ANTIMICROBIAL RESISTANCE

PUBLIC MEETING

PRE-APPROVAL STUDIES AND PATHOGEN LOAD

BREAKOUT GROUP DISCUSSION - RUMINANTS

WEDNESDAY, FEBRUARY 23, 2000

2:00 P.M.

DOUBLETREE INN

1750 Rockville Pike

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Regency Room

I N D E X

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Keynote: "---" indicates inaudible in the transcript.

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(2:08 p.m.)

CO-CHAIRPERSON HESLIN: Okay. I think we will go ahead and get started, it is a few minutes after two. What I would like to do is introduce myself again, talk a little bit about this session, and then the others will introduce themselves and what our respective roles will be in the process.

There is sort of a technical problem, in that as the discussion is going on, I would ask that you either speak loudly so that your voice can be picked up so it can be recorded, or move to the microphone. I think we are going to try to work this out so that if you are not being picked up we will try to encourage you to go to the microphone.

My name is Jim Heslin. I am with the Food and Drug Administration, Office of the Commissioner. I am the agency training officer and I have been asked to be here today to help facilitate this discussion.

I am certainly not an a subject matter expert. My purview on the agency is leadership training, but I will be here in the role of facilitator. I would ask that we speak to the issue. There are five questions and actually there is a sixth evolving question and address those questions. Speak to the issue.

What I would like to propose is that since we have roughly six hours, this afternoon and tomorrow morning, to get through this and also recognizing that Dr. Riddel needs to be ready to give a presentation, that maybe each of the questions -- and I am putting this out for consideration -- that we put about 45 minutes to an hour for each of the questions and that should allow us some time at the end.

We will try to work a break in here again this afternoon and again tomorrow morning. And basically, that is the ground rules. Any questions or comments so far?

(No response.)

CO-CHAIRPERSON HESLIN: All right. Susan, do you want to introduce yourself.

MS. HARPER: Okay. My name is Susan Harper. I am with FDA Center for Veterinary Medicine. I am a reviewer for new animal drugs in the division of therapeutic drugs for food animals. Prior to coming to CVM I was in large animal practice in Lancaster, Pennsylvania for eight years.

I went back to school, got a masters, was in academia for a while, went to NIH, and now I am at FDA and very happy to be there.

My role this afternoon, I am going to try to concisely capture the key comments and try not to demonstrate my ignorance of Powerpoint in the process. So, if I would

inaccurately capture anything, please bring it to my attention.

DR. RIDDEL: Well, I am Gatz Riddel. And I got introduced yesterday and you need to understand that I am in the position of volunteering for something that I didn't really know what it was going to evolve into.

My background is the last 15 years I have primarily had a dairy emphasis at Auburn University. So there may be some gaps in certain aspects of ruminant medicine, from small ruminants to big feed lots that I need some of you people to help educate me on.

Because I am supposed to represent the ideas and the concepts that come out of your discussion here directed towards the five or six questions, but also I think we are really supposed to be designing or inscripting things that are going to impact food animal medicine, especially in the area of ruminants from an industrial perspective, through the end-user, to the human consumer. So I really think that we need to look at it as an overall package.

I am sure we are not going to have any fist fights or anything. We need to make sure that we do speak up as our facilitator has pointed out.

I guess I would like to throw the discussion open by maybe skipping all five questions and if you all would help me out, what should the objectives of pre-approval studies --

understanding my background being kind of negative in this -- what are the objectives or what would be the primary objective for pre-approval studies to bring an antimicrobial drug to market?

Don't everybody jump up all at once!

Well then, I guess I am probably going to have to pinpoint specific people and I know limited people in the room and you probably know who you are, and so you probably need to get ready.

Tom Shryock, if you would would maybe give us some of your perspective. Tell us from industry what you think. Because everybody's goal, to me, and disagree if you do, should be from my perspective, to get products to treat the animals that we are going to deal with, promote efficient food production and safe food production, and have a product that the consumer will be pleased with and will feel safe with.

Throw in one more. We have to always deal with the ever present antimicrobial susceptibility issues.

DR. SHRYOCK: Thanks for picking on me Gatz. I will take that as a --

DR. RIDDEL: It is a compliment.

DR. SHRYOCK: -- compliment and we will throw out some strawman ideas here just to get things rolling.

There are a lot of things. We want to have the

safety, the efficacy, the quality, all of those sorts of things, but also keep in mind public health issues. But those are the big "feel good" kind of statements to make.

I think what it really comes down to is we are charged with coming up with specific study designs or objectives for specific studies, then that is where the rubber meets the road and we have really got to get down into some of the sub-objectives.

What do we need to prove in pre-approval situations? You know we have heard a variety of things today with regard to in vitro studies. I think Fred brought up a number of interesting points. Each one of those could take six hours or more to discuss and a full literature review to support that pro and con.

That may be worthwhile in part to do that sort of thing. Animal studies with regard to pathogen load. I am not sure that those really have a significant role, if any, in terms of the pre-approval contributions that they make for public health issues.

We can do them, but the relevancy, the validity, and the predictiveness are subject to question in my opinion. Resistance selection studies might reinforce some of the in vitro studies, but again careful design would have to be applied to those.

I guess the real bottom line is industry would be willing to do some studies as long as they can be reviewed with the idea that there is supportive information, not a pass/fail situation. Maybe we do need to consider some of the post-approval scenarios with surveillance, etc. as a more appropriate place to consider some intervention strategies.

I am just trying to throw out some ideas to get the discussion going. I am not voicing these on behalf of AHI or Elanco. I am just trying to throw out some ideas that I picked up and see what others think.

DR. RHODES: I will break the ice. I am Linda Rhodes from Merial. I am also an ex-large animal veterinarian. I used to be in dairy practice for many years out in Utah. I went back and got additional training at Cornell and I have been in the industry for about 10 years.

