how things are going to fit into that standard because you may arrive at different conclusions depending on the standard. So I think there is a lot of people's interpretation. And that is something we need to get squared away right at the beginning.

DR. STERNER: I'm not sure we have any panel members really qualified to respond to that, Robert?

DR. CRAWFORD: I am not qualified, but I will respond.

(Laughter.)

Well, I have known and admired Dr. Condon for over 45 years. But I think, Bob, I am sure you are not saying that just because we are not gifted in the law that we

shouldn't be addressing the problem of antibiotic resistance. And unless you are saying that, you should sit down and not say anything else.

(Laughter.)

DR. CONDON: No, it's not -- but it is what the standard -- do you use the standard of, you know, is there harm? Is it the standard that keeps showing that there is no likelihood of harm?

DR. CRAWFORD: Yes, but give us a break. I mean, we were asked to come up here and comment on the thing without worrying about having a lawyer sitting on each shoulder. So we don't need that.

DR. CONDON: No, it is important. Okay, because going down the panel --

DR. CRAWFORD: Well, maybe you and I should go outside or something.

(Laughter.)

DR. CONDON: But, no. People have made their comments in interpreting and based it on different standards. We've got to try to get people together so we are thinking of the same part. As long as somebody is using one standard and it is different -- and you might go off and develop a risk assessment that is great for this other standard.

But it is no good to CVM because it doesn't apply

to their section of the law. That is all I am saying. And whether it's -- you know, I am not saying it is your job to do it. But that is something that CVM has got to do because just in discussion of the panel, it points out there was at least three different interpretations of what the standard was.

DR. STERNER: I don't see anybody at a microphone right now. And I am going to give panelists a chance. But before we do, it may cut to the chase just a bit if I offer at least somebody from CVM the opportunity to respond to Dr. Condon's comments. And I think it is very germane to the task of the panel here if you would like to do that, anybody.

They are conferring right now. In the meantime, in the interest of keeping the proceedings moving, Dr. Angulo has a comment.

DR. ANGULO: Well, I just -- maybe it is tangential. But I like the image of an elephant. And I think it paints a good picture. But please recognize the elephant is moving and perhaps going down the hill. And it has been going down the hill since 1995 when serafloxacin was approved. And it gained speed when enterofloxacin was approved for poultry use.

And in the meantime, we were hoping to slow it down. And we see eventually slowing it down through the

framework process which was announced a year ago. And it has been a year. And we are at this destination which is wonderful step progress, a wonderful step forward. But we really need to gain momentum and address this issue.

And the way to address this issue is we believe that we really could diffuse much of the consternation on this issue of the framework if we could categorize the drugs. If the drugs were categorized, at least the strawman to allow people to comment on whether they think the categorization is appropriate, then those people that are concerned that the categorization would be over-stringent or under-stringent could begin -- we could then start that discussion.

So we need to categorize the drugs in the near term. We need to have near term discussions on where the appropriate thresholds are at -- on the one hand, it has been a Herculean effort to have this risk assessment. It was called for almost unanimously for it to be done. But at the same time, there was optimism when this meeting was first announced that this meeting would be talking more substantively about establishing thresholds.

And although -- not to comment negatively about the progress that has occurred, but recognize it is just a -- the delay is frustrating. And in the meantime, the elephant is still going down the hill. And we need to

mitigate the emerging fluoroquinolone resistance.

DR. MORRIS: Actually, if I could add to that, I would also second this idea -- this concept. Again, speaking as someone who is taking care of patients on a regular basis, we have an elephant who is sort of rolling down hill. Our resistance rates are rapidly rising. What was the rate for Campylobacter in the '99 data?

DR. ANGULO: Well, we don't have December data yet which might dilute it. But it is 21 percent. And last year, it was 13 percent. And that is not final data yet. But it is going to be two to three to four to five percent higher than 1998. And it is likely to increase at a rate of two to five percent a year.

DR. MORRIS: I have this vision of Rome burning as Nero fiddled sort of thing. And I can say that because I am not in the government. But we have a very substantive clinical problem on our hands. We have gone -- you know, there has been a substantive jump in resistance over the past year.

And we get into -- we could argue about thresholds for years. And as I said, it comes back to my concept, this is not a static process. We can't argue over the thresholds in the '98 data because they are already out of date. The process is moving much too rapidly for this.

And there must be a sense of urgency in this

because although I am concerned about the resistance in Campylobacter, I am scared, you know, I won't say what, about the emergence of fluoroquinolone resistance in Salmonella. And, again, that is not quite yet on the radar screen.

But the data that are coming out of Denmark says that even when you are not seeing at the clinical breakpoints, you are beginning to see clinical effects. And I don't want to be arguing three years from now about quinolone resistance in Salmonella when we are up at a rate of ten or 20 or 30 percent. I think there is a sense of urgency which needs to be instilled in the process. And I will stop at that point.

DR. STERNER: Dr. Beaulieu, it is your opportunity to respond for CVM to Robert Condon's comments.

DR. BEAULIEU: Yes, and I don't want these comments taken in any way as a response to what we have just heard since --

DR. STERNER: Sure.

DR. BEAULIEU: -- Bob's question came up. I would have to agree with Kent McClure's assessment I think. There is no safety standard per se established in 512. There is a lot of legislative history that would argue that it ought to be reasonable certainty of no harm. That I think is debateable to some extent. Some Courts have found that to

be a reasonable argument. Some Courts have not.

Even if we accept reasonable certainty of no harm as the standard, we still have to define what harm means in this context. And what we asked the panel for was their judgement about what they thought harm might mean in this context.

I agree that CVM, the Agency has to define at some point, has to try to quantify what is an acceptable risk in this context and start working from there. That is not an easy thing to do. We are charting new territory here. And I thought it was very important this morning that we heard how other federal agencies are dealing with this same issue and the kinds of standards that they are establishing to deal with some of the risks.

We will take all that information under advisement and we will certainly try to come up maybe in further processes like this with a standard that hopefully we can all live with. I appreciate having said that. There is some urgency to get on with this. We are concerned about the issue as you folks are.

There are things we can do in the meantime to try to mitigate this risk. And some of them are already ongoing now in terms of increasing judicious use of drugs in animals and so on. And we will certainly continue to do all that as we seek to try to quantify the level of risk that we deem

acceptable.

DR. STERNER: Other questions for the panelists? Fred, you had a comment?

DR. ANGULO: I think the point about is there something that can be done to mitigate the risk short of withdrawal of the drug which I agree completely, withdrawal of the drug demonstrates I guess failure might be -- I mean, it didn't work -- isn't there a way that we can figure out how to mitigate this problem short of the draconian approach of withdrawing the drug?

That doesn't serve anybody's purpose perhaps except for -- well. So is there -- can you mitigate the risk? And mitigate the risk, you can mitigate the risk by either decreasing drug usage or decreasing transmission.