I think what we need to start out with is first of all do we accept the premise that pre-approval studies are necessary? I think we are starting by saying okay, we need to do something, how are we going to design those studies.

I think the first topic of discussion really ought to be based on the presentations that we have seen up until now. Do we really think there is enough information, enough background, enough science to do some type of pre-approval studies?

I think clearly the question on the table is public health. I didn't hear a lot of interest in developing resistance for bacteria because we were concerned about tetracycline not working in cows. That is clearly not on the table here. What is on the table is resistance and its impact on human health.

So I think my question, initially from all I have heard, is I don't think we are ready to design any sort of pre-approval studies. I think the list of questions that Dr. Flynn presented and that numerous speakers reiterated, about how could we possibly do this? Are they predictive? Are they reproducible? What kind of statistics would we use?

What kind of bugs? What kind of load? What kind of duration? We have got about 20-page D thesis to generate, I think, before we can even begin to sensibly make some recommendations about pre-approval studies.

So, I would like to put on the table for discussion at the start, does anyone feel that we realistically should be considering doing pre-approval studies at this time?

CO-CHAIRPERSON HESLIN: Keep in mind that reactions to the questions and so forth -- this is not a consensus group. This is an opportunity for people to give their points of view, as divergent as it may be.

MR. WATTS: Jeff Watts, P&U Animal Health. When we

talk about pre-approval studies, I am going speak to it more from a discovery perspective. And that is, a lot of what we do and a lot of what I have heard talked about is really things that we do early in discovery just to understand the compounds.

Now, mutation frequency studies are fairly easy to do. Understanding the spectrum of the compound in terms of just simple initial survey work, just to understand microbiological activity. Is there resistance? Is it in a class where there is no resistance mechanisms? How prevalent is that resistance mechanism?

Some of those things are very basic and they are the first pass cuts that we make, whether or not we even make the compound. And so those things I think become, to me they are fairly obvious to do because we are already doing them.

And so, I want to start back in discovery at that level because one of the things that I think is useful for us in industry is can we make a cut on compounds early? One of the things that is difficult to do when we talk about pre-approval studies is to get out into Phase III trials and then have a compound cut out.

We don't want to have six, seven, ten years investment in a compound. We want to be able to drop that compound out quickly and move to another compound.

DR. GOOTZ: Tom Gootz from Pfizer. Just to follow-

up on that note. I think that is totally correct, but there is another issue most larger companies that discover and develop and sell antibiotics for animal health also have similar antibiotics for human health.

Unfortunately, the amount that is taken in in terms of revenue is very different for both of those. It is a much bigger industry in human health. The last thing that a company would want to do who is in that situation is throw out on to the animal health market a drug that is going to very quickly induce or promote cross-resistance to something else they are currently selling for human health or animal health. Or something they may be selling down the line in either of those two.

So, upper management for pharmaceutical companies are the biggest stakeholders of making sure that we make those right decisions and get rid of a developmental compound quickly if it has an obvious fatal flaw. Just like we do with tox studies.

They are not always successful, but we always try to do well-performed and standardized tox studies on animal health or human health compounds to make sure that that compound is not an outlier, that it doesn't have a fatal flaw.

No one would knowingly want to put such a compound into animal health or human health because you would have to

pull it back. And that is the worst thing that could happen.

So I think how this relates to pre-approval studies is that, as I said before, I don't think you could reach consensus on the meaning or value of a pre-approval study. If we have to do them, it might only help us identify outliers.

I can't even imagine what the mechanism might be, but it might be a compound, let's say it was brand new. There was no other compound like it known to humans. And we put it into clinic, the field, for development of an animal health product and for some odd reason that scientists couldn't predict, on an auger plate in a laboratory it selects resistance in animals for, who knows why?

A pre-approval study might be a way to try to identify an outlier. And say wow, you don't want to review that compound, we don't want to develop it. Not necessarily in that order. We don't want to develop it period. And so it could be a way of identifying outliers.

But, I agree with the other speakers, I don't think -- I just can't see how pre-approval studies, no matter how they are set up, are going to predict the success of an animal health compound, or a human health compound for that matter, and how quickly resistance is going to develop in the real world.

People said well, resistance will develop, that is a

given. Of course it will, to some degree. Penicillin resistance began to develop in South Africa in strep-pneuma in I think, 1976 and today, if you go out into the clinic, in the human health area, and you talk to physicians they say well, I don't really care about penicillin resistance, I use a drug that circumvents that.

So, I will just stop, I am just saying I don't see how some of these pre-approval studies will really show us animal health with all of these parameters we have been talking about. It is too complicated.

I guess I would just say that what we should do, is maybe we should put the money towards better and more inclusive surveillance studies to get a much broader view in our market-place of what the resistance really is. Here I think I guess I am talking about mostly carcasses because that is the last stop before it goes to some form of human consumption.

So, it is a difficult problem but I don't think we are going to solve it by a real difficult model solution. I think there is some pre-approval stuff, all of the micro that you guys mentioned, of course you do that.

But, the threshold concept and having any one test in vivo have one resistant isolate, I think that all of the speakers in two days have shown all of the different ways that that could happen, but still not really be an accurate

reflection of how that drug will perform once it gets into the marketplace and into the field.

So, I think it is very risky. The threshold concept, that is the part to me that seems most frightening and non-valid scientifically.

DR. RIDDEL: Well, explain to me your understanding of a "threshold" concept. Are you talking about in terms of pre- or post-approval?

DR. GOOTZ: I will just mention post-approval. Excuse me, pre-approval because that is generally what the framework document is talking about in terms we have to do.

Since it hasn't been defined I can't tell you what it means, but to me it could mean if any of these tests either in the laboratory if you show genetic transfer of resistance gene from a salmonella to an E. coli in the laboratory or in a mouse; or somehow if you showed the transfer at some low level in a food animal.