And ideas on how to mitigate -- how to reduce drug usage -- well, first, I think it would be a wonderful show of good faith, although there is no legal requirement for it -- it would be a wonderful show of good faith, now the public health has shown -- believes that there is a harm from the use of fluoroquinolone in poultry, for the industry to provide the data -- drug use data freely to show how much fluoroquinolones have been used to the public; a show of good faith that you share the equal concern the public health has, provide the data.

And it would allow us to feel more or less

comfortable with this escalating resistance. If the drug usage is remaining fairly constant, we could interpret perhaps changes in resistance we are seeing with some -- have some understanding perhaps about whether it is -- whether mitigation is possible.

So I call on a show of good faith from the drug industry to provide, as they did in an excellent example in the United Kingdom when they provided fluoroquinolone use data in the United Kingdom in a similar manner. Kilograms of useable by animal species by year would help us understand the risk. If they share the concern of the risk, I think they could demonstrate good faith by providing that data, although there is no legal requirement for them to do that, obviously.

Secondly then, in terms of mitigation of the risk, decrease in drug usage, it is a wonderful development in terms of develop the judicious use programs. The one developed by the American Association of Avion Pathologists is a major step forward. And it would be very useful to show implementation of that and then to, as anything that is implemented, fine tune it according to what is or isn't working.

You heard the problems this morning with such a program for physicians. It is being fine tuned by studies that demonstrate where the barriers are, etcetera. Can such

studies be done amongst the relatively small numbers of poultry practitioners and just to see -- it would help ourselves as the risk identifiers. We would be assured if we knew the extent that the poultry veterinarians were adhering to these guidelines. So maybe a self-survey of how they are adhering to the guidelines that are developing would be useful.

Other ways to decrease drug usage is there could perhaps be evidence provided on the culture sensitivity necessity of using fluoroquinolones. And an interesting development in Denmark is that Denmark is now soon to be -- or will soon be implementing a requirement that before fluoroquinolones are used -- as I understand it, before fluoroquinolones are used for a second time on a premise, they must have culture sensitivity data that demonstrates its utility.

Thirdly -- then I mentioned that you could also mitigate the problem by decreasing transmission. And one way to decrease transmission, I don't know if it is practical, but perhaps those houses where birds receive fluoroquinolones, the integrators could schedule their kill schedule or their slaughter schedule so that those houses that get treated with fluoroquinolones, that they just simply go to slaughter immediately before clean-up.

And, therefore, we might decrease the transmission

at least to other houses that haven't been treated with fluoroquinolones. And then a house that is treated with fluoroquinolones, the -- doing studies to see whether it is useful to clean out the litter and spray wash the house before repopulating it with the next chicks would be very useful and might be a practical intervention.

Well, of course, all of these have practical concerns and economic costs. But they would help us in public health feel that at least the people share our concern and are beginning to address it. The reason why we feel the -- for an analogy, but the reason why we are frustrated that the elephant is going down the hill is because we have been calling for evidence of some mitigation for a number of months and perhaps years. And we are still unaware of any concrete evidence of mitigation.

DR. WAGES: Dennis Wages. I am a Professor of Poultry Health Management at North Carolina State University at the vet. school and also the Chairman of the Drugs and Therapeutics Committee of AAAP which are writing these guidelines Fred, they are not done completely.

The guidelines are I would say 75 percent complete. Ninety percent of the bacterial infections that we deal with, the guidelines are written and there are certain approvals.

And as most of you noticed, we have looked at

taking the neomycins and the streptomycins and the drugs that physicians would not consider important and we would consider are older standard drugs and use them labeled or extra labeled before we would go to a fluoroquinolone. And that violates -- that is against federal law.

And until we get some regulatory direction, we will still finish the guidelines. They will be as good the paper they are written on without AAAP and AVMA backing. So that is what we are kind of waiting on. But they will still be out there.

And things are being done. You know, every time that we get into a situation -- and I can't speak totally for every integrator in the United States. But every time that we get into areas where we try to go a direction, people that don't understand the poultry agriculture and the way we produce birds, it all comes back in our face as a negative connotation versus a positive act.

We have got companies that have purchased irradiating areas and companies that have done extensive research on pH adjustment of chillers to negate everything but Listeria at least, to reduce Campy through whole bird washes.

We have -- it is a practical -- when you -- you know, when you look at a suite and it has, you know, 100 growers or whatever and we have 100 growers in one county in

North Carolina and you try to truck chickens, it's just the logistics -- it's like, you know, when people say that a ten-percent increase in a production efficiency.

And just in chickens alone, that is 32.5 million tons of grain that we need extra. And then that lack of efficiency has to go somewhere in a clean-out. You want us to clean out every time. I think a lot of people would like to do that on certain areas. I have EPA over here telling me I can't do that because I can't do the deal. You know, it is just not a simple thing.

But it is unfounded I believe in my opinion whole-heartedly to think of this issue as -- I used to have a lot of hair. And I thought it was going to turn gray and it didn't. It fell out and turned gray.

(Laughter.)

But they do and they care. And their product has their names on it. You know, if they go down the tubes on bad product, that is their livelihood. And I am not, you know, sitting up here saying that I am going to equate sick chickens with a human. And I am not going to do that and I don't think we should.

But we still have a job to do, too, to provide protein. And we still feel that consumers are choosing either a chicken or soy bean or beef or whatever. And there is a need for the consumers to own up to some responsibility.

But we intend to take as much action as we can to try to mitigate, if you will, and look alternatives prior to product removal. That may have gotten into public comment and I am sorry.

DR. STERNER: That's all right. It is germane to the discussion. Are there other comments from the floor for our panelists? If not, seeing none, we are slightly ahead of schedule.

Mike Bolger is scheduled to come in sometime. And he has yet to make an appearance. But when he does, we are going to afford him the opportunity to do ten minutes just ahead of our next start time. We are scheduled for a break for 15 minutes. We will break for 15 minutes from now and start then. Thank you.

(Whereupon, a brief recess was taken.)

DR. STERNER: This morning's speaker, Dr. Mike Bolger, did finally make it down from Annapolis. And he has quite a tale of woe to tell. But that is not germane to the deliberations at hand this afternoon.

Dr. Bolger is the head of the Contaminants Branch in the Center for Food Safety and Applied Nutrition, that is CFSAN. His group is responsible for the hazard-safety risk assessment of natural and anthropogenic food-borne contaminants. Dr. Bolger.

ASSESSMENT OF RISK: CONTAMINANTS

Dr. Michael Bolger

DR. BOLGER: Well, I want to apologize for my tardiness. Unfortunately, on the way in from home, I blew a tire and was on my hands and knees about the time this presentation was supposed to be made, changing my tire. I had to return home, find my wife, get her car and start all over again. So I did have the best intentions of being here. Unfortunately, my rather dated car didn't want to cooperate this morning.