In theory, that could be a non-starter. One result in theory, in the worst, most extreme example could say that we won't approve this drug.

DR. RIDDEL: Now, would you look at that to be something that CVM is going to impose on you or do you think that would be something that the industry would say we figured this out and even without CVM putting any regulations in it, it

is something that is not likely to make it to market and stay in the market and therefore there'd be the decision made not to even pursue it. Like some of the others.

What I am trying to do is get an idea of what could be required to ease the transition through approval into the post-approval phase which to me is really where "the rubber meets the road". Ease that, answer any questions CVM might have, but in the pre-approval area actually ask questions that you wouldn't already have asked.

You said that already in the pre-approval and in the discovery phase you are doing at least three of the objectives that Dr. Angulo mentioned this morning, right?

DR. GOOTZ: I think the issue is that in vivo pre-approval studies models which are not yet defined, but are asked of us by CVM could prevent even in the therapeutic area. And obviously has prevented food additive antibiotics that there are some no passes on those slides.

We don't know who they are, why they didn't pass, but evidently there are compounds in those additives that didn't pass the 550815. Big mystery, nobody seems to know other than the sponsor and you.

But, what we are concerned about is for therapeutic, new antimicrobials that we might stake 10 years in or 20 years to discover from a chemistry-driven program for another part of

the country. Makes it up, we have one in vivo test, pre-approval, that we have done and somebody somewhere detects by a method, culture, PCR, it can go to any degree.

We are concerned that some positive result in there will via the agency stop that drug from going forward. If it was, again an outlier of growth change, we probably would see it before it got that far. I can't guaranty that we would, but I bet we probably would.

But if the pre-approval stage was the first place we saw it and it was dramatic, then yeah I think we would have an internal -- I would think, our project teams would have a real internal discussion.

We don't really care about you, we'd be more concerned about ourselves: resources and going to upper management explaining why it is we are supposed to be experts in antimicrobial therapy and pharmacokinetics and we wouldn't push a compound for five years. That doesn't make sense.

Personally, I am actually more concerned about that than I am about your group. But, nonetheless I think we are concerned that for the non-obvious compounds, which I think based on history will be ball compounds, antibiotics, we are concerned that just a positive test, a positive result in some of these assays that have been talked about in pre-approval will from your perspective stop the development of that

compound or, hold it up.

So we will do another test, another test, another test and pretty soon we are six years into the patent life and it is not our compound anymore anyway. If you know what I mean. It takes so long to recoup the investment on antibiotics, particularly in animal health.

We just don't make a lot of money on them quite frankly. It may sound like a lot to an individual, but it isn't a lot in terms of a company. So, at least that, it is my understanding is the concern that we have that CVM, some of these models just stopping or indefinitely prolonging the progression of a new agent into development, into acceptance.

DR. SHRYOCK: Tom Shryock again. If I could just add to that. We also have to keep in mind that this does not necessarily apply to pre-approval studies in the sense that new chemical entities will be coming forward. But that these studies could also be used for a retrospective analysis of existing products.

And that can complicate a lot of sponsor's portfolios depending on how things may be evaluated. So, if we did have a situation of a pass/fail, this becomes a rate-limiting step. There is a whole cascade of consequences that would have to be dealt with in that particular situation.

MR. LADELY: Scott Ladely, USDA-ARS. One of the

things on the first question, can some monitoring of antimicrobials for resistance during the efficacy studies in development of a drug, can that predict resistance patterns in the future?

And I don't see any way it can. There are too many factors that enter into the development of resistance. The amount the drug is used. Even if they did other efficacy studies and never found a resistant isolate, that doesn't mean that two months after the product is on the market that somebody's going to find resistance. The more animals you put it into the greater chance that is going to be.

So as far as the main goal of pre-approval for predicting resistances, if the drug makes it on the market there is going to be resistance developed. That is the bottom line of what is going to happen. But at what levels there is no way to predict it that I can see.

And, as Tom stated the pass/fail deal, Dr. Mevius suggested that there is an optimum level, a dose that corresponds to resistance development. I think that is good information to have, but I think that that should in no way have any value in deciding whether a drug can be used at a level for therapeutic or sub-therapeutic.

It is good information for risk assessment, but it shouldn't have any merit on approval.

DR. SINGER: Randy Singer, University of Illinois. I am also confused about the idea of this pre-approval study. It seems that in some ways that if the post-approval monitoring system were improved and maybe more active in what it was doing, the pre-approval step might almost become moot.

For instance, if we look through some of the articles, there have been recent publications showing resistance trends. Clearly the flaws in those studies are the time frame at which resistance was being assessed. And the geographic scale at which resistance was being assessed.

There is a mismatch between isolates that may have been collected in hospitals versus the monitoring that actually went on on the farm. So, if we had a more dynamic monitoring system post-approval, one that not only looked at antibiograms or susceptibility patterns, but actually was looking at the prevalence of genetic mechanisms as they were in spatial and temporal scales.

I think we could get a better understanding for where future drug design might be most appropriate. You'd have a better understanding of the resistance mechanisms that are already out there and maybe a better idea of how to circumvent the problem of immediate resistance development.

The other issue with this, I guess my confusion with pre-approval studies, well, actually I am going to skip that

point for now.

But, I am still not certain where we are heading with pre-approval studies. It seems that in drug development and very active post-approval monitoring is where we are going to get an idea of the rate and extent of resistance development. I don't see being able to predict that through a pre-approval study, at least to the point of saying that drug may pose a risk.

We already know that there is going to be a risk of resistance development. It is going to happen.

MR. FLYNN: Bill Flynn, CVM. Just to make a couple of points, maybe to help the discussion on this objectives question. One, I guess really I think the pre-approval studies may be just one piece of this whole, of many different things that need to be done in terms of addressing resistance.