My task, as I understand it, is to give you a very brief, ten-minute overview of how we deal with contaminants in the food supply. And I -- when I talk about contaminants, as indicated in the introduction, we are talking about contaminants that are either natural origin or of human-derived origin.

Now, I know that you have had several presentations on pesticide, safety assessment, risk assessment and I believe food additives. I will try not to go over the same material. Oh, right here. Go it.

(Slide.)

But as any true risk assessor, I always have to start off with my risk assessment paradigm. It gives me an anchor by which I can move from. And in terms of how we approach safety risk assessment in dealing with contaminants, this is the paradigm that we generally work

in. We don't have pointer, right? Okay.

So in terms of risk assessment, I make a fairly pronounced distinction between what I call safety assessment which is what most people are thinking about and talking about when they are talking about risk assessment, and in terms of quantitative risk assessment.

So most of the time when we are talking about risk assessment, we are really talking about safety assessment which is very much like what you have heard about in terms of the pre-market safety assessment paradigm that is practiced in terms of pesticides and food additives. Okay. Could I have the next slide, please.

(Slide.)

And I will come back to this paradigm here. I have no way of forwarding this. And but remember that in terms of how we deal with safety and risk assessment for food-borne contaminants, the standards that we use are really dictated by what Congress has delineated in the act. And, again, I think for pesticides and food additives, those standards were already described to you.

For contaminants, we deal with a section of the Act called 402(a)(1). And there are two standards that apply here. One refers to it may render injurious to health. And that is for substances that are added.

And when I mean added, in other words, there has

to be the hand of man evident. It doesn't have to be completely responsible for the presence of the contaminant. And a good example is aflatoxin where part -- aflatoxin is found because it occurs naturally. But, also, you have elevations of the levels of aflatoxin because of the storage conditions under which the grain is kept and therefore the hand to man in part dictates the total level of aflatoxin you would find in the grain.

Then the other standard for contaminants is the ordinarily rendered injurious to health. Now, Congress doesn't really tell us in a quantitative sense what is the difference between these two standards. And when I say ordinarily rendered, this is for contaminants where there is no obvious hand of man present, okay, or acting.

Now, what I usually describe the ordinary rendered injurious to health standard is I call it the body bag of evidence. And what I mean by it is that we actually have information of adverse reactions at the exposure levels that we are concerned about to that particular contaminant.

Now, we could go with evidence based on laboratory animal work. But generally, when you look at the dose range used in laboratory animal work, they are quite a bit higher than what you normally would find, okay, in terms of exposure levels to the contaminant of concern. So you are always making an extrapolation of dose from the animal work

to the exposure levels that you are concerned about. And they are many-fold different.

And it is rare that we actually have effects in animals in the dose range that is equivalent to the dose range that we are concerned about in terms of human dose. So generally it will come down to we really need evidence of adverse effects in humans.

Another standard that I just want to briefly mention is that -- that applies to dietary supplements which you haven't heard about and I don't really have time to go into. And there Congress identified the standard as the dietary supplement presents a significant or unreasonable risk. Okay.

But I just wanted to point this out, that within the Act itself, you have these different standards of risk that Congress has identified as to whether you are talking about contaminant, a dietary supplement, a pesticide, a food additive or whatever. Can I have the next slide?

(Slide.)

All right. Thank you. Now, one of the -- there are some key issues that we have to deal with in terms of contaminants in terms of setting a formal standard which we call a tolerance under Section 406 of the Act. And one of the distinctions which I have already alluded to is this distinction, is the hand of man evidence.

Another is avoidability. In other words, whatever standard we set, there has to be a reasonable expectation that you can avoid that level of exposure and that standard will meet that. In other words, if you set a standard so low, okay, that it is -- no matter where you look you can't avoid it, then you failed the standard as defined by the Act.

Another one is detectability. You could go through the safety assessment paradigm. You could identify an acceptable daily intake, a tolerable daily intake, a reference dose, a minimal risk level, all of the same terms for a safe level. If it is well below what you can actually measure, then the Act says, no, again, you have failed the detectability standard as delineated in the Act.

Then you also have to consider multi-source and pathway analysis. In other words, with lead, we couldn't just consider lead from the diet. We had to consider lead from all the other sources and pathways that humans are exposed to in terms of realizing their body burdens.

And then another factor that we have to take into account is the competing dietary risks. In other words, if you set a standard and you eliminate a certain portion of the food supply by that standard, what are the resulting competing risks that you have to take into account in terms of the nutritional loss and risks, in terms of the fact that

if you remove this source of protein and the population has to go to another source of protein, have you considered the competing risks?

A good example is if you are concerned about a chemical contaminant risk, you do something that -- in other words, you come up with a risk management decision that results in someone consuming less of this source of protein that you are concerned about, you go to another source of protein where there is a great microbiological risk. So you have to weigh these competing risks in terms of the standard that you finally decide on in terms of a chemical contaminant.

(Slide.)

I have already gone over that. Just briefly in terms of, again, when I talk about safety assessment, in terms of what you heard about food additives and pesticides, I mean, this is a paradigm that was set up by Arthur Layman and Fitzhue in 1954. And basically, it comes down to the use of what we call, for instance -- in food additives, it is called safety factors.

At EPA, the reference dose is called an uncertainty factor. But they are basically -- you know, they are. They are the same thing. Okay. They are a different term for the same thing. You are trying to account for really two issues in terms of the ten-fold

safety factor, to account for inter-species extrapolation -- in other words, going from laboratory animals to humans. And then also to account for human sub-population sensitivity, you use another ten-fold factor.

Now, you know, since Layman and Fitzhue set this up in '54, there have been further modifications to this. One is the additional use of another ten-fold factor that is used for the reference dose where you are taking a sub-chronic, in other words, a less than lifetime study. And you are extrapolating to a reference dose which is intended for chronic exposure. You would then apply another ten-fold factor to account for that.

And then there are other factors that are called modifying factors that are applied sometimes to account for uncertainties that are surrounding the severity of the response. You have preliminary information on particular end points, immunological or developmental. But it is very sketchy, highly uncertain, but somewhat suggestive. And depending on how conservative you want to be, an additional modifying factor could be applied.

(Slide.)

Another important distinction here though, in terms of the safety assessment paradigm that I have been talking about, and I am sure you have already heard about this, but bear in mind, in terms of the safety assessment

paradigm, there is a distinction in terms of when we are talking about a non-carcinogen versus a carcinogen. The methodologies are different.

I have just told you about the safety assessment paradigm that applies to non-carcinogens. Now, for carcinogens, basically, what the process involves is the extrapolation generally using dose information from a bioassay. And it is a downward extrapolation because, again, the dose range that you are studying in a cancer bioassay is many-fold higher than the dose range or exposure range that you are concerned about.