A lot of people have mentioned post-approval monitoring as being an important component, which is. So, I think one reason for us being here is in what role can pre-approval studies -- in other words, doing things sort of upstream.

What can we do upstream to try to help this whole issue which is the development of resistance. So, I don't think we necessarily have to, when we are talking about objectives, be locked into the thinking that it has to be a

study that is making a prediction.

I mean an outcome of this may be well, we just don't have the science to do this. But, if that is the case then what value is there to studies done prior to approval that can help mitigate concerns about resistance.

I think a number of people have stated it already I think, in terms of how can -- can these studies be used in terms of optimizing how a particular drug is used.

I think some of the concerns are when you use a particular class of drug in a particular animal species, using a particular dosage form, at a certain dose for a certain duration, that perhaps with the right combination of all of those factors you may have a high likelihood that you may have resistance developed.

Whereas, perhaps under some other different conditions it may not be as likely. So, I think part -- in that thinking we made what role can these studies serve and it may be that it needs to be moved upstream early in the development phase of antimicrobials in terms of when companies are trying to determine what is the best use of this antimicrobial that resistance is brought into the decision-making process for developing that product.

So, I don't think we need to necessarily say that it has to be a study to predict, that can predict when resistance

is going to occur. I mean it would be nice if you could do that, but it may be that it can't be done. I don't know.

Then one other point about thresholds. I think in my talk yesterday I tried, because I knew this was going to be a confusing point, if we think that thresholds are directly linked. In other words, if we need to have thresholds, if thresholds are what you make a decision on based on if you run a pre-approval study and then you have to evaluate that study relative to some threshold in order to make some decision about approval.

Well, if we don't know what we are doing with thresholds it is going to be pretty hard to design a pre-approval study. But I think what we said yesterday, that they are not necessarily tied together, that yes in certain circumstances it may be decided that it is necessary for post-approval purposes that there be some threshold set for monitoring.

So that we know when actions need to be taken based on the results that are coming out of monitoring studies or monitoring surveys that are going on. But it is not necessarily linked to pre-approval studies.

MR. MUSER: I am Rainer Muser. I am a private consultant as my label reads here. But I immediately have to say that my leanings are towards the industry view because

before I was put out to pasture I worked for industry.

I would like to put in an element that probably was underlying quite a few of the comments we have heard lately, but I think it needs to be put out clearly. And that is there were several people who spoke up in the last day or two about the essence of time.

One camp would say we don't need any more information we just know there is a problem and those productions should come off the market. I cannot share that view, obviously.

But there is another element too, industry needs those products to come under market and not being delayed beyond reason. And it occurred to me that one way of keeping products off the market would be to try to design the ideal study or number of studies that would answer all of the questions that were asked the last couple of days.

It is impossible. It cannot be done. So, then going from there, knowing that we are not looking for agreement in this meeting just trying to come up with points of view it should still be helpful to see the point of view that came out from various camps and seemed to point in the same direction.

So, let me try to avoid agreement, but say what I heard would possibly be common ground of the scientists. One of them was for instances that there maybe a better way of

using resources than doing pathogen load studies. So, I think it is worth pursuing that idea. Is it really necessary to do those studies or can we do without them and come up with an acceptable solution.

Another one was, I heard it in several different versions, that it may not be possible to design one study that fits all antibiotics, whoever they would be considered, so it might be better to say yes indeed some studies have to be done but each product requires an individual design for one study, packet of studies, whatever comes out. And it would have to meet the characteristics of the products, if it is related or not related, and so on.

And then the other element is even if we agree that we only want to study a limited list of subjects in those studies, perhaps it is not possible to come up with an ideal study right now. But, it may be possible to come to a workable solution to tide these things over, that FDA/CVM can make decisions until the final package is ready so they don't have to wait five years before everything has gone through the mills that has to be done. In the interest of making decisions.

Because, my concern is that indecision is a problem too. Not only making wrong decisions, indecision is a problem and if it cannot help -- and I am sorry to say that -- but I consider the people in CVM colleagues and I would like to help

them make decisions.

And, if we can do that with a workshop like this, wonderful. But decisions have to be made. And this is my plea to everybody in the room: let's try to help make decisions.

MR. BOETTNER: Alexander Boettner from Intervet International. I would briefly like to come back to the reason why we are here and the reason discussing these pre-approval studies as a basis, as a framework document.

The framework document classifies antimicrobials and depending on their classification, the sponsor has to provide data on pre-approval studies or not. So that for us, from the industry point of view, tells me that for certain types of drugs these data are required to estimate the rate and extent of resistance development in view of human health.

So this is what I believe the objective of the FDA, why they are asking sponsors to do these studies. From what I have heard over the last couple of days from our discussions, I think that it would be very difficult, if not impossible, to determine the rate and extent of resistance development before a drug is actually licensed and used in the field.

Of course I think what Mr. White pointed out, it would be very important to address certain things in view of the characteristics of the drug. I probably wouldn't call this pre-approval studies, but rather refer to this as to evaluate

pharmacodynamic properties of a drug during the development process.

Which I think is fine, but not with a view to regulate drugs in terms of resistance development and a possible ban of these drugs because there could be a negative impact on the human health. So probably the wording on pre-approval studies per se is not really appropriate.

And coming back to the comments made by Bill Flynn when he just said that pre-approval studies are just one piece, or a little piece within the entire assessment, we have to keep this in mind as well.

And here it would be important for industry to know more about the real intentions of the regulator, how they would like to address these issues. And again, I am emphasizing that this property can only be done once a drug is licensed and by means of post-approval surveillance, monitor the development of resistance and then make any assessments on the possible impact this resistance development can or possibly have on the human aspect, on the human medicine.

CO-CHAIRPERSON HESLIN: I had a question. You mentioned Bill's comment. Do you see any application of the pre-market review process, you know it is a total process. He was trying to identify what role could it play. Do you see that it would have any role?