So it is an extrapolation downward. And it could be linear or it could be sub-linear. It could be super-linear. It could be, you know, any way you want to model it. Now, generally the default way to do it is through a simple linear extrapolation, through zero. But I just wanted to point out this distinction in terms of safety assessment in terms of these two general categories of end points.

(Slide.)

It is important to bear in mind though that this safety assessment paradigm is really a first step in an iterative process. And I showed you that model, that paradigm in the beginning. And as I pointed out, there are many terms that have been coined to -- that really do mean

the same thing.

And I think sometimes this lends some confusion that when somebody hears the term ADI, TDI, reference dose or minimal risk level -- this is the Agency for Toxic Substances' terms -- that these are different paradigms. They are not. All right? It all goes back to Layman and Fitzhue in 1954. So I think you need to bear that in mind.

And it is a very useful screening paradigm for rooting out or eliminating trivial public health problems. And that is that by and large it serves us very well. It provides us with the answer to say this answer is sufficient to assure us of a level of safety and we need to go no further.

And as I said, by and large, when you are talking about pesticides or food additives or contaminants, that is as far as we have to go. Now -- but there are problems and there are instances where it doesn't always serve us that well.

And that is those are the cases that you hear a lot about and that is the leads and the dioxins and the PCVs because when you go through this safety assessment paradigm where you end up looking at a whole data set of information, you select one study.

You identify one dose level called the no observed adverse effect level or the lowest observed adverse effect

level. And you apply your uncertainty safety factors. You end up with an ADI, TDI, whatever term you want to call it. And you compare that to your estimates of exposure. And lo and behold, your estimates of exposure are over this safe level.

And so -- okay. And so you reach the conclusion that it is unsafe. Well, from a contaminant standpoint, going back to what the act mandated to us in terms of avoidability, detectability, competing dietary risks, we need to think about risks above the safe level because we have to weigh our risk assessment at the end of the day against these other issues.

(Slide.)

So -- and just to point out that in some minds and in some circles, the uncertainty safety factor issue is deemed to be not a science issue, but a risk management issue. In other words, it is -- and the size of that uncertainty safety factor range is dictated by your level of ignorance. In other words, the less you know, the bigger it is. Okay? And so some people look upon that at the end of the day as a risk management tool. And just let me --

(Slide.)

So just getting back to this paradigm, for contaminants, many -- most of the time, we operate very well within the safety assessment consideration of paradigm. But

there are issues like lead, PCVs, methyl mercury, where we really need to move to the next level of the paradigm and deal with issues of the degree of adversity, the variability and uncertainty of dose response.

(Applause.)

DR. STERNER: Questions for Dr. Bolger on contaminants? That was very clear and very understandable. After the day you have had, we appreciate you just showing up. It is just good to have you here. You can go down here. We are all set. We are moving here to the public comment period. So we have an hour scheduled for this. Dr. Sundlof, did you --

DR. SUNDLOF: No, I am just going to sit up here.

PUBLIC COMMENT PERIOD

DR. STERNER: Okay. Good. We will ask that speakers who -- will identify themselves who come and wish to make comments about this portion of the deliberations, identify themselves and their organization. You will have three minutes. Jim will signal you when you have 30 seconds left. And we expect you to bring it to a close at that time. So with that, we are open for public comments. Richard.

DR. WOOD: Thank you. This way I get to catch my airplane. I am Richard Wood. I am the Executive Director of FACT, Food Animal Concerns Trust. We work on food safety

issues related to meat, milk and eggs. We also have a model layer operation where we -- since 1991, we have had Salmonella enteritidis controls in place on our farms and market the eggs on the east coast and in the midwest.

According to a presentation we heard yesterday, I think it was Dr. Long, he indicated, and others have, as well, that science is but one of six inputs that are considered in a risk management decision making process, public values, economic factors and so on.

So my comments come from this broader perspective that must be considered in a risk management decision. Regarding the risk standard, the way that I think we would approach this is that since the goal of risk management as defined by the risk assessment is the reasonable certainty of no harm, and since this particular risk assessment that we have been presented with has demonstrated that there is potential harm to at least 5,000 persons, then we believe that mitigating steps must be put in place immediately.

To look at this as a risk assessment model, what I am trying to say is that you give us data that shows that there is potential risk to X number of people, 5,000 or whatever. Then we want a response. We want to see some risk mitigating steps put in place and, in fact, would support a moratorium on the future use of fluoroquinolones in treating poultry as an optimum mitigating step.

Does the FDA have the power to take that step? Well, it is my understanding that removing a product from the market can be a lengthy legal process that may take up to six years. And in raising this issue with them, I am told that it is highly likely though that if the FDA is seen to have its ducks in line, I think someone has said earlier today, and the elephant is going down the hill, to use another image, that perhaps there would be cooperation on the industry side to respond to any mitigating steps that the FDA had arrived at.

And yet the recent experience with FSIS with the Texas plant suggests that good will may not always abound. And so to meet its obligations under this risk assessment, the FDA should pursue statutory changes that will give it full enforcement powers.

At a minimum, we would call on immediate steps to be taken to reduce resistance coming from poultry. And I thought that in this two-day workshop, that there would be a greater emphasis placed on discussing actual mitigating steps that would relate to this model.

And we have heard some of those. Yesterday, on-farm interventions were suggested by one speaker. Dr. Cray suggested processing contaminated flocks first. Dr. Angulo was offering some steps that the industry might take. But as a consumer organization, we believe and ask that there be

mitigating steps taken immediately or as soon as possible.

What is the appropriate population on which to base the standard? Well, yesterday Dr. Bell indicated that fluoroquinolone use may soon be appropriate for children which according to another chart that we saw yesterday from Dr. Smith may -- is the largest population infected by Campylobacter. As a group such as ours, concerned about public health, children, the immunocompromised and the elderly, the high risk populations are the appropriate populations for us to consider in mitigation steps.

What is the appropriate legal standard? Well, we are not equipped to answer that question. But I would like to affirm that the risk management plan and the threshold setting should be established through a public process as we are going through today with public notice, public comments, public meetings and formal agency action.

As the risk assessment is a valued process partially due to its transparency, so, too, must its risk management be. Thank you.

DR. STERNER: Thank you. Further public comments? Dr. Sundberg.

DR. SUNDBERG: I am Paul Sundberg. I am a veterinarian with the National Pork Producers Council. And perhaps I could start with just a comment to expand a little bit on Richard Wood just said. One of the things about the

whole process of this issue is the two-day workshop that would help give some input into the process. And the whole process is what we are really concerned about right now.