MR. BOETTNER: Oh yes, yes. I would see it as more from a pharmacokinetic/pharmacodynamic point of view that these types of studies or these types of data could probably give us some basic information how to for this compound or for this class of compounds, how this sort of -- how to design post-approval surveillance. Or their might be special things one should look for once a drug is marketed and once post-approval surveillance is done.

It would be just one piece of information or basis and not necessarily the result of a study where the regulatory authority would make a yes/no decision on the approval of the drug.

DR. GOOTZ: I guess I have to say my name every time I get up, do I? Tom Gootz, Pfizer. Looking at the printout that I brought of the proposed framework document, I guess just updated in December of last year. I highlighted, since I was very new to the area, I highlighted this whole thing for things that I thought were deserving of attention.

And it is all highlighted. I have nothing that is not highlighted.

DR. SHRYOCK: --- another marker.

DR. GOOTZ: Good idea. Getting down to the bottom line here, it would be dangerous to our health as pharmaceutical company representatives if we brought, I think

-- not being facetious -- but to our management anything almost other than a Category III drug, as outlined in this document.

If they see this and you come up with a new quinolone or a new compound they are going to, you know, do that (indicating). And you don't get it. But, if you look in the Category I description, points one, two three.

The last one says that if it is essential treatment for serious or life-threatening diseases in humans, with no satisfactory alternative therapy, important for treatment of food-borne diseases in humans. Mechanisms of action or nature of resistance reduction is unique.

Last sentence: In addition, any antimicrobial that can induce or select for cross-resistance to a Category I drug automatically becomes a Category I drug." Okay? So, you are guilty by implication.

And also, from all the speakers this morning you have heard how we don't even understand in bacteria how giving one drug all of a sudden can somehow elevate resistance levels to unrelated drugs. That may be due to inducible systems, afflux, who knows what.

Then you finish by saying the following examples are types of drugs that would be included in Category I: quinolones, vancomycin, sinerset or things within those classes. And then the fourth one is third generation

cephalosporins.

That is most of the drugs that we work on in the pharmaceutical business. I mean yeah we have macrolides and we have other things that are used for animal health. We have ionophors, polymixins, and Category III drugs, but that severely limits, I think, the structural motifs that we can work on and submit if your labeled a Category I drug. Or can fall under the skirt, if you will, of a Category I drug.

So, I think that we obviously want to help you and you want to help us approve drugs. We want to do the right thing. We want to try to satisfy to some degree the physicians -- what are they -- the concerned physicians of science, whatever. They were here yesterday. Their issues.

But, you know, this sounds to us at least I think, very strict and legalistic. I think this document. I know it is precise, because you want to be precise for us, that is the way you work and that is good. But, it does kind of take on the oneness of almost a legal document in which we are sort of becoming almost liable or painted into a corner I think of bringing forward a number of different types of antimicrobials which could fall into this category.

So, anyway, I have here a note, "not much left". In terms of what we could bring forward in terms of ---. So, that is what we responded and so I think in some of this it is very

confining.

And if you are going to uphold it by using pre-approval studies and uphold these concepts to the letter, it would be very easy for you, I think, under pressure even though it might not have been your initial intent, to just stop the development of the drug. Or even worse take it off the market once that first genetic experiment comes back and says "ah ha".

--- or whatever we would call it does see resistance in campylobacter. Well, that gives you a lot of power to take drugs off. So I guess we are just concerned about that.

CO-CHAIRPERSON HESLIN: Other comments or perspectives? You know even if you are still in substantial agreement with the some of the things that are said, I think we are trying to get a sense of the group position on this.

Yes?

DR. RHODES: Linda Rhodes from Merial. Just to change gears a little bit, I think it is very interesting that we have broke out by species groups. And I think that one of the things that that suggests to me is that there is a clear understanding that there is very different uses of antibiotics in different species.

And since we are in ruminants, we might take a minute to think about how differently antibiotics are usually used in the ruminant species. As ex-practioners well know, we

don't want to treat cows multiple times with injections. And it is too expensive usually to treat cows with therapeutic antibiotics in the feed or water, although occasionally that is done.

And most of the antibiotics that are developed for the primary, the BRD market, are injectable single, or at most two or three days worth of dosing. So I think this really brings up a question which is should there be different kinds of regulations involved with inducing resistance for different ways that antibiotics are used?

And this is implied a bit in the framework document where they do talk about dosage regiments, number of doses, times between the therapeutic use and slaughter, the withdrawal time. This is mentioned as part of that high, medium, and low risk area.

But I think one of the things we should be thinking about is do we feel that its less likely that we will induce resistance with for example a single dose of tilmicosin on one day that is not repeated and then the cow goes on to have a withdrawal time of more than 28 days before slaughter.

Versus a constant low-level exposure to a single antibiotic as I do with my son when I treat him for an ear infection and I can't get that full dose of medicine down his throat three times a day, every single day, and so he gets

exposed to a sub-therapeutic level whether I want him to or not.

So, I think we are talking about ruminants. We need to think practically about how these drugs are used in a field situation. And it may be that that needs to be taken into consideration from a regulatory point of view. In a more stringent way.

Because although there are varying amounts of data on that, I think the general sense is it is less likely that we will induce resistance problems with a high, single dose therapy then we will with a low-level exposure. And there are many analogies to this: malaria and quinine resistance and tuberculosis.

Many, many other disease situations in human health where this has been fairly well worked out. So, perhaps we ought to be looking at this from a very different perspective, depending on what species we are working on.

DR. RIDDEL: I think without a doubt, the feed additives appear to be the target for right now. They impact some aspects, not many of which I am that familiar with as far as ruminant production, i.e. some feed lot use.