We would like to make sure that we have adequate opportunity for input. And that includes perhaps a suggestion of a real workshop type of format that we could work off of for the coming meetings. So we've got examples of veterinary feed directive. We've got examples of HACCP process. We have got a number of examples that offer stakeholder input.

And it really comes down then to stakeholder communication. Communication from FDA CVM to the stakeholders here is one thing. And I think offering that kind of input and that type of process would very much help.

Dr. Lieberman made the comment that she was questioning what is the impact going to be. And if we would have -- we would use the transparent and open words. But if we would have a format that we could offer discussion and real input, we might feel that we have more of an impact into the process. So that comes under communication with the stakeholders.

Another opportunity is communication. And the stakeholders -- when I am talking about stakeholders here is these that are at the meeting. We know what the issue is. We know what is going on.

Another real opportunity here is to take advantage of Dr. Hueston's eloquent comments and also other comments that have called for communication -- outreach communication if you will, risk communication. As I think Dr. Hueston said, saying that the process is done isn't enough as far as communication goes. The real challenge is going to be to be able to communicate what has happened, why it has happened, what the next steps are. And that also then to be effective should include all the stakeholders into that process.

Finally, one comment and I think the risk communication, the very importance of that is to maintain consumer confidence in the products we have. Without that, as I think it was said before, you will hear numbers and you will say risk and that is all it is going to take. But in order to communicate clearly the real risk and really the process, that will help maintain consumer confidence in the food supply.

Finally, adding NPPC's congratulations to the chorus of congratulations that have come in bringing forth the risk assessment certainly is in order. One of the things that we are concerned about is that we have only, as everybody else, have had just a few days to take a look at it.

And that is very important that CVM remain open to input in this process. We will be submitting written

comments, further written comments that will give specifics on the risk assessment. Thanks.

DR. STERNER: Thank you. You get an extra ten seconds for compliments, by the way.

(Laughter.)

DR. PRETNICK: Steve Pretnick with the National Chicken Council. We would also like to congratulate CVM for going through this risk model development. We do have a number of concerns, however, with some of the assumptions that were made, as well as the scope of the model. And we will address those in writing in detail.

I would also like to add that we, too, support a workshop. We feel that some of the concerns that we have with the model could have been addressed if there were an opportunity for the industry to have a dialogue with CVM. We could have worked out some of what we think may be erroneous assumptions.

But, anyway, we, too, would like to be a part of this process. And we think it would benefit all the stakeholders if we could have such a workshop and move forward.

DR. STERNER: Thank you. Dr. Berkram.

DR. BERKRAM: I am Tom Berkram, Executive Director of the American Association of Swine Practitioners. And first of all, I would like to make a bit of a correction,

with the permission of my esteemed colleague from North Carolina, about poultry when he was listing the different commodities.

I am sure it was an oversight, but he forgot to put pork on that list. So I would just include that right now.

DR. WAGES: I apologize.

DR. BERKRAM: Apology accepted.

DR. STERNER: The other white meat.

DR. BERKRAM: Right. Now, at the risk of turning this into a love fest., I would commend Steve and his staff for doing this risk assessment. We think that it is a good first cut. And that is a quote from a statistician that we have engaged to review this risk assessment. Given the short period of time though, we haven't done a complete review.

And in the preliminary review, we have discovered some areas that we feel will need to be clarified, modified and corrected. And we will be offering complete comments in writing at a later date.

Just as the risk assessment is a good first cut, we feel that this should just be the first step in the ongoing discussion of this particular issue. And I would echo the comments from a number of the people already that although we recognize the value of this format being a

lecture format for a meeting.

For transfer of information and knowledge, we think that a really substantive and interactive workshop would certainly advance everybody's feelings about this, to feel more comfortable with the risk assessment and the stakeholders having that input.

Lastly, we would urge the FDA to continue to recognize the complexity of this issue. Although I can now describe this risk assessment as a very simple mathematical model, although I often question that, that really belies -- that description belies the fact that this is still a very complex issue. And we would certainly not want to see simplistic mitigation tactics or strategies imposed on an industry -- on the animal agriculture industry without some consideration being given to all the consequences, intended as well as unintended. Thank you.

DR. STERNER: Thank you. Any other comments? It is about that time per day. I have seen many post-prandial insulin surges here and some eyelids being stared at from the rear side. It probably would be good to stand up and recirculate static blood for about five minutes. And then -- please, Dr. Sundlof.

DR. SUNDLOF: Yes, I just -- I made a terrible oversight yesterday in not recognizing one individual who was more or less responsible for the creation of the risk

assessment and that was Peggy Miller who has left CVM for bigger and better things. And for some reason, when she walked out the door, she kind of checked out of my memory.

(Laughter.)

But I think it is very appropriate to make sure that Peggy Miller does get recognized for having the vision to put this whole thing together.

DR. STERNER: So we have a five-minute break here. And then Dr. Thompson will start.

(Whereupon, a brief recess was taken.)

SETTING THRESHOLDS AND NEXT STEPS

Sharon Thompson, D.V.M.

(Audio missing.)

DR. STERNER: --- small animal and exotic practice. She holds her bachelor's degree from Harvard University -- excuse me, Harvard University in 1983 and a D.V.M. degree from the Virginia-Maryland Regional College of Veterinary Medicine, 1987. Dr. Thompson, it is my distinct pleasure to turn the podium over to you.

(Slide.)

DR. THOMPSON: Okay. Well, my big benefit was going to be that I was going to get us out of here early because I had budgeted extra time so that I could accomplish that. But you have done such an excellent job, Keith, that we -- I don't even have to work at it.

I wanted to just spend a minute commenting on some of the points that people made in terms of I guess their disappointment that we had not gotten more into the subject of thresholds at this particular meeting. As many of you know, initially in the planning of this meeting, we did plan to have a whole session to talk about the establishment thresholds.

But similar to you, we basically got -- CVM got the draft risk assessment model very late. And that was through no fault of anybody's. But that was the reality. And we just did not feel that we would be prepared to discuss not only the validity of the model, but exactly how it would be used in terms of the establishment of thresholds.

So just to explain to you that we certainly do think that the issue of thresholds is an important issue. I am going to provide you some very preliminary comments today. We do plan to look more at this issue in the future. And so just to give you a little bit of background on that.

(Slide.)

First, I wanted to start by giving people some history in terms of how we talked about thresholds in the Framework Document and then to talk about how this could fit into the risk assessment model itself. In the Framework Document, the FDA talked about two different kinds of

thresholds, a resistance threshold and a monitoring threshold.

The resistance threshold really was envisioned as being the upper limit of resistant bacteria that could be transferred from animals to humans and still be considered safe. And in the document, we basically had talked about this threshold being established in humans.

The monitoring threshold was viewed as being established either in humans or in animals. We didn't define which and actually asked for comment on that. But it was envisioned as being an early warning system so that when you were approaching the monitoring threshold, basically the monitoring threshold could either be loss of susceptibility or frank resistance in terms of a resistance prevalence.