But I think that we need to stay positive and rather than say there doesn't need to be any pre-approval work, we need to maybe try to guide it in a direction that would not be

too onerous and would not defacilitate the approval process too tremendously.

To the best of my understanding, that many of the people who talked about modeling suggest that there is no one good model and it is going to be very difficult to do. But, from an industry's perspective, when you look at the overall process of getting a product to market, what types of studies could be required that would be truly unacceptable?

What could be designed that would just make it to a point that you would just have to give up? Another question is -- I guess this is because of my ignorance -- if a drug today is considered a Category I drug, that is defined by the current level of human medicine, correct? Can that change?

Can a company -- is there any way that a company can take a product and make a case that it should be categorized at a lower level than what would be most obvious when you first looked at it? I guess that would have to come from the microbiologists in the group.

I would like to know what kind of things would be the worst-case scenario or hurdles you would have to jump to get to the approval table? Somewhere along the way I am also going to have to ask questions how can we blend these pre-approval studies into a workable post-approval monitoring program to facilitate things.

And then also look at -- some of the people I have talked to say an important step is categorizing the drugs, like it may not be a given.

DR. SHRYOCK: Tom Shryock. I will venture a worst-case scenario here. Hopefully the Frankenstein situation will not appear. I think what that could look like would be one of these pathogen load studies that becomes a mass epidemiologic investigation.

Which is a multi-site location field trial late in a development stage which requires that you have a bona fide test article that has been characterized; final formulation. You have got to buy all of these animals by taking them say to a slaughter situation. Doing all of your microbiology and tracking for up to a year in say a feed lot situation.

You are investing maybe a million to two million dollars, I don't know. And then having some sort of data analysis that you have failed because you missed it by 10 percent of a prevalence type of situation.

To me that represents just chaos in something that none of the colleagues in industry could stand to bear. And that is why we really want to try to back that away from that kind of situation as early in the pipeline as possible.

DR. RIDDEL: Tom, help me out just a second. Can we, for me, is it inappropriate for me to try to separate the

two issues: antimicrobial susceptibility in the pre-approval arena from pathogen loads?

Because I am not familiar at all with pathogen loads and I have heard a lot of people say that this may be irrelevant. We shouldn't use relevancy to bog down the whole thing.

So, I guess I would like to -- I asked my question wrong. I would like to look at the antimicrobial susceptibility because that is the headliner issue right now. There are so many other things impact the pathogen load. Haslep from there on out. That sure was an unworkable scenario that you laid out, but are there equally unworkable scenarios for dealing with susceptibility issues?

DR. SHRYOCK: If you wanted to take it to that extreme and say that you are going to look at salmonella or campylobacter or an E. coli 157 on the basis of resistance, that could be the worst-case situation compounded.

If it is just looking at susceptibility testing by going out and collecting isolates, field isolates, that is to my way of thinking not as onerous by any stretch.

DR. RIDDEL: Would it be inappropriate to suggest to CVM that the pre-approval cannot in any way, shape, or form be as comprehensive or all-inclusive as a post-approval monitoring program, right? Or should not be?

DR. SHRYOCK: It depends on how you -- there may be infrastructure systems to go out and get those isolates. You may be able to draw NARMS for example and get those 60,000 isolates from Paula's freezer bank in the basement.

DR. RIDDEL: So you'd be looking at pre-approval susceptibility where hopefully that product -- the organisms haven't been exposed to that product to any great degree? They may have been exposed to related products but you'd be looking for kind of setting a time zero susceptibility upon which you would base other thresholds for development of resistance, right? And rate of resistance?

DR. SHRYOCK: I don't know if I would take it to the point of using that to set a threshold because there are a lot of implications there. But I think -- we do a lot of baseline surveillance work in a very early discovery phase. You get field isolates in, you see what is out there. It is on a class-representative basis.

If you are going for another macrolide, erythromycin is a good representative of that class for example. Although there can be differences, as Paula pointed out, between tetracyclines. You can explore that to a certain extent.

If you have these collections that are historically available, you don't necessarily know their exposure history. But you kind of get a feel for what is out there and that is as

good as you can do in some of these cases. Unless you are really going to make this a 50-state, mass epidemiologic collection which is a very difficult thing to do.

So, you have got to maintain some of the practicalities in here and get a sample that is reasonable to work with, that is fairly representative and go with that and make your best guess decisions.

DR. RIDDEL: But it wouldn't be inappropriate to suggest that the pre-approval studies dealing with that should just represent a sampling, a random sampling of isolates out there as far as current susceptibility and leave it at that?

Plus, other things that you might learn about predictability of the onset or resistance from some of your very early studies?

DR. SHRYOCK: Well, you keep adding all of these extras on here Gatz. The sample collection, I think pretty much everybody will do that to a certain extent more or less. Or that could be done relatively straightforward.

If you wanted to explore resistance frequency, rates or something that gets into some other substudies: which bug, which drug concentration? There is a lot of subissues along those lines that to varying degrees, again sponsors do some to many of those kinds of studies.

It ultimately comes down to what are you going to do

with that data in terms of evaluation? To make pass/fail or is this ancillary information? And at what stage? Is this internal within the company that never even makes its way to Rockville or is it something we then need to consider to build into a package if we take it forward because it is supporting evidence then? So, some open questions perhaps.

DR. RIDDEL: Because I don't know and if it is proprietary information tell me. What types of studies would a company normally -- or, what extent would a company with an antimicrobial normally investigate as to giving themselves a feel for the potential for a rapid onset of susceptibility?

How many, I would assume these would be field trials where the product would actually be out and be in its appropriate use, or not?

DR. SHRYOCK: No, field trials really are the last step that you go to because they are so doggone expensive.

DR. RIDDEL: How would you try to -- if you were -- I mean several people -- I understand the economic realities. If you were wanting to protect yourself from the marketing people and from management, how would you want to take a product you are trying to champion and give yourself a comfortable feeling that you could take on, say this isn't just going to blow up within six months after we put it out on the market and be worthless?