And when you were to approach that, the sum action would be taken, basically mitigation action in terms of further investigation or potentially changes in terms of how the drug was used on the farm, changes in management practices. That was what was envisioned in terms of a mitigation action.

As I said earlier, basically the resistance threshold was defined in humans. And for Category 1 drugs -- I would like to focus on that today -- the Framework Document stated that the resistance threshold would need to be zero or very low. This doesn't necessarily mean that

resistance in animals would also necessarily have to be zero if data was available to show that some level of resistance in animals would not result in crossing the resistance threshold in humans.

For each Category 1 drug, the Agency would need to define the end point of concern. And what I mean by that -- I will give you an example. The Framework Document discussed resistance in Salmonella as the end point of concern for quinolones. Therefore, resistance developing in other pathogens such as Campylobacter would not necessarily raise the same level of concern as resistance developing in Salmonella.

I don't mean to say that we would not be concerned about resistance in Campylobacter. Just in terms of the human health impact, we would be more concerned about resistance in Salmonella.

The end point is, obviously, very directly related to the risk standard. Now, as Linda earlier had mentioned, in terms of the Framework Document, that was defined as the loss of availability of safe and effective antimicrobial drugs to treat human disease. For Category 1 drugs, the end point was more specifically highlighted as the loss of significant human antimicrobial therapies when alternative drugs were limited. So there was a consideration of alternative therapies in terms of the categorization

process.

Linda had also mentioned that we have put out an analysis of the comments that we received on the Framework Document. And in case anyone has not gotten that, it is out on the -- copies are out on the table outside.

But I wanted to briefly mention a few points with respect to the thresholds. Basically, we received many comments as were made earlier, as well, about the need for extensive public dialogue and stakeholder involvement as we move forward, and especially on the issue of threshold. FDA definitely agrees with that.

I think we -- and the reason I was late getting up here -- and I apologize -- was that I was following up with Dr. Sundberg in terms of what were his thoughts on how we could design a better process in the future in terms of interaction in a workshop. So I do think that that is very important.

We also mentioned in the comment analysis that because really of the difficulty that we envisioned in establishing thresholds, that we are considering limiting that requirement in terms of a formal threshold only to those products that would be classified as a Category 1 product.

(Slide.)

Okay. In terms of setting thresholds, we really

envision that there is two ways that it could be done. One way would be what we consider a technology-based method and the other would be more of a health-based method.

In terms of a technology-based method, what we mean by that is that a technology-based threshold typically would be established by measuring the amount of contaminant currently present. So, for example, HACCP limits for Salmonella contamination on carcasses were established by measuring the current level of carcass contamination.

And then if a qualitative risk assessment were to suggest that that amount represented an unacceptable risk, then further regulatory action could be taken. In the HACCP regulation, USDA concluded that the current food-borne disease burden due to Salmonella was too high and required the levels on carcasses to be lowered.

For antimicrobial resistance in animal food-borne pathogens, a technology-based threshold could be established by measuring the amount of resistance present in the food-borne pathogen for approved products or the amount projected to develop based on pre-approval studies. And if that level was viewed as representing an unacceptable public health risk, strategies could be developed to decrease the disease burden or the resistance level.

While technology-based thresholds have an advantage in terms of the ease of establishment, the values

are not necessarily tied to public health outcomes.

The other method that is routinely talked about in the literature is health-based thresholds. And these are usually established based upon a safety assessment. Since public health risk is a product of hazard times exposure, health-based thresholds are generally established by performing a comprehensive evaluation of both the hazard and exposure.

Establishing health-based thresholds, however, on the basis of a quantitative risk assessment for all antimicrobials and all pathogens would be difficult and resource intensive due to the lack of quantitative data on public health outcomes related to the use of antimicrobials in food animals. And in some cases, these also may be difficult to directly relate to public health outcomes due to uncertainty and the quality of available data.

The risk assessment model does facilitate the establishment of thresholds because it builds a link between resistance levels of animals and resistance levels in humans and ties that to a human health impact. The ability to link these two can assist us a regulatory agency in setting thresholds.

But, however, as we heard during this meeting, we really must first define certain questions including a more clear definition of the risk standard. And then we must

also talk about what is the regulatory end point of concern.

If we go with the definition of reasonable certainty of no harm as defined in the Framework Document where we look at loss of available therapy, then we would need to look potentially at the particular drug or class of drugs and say what are we most concerned about in terms of resistance development with this particular drug and the particular pathogen of concern.

So one approach could be to use a hybrid of a risk assessment and a safety factor approach to established thresholds. For example, the complete risk assessment would be conducted for the pathogen that develops resistance the soonest or what we could call the sentinel food-borne pathogen in the animal species associated with the most food-borne disease due to that pathogen. And we could call this the reference animal species.

For example, with quinolones, we could choose resistance developing in Campylobacter and this would be the sentinel food-borne pathogen, in chickens, which could be the reference animal species. The risk assessment model could then be used to determine when an unacceptable human health impact is reached for the resistance threshold established in humans.

And furthermore, to calculate the level of resistance permissible in the sentinel food-borne pathogen

on the reference animal species at slaughter -- and this would be the monitoring threshold -- the monitoring threshold could then be applied to all other species and be protective of the public health because the food-borne disease burden from other species associated with that particular pathogen should be less than that of the reference species. And that is inherent in how you define what the reference species would be.

(Slide.)

For food-borne pathogens with health impacts greater than that of the sentinel bacteria, it may not be possible to wait until resistance develops to assess the public health impact. And this point has been brought up during the meeting before, that you may not want to wait until you have enough data to a quantitative risk assessment and judge what is the human health impact because at that point, you know, you are already too far.

So, for example, specifically mentioning the issue that has been talked about, the Agency may not want to wait until fluoroquinolone resistance develops in Salmonella to support a full-blown risk assessment on this Salmonella-related human health impact.

In this case, a safety factor could be determined and applied to the monitoring threshold established for the sentinel bacteria to be protective of the public health.

And mitigation action could be warranted when either the monitoring threshold in the sentinel bacteria or other food-borne pathogens would be reached.

So in this kind of approach, we would have more than one monitoring threshold for fluoroquinolone resistance that would trigger the need for mitigation. One might be in Campylobacter derived from a quantitative risk assessment and another might be in Salmonella, either reduced susceptibility or low level resistance depending on where we go, derived from a more qualitative risk assessment and the application of a safety factor.

(Slide.)

I want to talk a little bit also about some other critical risk management tools. I mean, we are focusing here on thresholds. But I really do think it is very important that we believe it is critical to also look at judicious use of antimicrobials. I think we -- Dr. Sundlof mentioned this and others have mentioned how supportive we are of the work that is going on by the AVMI. And we really do believe that this is a critical piece of the equation.