DR. SHRYOCK: Things that are currently done, using existing classes as the prototype, because I don't think we are going to have a whole lot of new chemistry coming on board, go to literature. There is a wealth of information there.

I will pick on macrolides because that is my basic experience here. You have got all sorts of resistance mechanisms, mutation rates for a variety of bugs. You can find that out and have a pretty warm, fuzzy feeling of what is out there and what you can expect.

The second thing that you would do is go to a target population. One that you want to get your claim on. And survey that. See what is out there. Ask the diagnostic labs for their specimens. Go to some field situations, get in some clinical isolates.

This whole issue, however, isn't on target pathogens. It is on food safety pathogens. In that case we are going to have to go where the bugs are. And that makes it a lot more difficult. If you want to go to those particular farm animal situations, since this is a ruminant group we'd have to go to feed lots for example.

That is very difficult to get access to get ample sample numbers on your own. So you'd probably want to go say to the NARMS program and see if they could provide some bovine isolates for example. There may be other companies that do

their own monitoring just as a component of their own food safety programs. Get a random collection there and see what it looks like.

You may be able to track some of the use history if you look and probe hard enough. That to me is about as good as you can do. Mutation frequency rates and all that stuff, yeah you can do that. I am not sure what the value of all that really becomes at that very early stage, you just want to know what is out there in the world, basically.

So that is pretty much what I would do. I would welcome comments from others because certainly my experience doesn't represent everybody's in this room.

DR. RIDDEL: Do you feel Tom, that -- and I am sure you would, so this is probably a loaded question -- that looking at food safety, the issue, the future of the animal health industry and animal agricultures, do you think that those steps should be satisfactory to get a product to where it can be put in use with an appropriate post-approval monitoring program?

DR. SHRYOCK: I would say they go a long way towards that. There are probably some other things that I can't think of here on the spur of the moment that could be added on there. That would be a good start. Ultimately the reviewers are the ones that are going to say thumbs up or thumbs down.

Their careers are on the line for making a good decision/bad decision which is kind of hard to predict the future and that is what you are asking them to do. So our job is to provide them with enough information to allow them to make a comfortable decision as well.

DR. RIDDEL: Then you all are going to have to help me because I came into this thinking that this is supposed to be development of a whole new paradigm, but if your telling me things --- things that are currently ongoing really should be answering all of the pre-approval questions that can be answered logistically or feasibly?

DR. SHRYOCK: There is a lot that goes on that doesn't even get above the water line of the iceberg here, that all of the companies more or less do, that helps sort the wheat from the chaff early on.

And those things that we do bring forward are the ones that we tend to discuss a little more fully. There are other studies that we could consider doing as far as just setting up susceptibility test conditions and some of the things that might support some of the prudent use or even the NCCLS guideline kind of things.

But that is all factored into the mix in my opinion. Blended in with some of the efficacy studies. You know, to set some of the dosage situations with the assistance of PK/PD

data, there is some real attraction to doing that.

We have also got to keep in mind that we might be rate-limited or bounded by top dose for a residue, efficacy. And then throwing in this other one, on minimizing resistance, we may be at a point where we can't change that does more than just a couple of migs per kilogram. There may be no change. We may be just stuck and we are going to have to live with whatever it is.

There are some issues along those lines too in terms of optimizing doses. We can look at all of that, probably should if we are not. But recognize that is not the panacea either.

I have probably talked way too much here. Will you help me out Bob?

DR. WALKER: I will help you out. Bob Walker, CVM. But I am a newbee at CVM so I am really saying this as an ex-professor. We have listened to a lot of dialogue over the last couple of days to a very, very complex issue.

I guess from my perspective, and again this is my perspective and not FDA's perspective or CVM's perspective, I think that what we need to look at, first off we have to ask why do we want to introduce an antimicrobial agent to the market?

I think there are three reasons. Two reasons.

Number one, increase profits for the company and -- this is not necessarily in order. Number two, is to try to address an infectious disease problem in the target animal species.

Now in conjunction with this, the pharmaceutical companies have been burdened with a third criteria. And that is the effect that that anti-infective agent has on zoonotic pathogens.

So, if we look at those three things and try to address what we are calling the pre-approval program, from my perspective, and I do this having done a lot of experiments peripheral to this, and I will try to bring you up-to-date on some of those things.

First off, if we take a fecal sample from a cow and streak it for isolation on a McKonkel's plate to where we get 30 isolated colonies. And we take each one of those colonies and subculture it. So where you now have 30 individual colonies collected from the same animal at the same time, and we do an MIC on each one of those whether it is against a flouroquinolone, a beta-lactim, or a aminoglycoside.

What we will get is a variety of MICs. In other words, those 30 isolates collected from the same animal at the same time will not have the same susceptibility profile. And there may be as much as a five-fold difference.

So, if we were to look at this as a pre-approval

study and the first time we picked an organism with an MIC of .5 and then we exposed them to the drug and post-exposure we pick an organism that has an MIC of .03, the drug has had a negative effect. Wow, let's go for it.

But if the reverse of that is true then we selected for a less susceptible organism when in actual fact we really haven't done anything. Because that was the population that was there to begin with.

So, another thing that we have done is we have looked at enteric organisms that have been exposed to a flouroquinolone over a five-year period. And we have found that with the E. coli that there was really no change in MIC 50 or MIC 90 over this five-year period. The same thing for Club C-pneumoniae.

But, we did find that with proteus, the MIC 90 jumped from .06 to .5. Now that would suggest to me that that is a very sensitive organism in terms of selecting for resistance or decreased susceptibility.

So, maybe that could be a sentinel organism. But maybe not necessarily that organism. So, if I were looking at pre-approval studies, one of the things I would want to do is I would want to take this new drug and I would want to take an enteric population of organisms and find out what is there.