The application of these principles are critical in managing the risk of antimicrobial resistance by limiting the use of important human antimicrobial in food-producing animals to only when it is really necessary and thereby reducing the selective pressure for the development of

resistance.

In addition, another critical piece of the equation has also been mentioned during the meeting, the impact of HACCP and what impact that has in terms of overall food-borne disease. While we believe the risk assessment was appropriate designed to estimate risk to human health from resistance food-borne pathogens associated with the use of antimicrobials in food-producing animals, the current apparent effect of HACCP is to reduce human exposure to food-borne bacteria which could concurrently reduce illness of people.

So this is something you can't ignore in terms of the overall management of risk because if overall food-borne disease burden goes down, then concurrently hopefully resistant food-borne disease would go down. So I think -- we feel that although we think we have looked at the issue from our prospective appropriately, we also feel that this is a very critical piece of the equation.

(Slide.)

Now, I just want to make a very few comments in terms of next steps, first, focusing really on the risk assessment itself and what we plan in terms of moving forward in terms of that. Basically, we do plan to review comments made both at this meeting, as well as comments made to the docket. And I have put here the docket number to

submit comments to us on the risk assessment model.

We will consider whether the model, itself, should be revised. There were some comments made during the meeting in terms of suggestions that we should have looked at certain aspects. So we will certainly review those and make an assessment as to whether we believe the model should be revised.

We will also consider any additional data that is submitted to us as part of the comment process, either data that is submitted or referenced either at the meeting here or in the comments. We will look at that.

We will also consider suggestions to generate new information to refine the risk assessment. For instance, if an industry group has an idea of data that could be generated that they are interested in collecting that would perhaps answer some of the questions or address some of the data gaps that are identified in the risk assessment, we would certainly more than welcome conversations on that and suggestions on the data that would be most useful.

(Slide.)

And then finally, we do plan to publish the final risk assessment after we consider the comments. We will try to address all the comments as much as possible in the final report. We will try to either clarify points or, obviously, modify things or include additional data. So we will try to

improve the description.

There has been a number of people who have pointed out certain things in terms of -- either during the meeting or on the side about some need to clarify certain pieces of logic in the report. And we will certainly do that.

We are also aware -- it has been made aware to us the inconsistencies in the current draft. It has been pointed out that there are variations between some of the charts and formulas amongst the sections. And we do plan to try to correct those inconsistencies and put up a revised draft in the next few weeks. So -- and basically, I beg your indulgence.

We were more concerned with getting it out to the public so that you would at least have some time to review it before the meeting and rather than the report being a perfect draft. So we do plan to correct that and we will post a revised draft in the next few weeks.

In addition, we will be putting up the -- a spreadsheet on the web so that you can actually download that and look at the data yourself. So we will be putting that up and making that available to people. And that will be on the CVM home page.

Now, moving from the risk assessment in terms of the issue of the risk standard, we would certainly also appreciate additional comments submitted to us in terms of

that particular issue. I think, at least I hope that you got a sense of the fact that this really is a very difficult issue that we are struggling with. And we do want stakeholder input on this issue. So we would look forward to additional comments.

We do also plan in terms of additional meetings, we plan to have a meeting on the design of pre-approval studies. That is currently scheduled for February 22nd through the 24th. And we hope to have an agenda, a draft agenda available soon. And that will be posted on our home page. So look for that, as well.

And we will also hold additional meetings as needed. Obviously, the issue of thresholds needs further discussions. So we do plan to engage the public on that issue, as well after we have looked further at the risk assessment and the comments that are submitted on that model and basically made some assessment of how we can use this.

So I think we do want to move forward as quickly as possible on that. But we felt it was important at this meeting to at least first get some validation and opportunity for people to give us comments on the validity of the model itself. So we do plan that. Also, monitoring that has been -- as some people have suggested, that we need to hold a meeting on that, as well.

(Slide.)

In terms of future risk assessments, I think many of you are aware that we are also planning to do a risk assessment on enterococci. And I was listening very closely during this meeting in terms of public process. And I think that one message that I am certainly taking home from the meeting is the need to begin the dialogue early.

And so I think that is very important. And I fully agree with that. And so what I would like to do in terms of as we move forward into the next risk assessment is to develop a public process, at least have some sort of notice defining the scope of the risk assessment that we are looking at and a call for information in terms of any relevant information on the issue and suggestions for how potentially the model could be designed.

So I think at least I have heard that very clearly from people. And if people have any other suggestions to make to me in terms of how to deal with communication in the future on this, I would certainly appreciate that, those comments.

And finally, just in closing, I want to thank you for everybody's participation in the meeting, especially the speakers who I know in terms of organization, I pressured a lot of people to come on very short notice to the meeting. So I really do appreciate that. I appreciate everybody's

input into the dialogue at the meeting.

I think that, at least from my perspective, it was a relatively balanced meeting and we had some good discussion, sharing of views but, as Dr. Sundlof said in terms of ground rules, no personal attacks. So I think that was excellent. So I will close there and answer any questions that I can.

(Applause.)

DR. STERNER: Questions for Dr. Thompson? Robert.

DR. CONDON: Could you clarify, you are going to put out another draft or something in the near future and would it be best to wait until that comes out and comment on it? Because -- could you kind of maybe highlight a few of the things you are going to change like some of the arithmetic differences and some of that?

DR. THOMPSON: Yes. And I mean mainly it has been -- and I may ask David Vose also to make a comment on this. But there were some -- we were working people in disparate places and people were out of the office for certain periods of time. And so there were some inconsistencies in some of the charts and the formulas from different parts of the draft.

In terms of really the discussion or the issues that were presented, that is not going to change. You know, we would clean up some of the typos, too. And that is -- if

you would like to wait for that, we do plan to do that in the next couple of weeks.

But in terms of the issues that we are posing and how the model is constructed, none of that is going to change. It is just cleaning up some of the presentational issues like that. I don't know, David, if he is here or if he wants to comment on that either. But -- sure.

MR. : I would like to make a suggestion that you when you do the next draft, you put line numbers so when we are making comments.

DR. THOMPSON: Okay, we will try to do that.

DR. STERNER: Dr. Richard Carnival is recognized.

DR. CARNIVAL: Yes, I am Rich Carnival from the Animal Health Institute. And, Sharon, recognizing there is going to be continued discussions on this threshold it sounds like and further workshops, there are some questions that have been bothering me for a long time about thresholds.

And I just thought it may not be fair to ask you these now because you probably can't answer them. But I thought I would want to get them out there for the record just to have people think about the idea of thresholds and exactly where we go with them.

First of all, it has been troubling me for a while as to how FDA would, in fact, enforce thresholds. I think

that is a big question on the industry. Now, one way I see that they could enforce thresholds is taking action against veterinarians and producers using the product. That is what happens with residues.

When tolerances are exceeded, there is usually investigation that occurs. And the FDA goes back and looks at who might be responsible for causing that residue so action is taken against the veterinarian and producer. Would it be envisioned that the FDA would put out some sort of general notice banning the use of this product or greatly prohibiting the product?

Short of that, it sounds to me like the Agency might be considering taking action against the producer -- or against the manufacturer. So it would raise a question as to why would the action be taken against the manufacturer, what justification would there be for that when, in fact, the manufacturer is simply supplying the product.

They are not necessarily using it and causing the resistance that is occurring. So there, I mean, there is a question in my mind how these thresholds would be enforced. So you might want to answer that one.

The second part of the question is the current HACCP sampling is really not statistically-based at the moment. It is about the best the USDA can do because they

are looking at Salmonella and they are testing Salmonella based on their program for trying to set standards for Salmonella plants.

But it is really not statistically-based. The kind of threshold monitoring you are talking about seems to me would entail a much larger program, one that is representative the nation's food supply as a whole with multiple species and multiple pathogens.

It sounds to me like a major increase in the NARMS type program. Is that envisioned and who would pay for that?

Finally, it seems to me that the methods that are used in the detection and susceptibility testing would have to be validated just like methods that are validated for drug residues. I mean, there is a very elaborate process that goes into validating analytical methodology for drug residues.

And we all know how expensive and difficult that process is. And this, obviously, would involve the NCCLS and other agencies in trying to do that. So I guess it is fine to talk about thresholds. And we have been talking about them and listening to different concepts for the last year.

But I think these are some real, hard core questions that at some point in time we have really got to

put on the table for the industry and say this is how it is going to be applied; this is how it is going to be enforced because, otherwise, I am afraid we could talk about this for the next ten years.

And as it stands right now, you know, the drug approval process is kind of being held hostage. So I just -- if you could answer any of that today, that is great. If not, we will hold it for another time.

DR. THOMPSON: Well, I will make just a couple of comments, Rich. Obviously, it is a very difficult area which is why we need additional dialogue on it. So I can't answer your whole question.

But in terms of really the first question you posed in terms of whose responsibility, you know, focusing in really on the monitoring threshold, I think we have had some dialogue on that with the industry. And what we envision with that is for that to be, you know, the point where we would say some mitigation is needed.

And I think what we put out initially in the Framework Document, as you may remember, was kind of requiring drug sponsors to do on-farm monitoring programs from the onset.

And so some of the information that we would be looking for in terms of information potentially to aid us in mitigation in terms of intervention strategies, we would --

our idea was we would have some of that information from the very beginning.

And that would aid the Agency in encouraging the industry, both the drug industry as well as potentially the individual producer in the industry, in terms of the appropriate mitigation so that the product could stay on the market.

If you have looked at the comments -- comment analysis that we put out, basically we are saying now we don't believe that we would need to have -- or we are not -- we are moving away in terms of saying that we would require on-farm programs for all products. So we have moved away from that.

But in terms of when we do start to approach that monitoring threshold, I think we would still go back to the sponsor and say we need to do some investigation because, otherwise, we won't be able to tell, for instance, the producers, we will not be able to make those appropriate label changes to allow the product to continue to be used safely.

So I think what we have envisioned and I may -- Linda, if you certainly have any additional comments -- but think what we envision was at that point in time, we would need to really do some investigations to try to identify what are the risk factors that could be addressed in terms

of mitigation so that, you know, resistance could be managed.

And in terms of action in terms of the Agency, what we may do may be certain changes in terms of how the drug is used, label restrictions, that sort of thing.

So I think it is a combined effort, at least that is how I would like to view it. But, obviously, at least from our perspective, the drug sponsor has a major role to play.

And in terms of the other more technical issues, in terms of laboratory validations, robustness of the NARMS program, statistical significance, I don't think we are there yet in terms of saying how we would define when we have reached a certain threshold level which I think is what you are getting at, what statistical basis there is in terms of saying that we have reached that. And so I think there is more discussion on those issues.

Linda, do you have any additional comments on --

DR. TOLLEFSON: No, I think you covered it well. I really do.

DR. STERNER: If you are going to talk, come to the microphone.

DR. TOLLEFSON: I am Linda Tollefson. I am Director of the Office of Surveillance and Compliance. And what Sharon said about the thresholds, I fully agree with

it. And I thought pretty much how we laid it out in the Framework Document.

However, you raised a question in the beginning about would we go -- would we treat it like a residue and trace it back to the producer or the veterinarian. And, no, is the answer. We never envisioned doing that. We see no purpose in it. If you want to provide comments as to why or what rationale.

I don't understand what that would get us. I mean, what you are thinking of is individual misuse maybe. Right?

(Away from microphone.)

DR. CARNIVAL: Well, I wasn't necessarily suggesting --- problem --- same kind of action taken ---.

DR. TOLLEFSON: Right. So you are thinking that it was being like a violative residue, we would be approaching the resistance or monitoring threshold. And, no, we never considered treating it as a result of an individual producer or veterinarian's actions.

(Away from microphone.)

DR. COPELAND: Linda, in that same regard --- resistance ---. And I think that needs to be ---.

DR. TOLLEFSON: Right.

DR. STERNER: Could you repeat the question for --

DR. TOLLEFSON: Right. Go ahead, Dennis.

DR. COPELAND: I'm sorry. I thought I could sneak it in without getting up to the microphone. I am Dennis Copeland with Bayer. And I just pointed out that I would envision that if resistance develops, you are going to have pockets of resistance where, you know, maybe in most parts of the country, there is no resistance. But there might be in one location. And I think somehow that has to be taken into consideration.

DR. THOMPSON: Actually, and I know Linda wants to say this, too, but I am dying, too, is that that is actually the exact reason that we said that we need more specific drug use information so that we could address that exact issue and look at things at more of a regional basis. But --

DR. TOLLEFSON: Right, exactly. If we rely on NARMS to monitor those monitoring thresholds, we will not know any kind of regional variation or differences. And, in fact, we won't detect it. What will happen is it will just simply be wiped out and we won't see an increase or decrease in susceptibility or increase of resistance because it is not powerful enough.

Combining the drug use information with the trends in susceptibility would give us a better handle on that. But even so, it is pretty difficult.

DR. STERNER: Further comments or questions for

various either panel members that participated today, speakers or CVM members? Your opportunity to speak is rapidly disappearing because it may have to do with the lateness of the hour. I will point out to you, however, that we appear to be 45 minutes ahead of the scheduled departure time. And with that, we are now officially adjourned.

(Whereupon, at 3:40 p.m. on Friday, December 10, 1999, the Workshop on Risk Assessment and the Establishment of Thresholds was concluded.)