And then I would want to take different species and

expose them to different concentrations of this drug and see which one could I change the susceptibility profile on? Which one could I make less susceptible.

And then use that organism as a potential sentinel organism so that when we got into other studies, instead of looking for salmonella which may not be there or may not change at all, or E. coli and which E. coli are we talking about? Are we talking about the one with the low MIC, the high MIC, 01587 or the numerous other serotypes that have the attaching effacing gene and the sugar toxin gene? I don't know.

So, look at this sentinel organism that we have demonstrated to be most likely to develop decreased susceptibility to this particular drug.

Then I would look at my target pathogen and I would do a concentration-dependent killing study on that target pathogen and also on this sentinel organism. And I would look at what concentration of drug I needed to maximize the killing effect of my target pathogen, but I would also look at a concentration-dependent killing effect and see at what concentration did I have the killing effect of the pathogen, what did it do to the sentinel organism?

Did it kill off the sentinel organism? Or if you have done any concentration-dependent killing studies, you know that a lot of times you get regrowth of the organism. If I got

regrowth of the organism was it the same MIC as prior to exposure or did I select for a higher MIC? This is data I would collect.

The next thing I would do is a pharmacokinetic study. A dose titration pharmacokinetic study. And here I would want to know what is my drug concentration at the site of the infection, in relation to my target pathogen, and maybe using a radioactive labeled drug to see what my drug concentration is throughout the gastro-intestinal track and see what that is in relation to this sentinel organism.

I would also collect fecal samples from that animal or those animals that I had done the kinetic studies in and look for this sentinel organism and see if I had affected its MIC at all in relation to time.

And based on this information I would have a dosing regime that I could look at for generating clinical efficacy, but I would also have an idea as to how it may affect this sentinel organism.

And then any studies I did after that I would again be looking for this sentinel organism and any zoonotic pathogens that we might happen to come across, but we would already know that they are not as likely to develop resistance as the sentinel organism. Because we have already demonstrated that the sentinel organism is the most sensitive for this

occurrence to happen.

That is just some food for thought that I would do in terms of pre-approval. Once it was approved then I would identify that sentinel organism, again the zoonotic pathogens, and monitor the changes in susceptibility profiles.

When you talk about resistance, the cat is already out of the bag. What you want to do is design your monitoring program in such a way that you can pick up slight changes in susceptibility.

And so if you have got pre-approval MICs of .03 and a year into the approval of this drug your MICs are up to .12 or .25, you are still susceptible, but you are losing it. And that is the point to initiate mitigating factors to alter the course before you totally lose the drug or before it adversely affects the human population. That is my thoughts.

DR. RIDDEL: Dr. Walker, are there any pitfalls to picking a sentinel organism that is not irrelevant to the target pathogen nor to food safety?

DR. WALKER: There might be. But, you know -- and this is just my thoughts on it -- but you know, describe to me a car. Well, what are you talking about? Are you talking about a Yugo or a Mercedes? They both have the same function, but there are different purposes.

And so what we are talking about here is a program

for a specific organism or a specific drug, or target animal species. We would have to tweak it for different animal species or different drugs.

In this particular situation I think if we could demonstrate that the sentinel organism was the most likely to have a change in susceptibility. Far more so than enteric pathogens. Then that is just an indicator organism. You are still looking for the zoonotic pathogens to see what is happening with them, but chances are anything that happens with them is going to be predicted a long time in advance by this sentinel organism because it is much more likely to develop the resistance.

And again it goes back to the proteus. The proteus that we looked at changed dramatically, but the E. coli, the Klebsiella -- I can't remember the other organisms we looked at. Unfortunately, we didn't have any salmonella. But, they really didn't change.

So, I think it is just an indicator organism of how things may happen. And I think for every drug, animal species it may be a different indicator organism, but I think it is something that could be established very early on.

And again, these are just my thoughts of how if I were in a pharmaceutical industry and I wanted to look at this, this is some of the things that I would entertain.

DR. RIDDEL: I guess because I am not industry-oriented in microbiology, from microbiologists, is there much of a risk of discarding potentially valuable tools because of this approach?

DR. WALKER: What do you mean?

DR. RIDDEL: You can have a sentinel organism that may truly not be relevant to anything other than the fact that it has the ability to develop decreased susceptibility rapidly, but it is not relevant to any zoonosis and it is not going to be a zoonosis.

It is not relevant to your target pathogen or disease process for your label indication. Is there a possibility that somebody could, inside the company, say we are not going to risk it because of this possibly irrelevant organism?

DR. WALKER: I don't think -- I think that all you are doing is generating data with this organism. You are not basing the approval process on this organism.

DR. RIDDEL: Well, I think decisions are going to be made at the industry level based upon this that could affect a products that I might have to treat animals with and a potentially valuable product could be --

DR. WALKER: But you are also doing the monitoring. You are monitoring that sentinel organism and you are also

monitoring zoonotic pathogens to see what it effects.

Do they use nalidixic acid in human medicine or in veterinary medicine any more? No. And yet nalidix acid is used on the NARMS study. Why? A sentinel drug. We are most likely to see decreased susceptibility in nalidix acid long before we see it with cipro. It is just an indicator.

And that is all we are saying here. It is an indicator organism that may give us an indication as to what effect this drug is having on the microbial population as a whole, it is just this particular species of organism has been shown to be more sensitive, more likely to change its susceptibility profile.

CO-CHAIRPERSON HESLIN: Just a quick comment. You may want to look periodically at the screen. Susan's trying to capture the essence of what is being discussed, but she may need some help in doing that. So, if what is conveyed up there is different than what you are hearing, let us know.

DR. RIDDEL: While we don't, I think Dr. --- said at the beginning that this wasn't something that was going to arrive at a consensus. I would really like to trust people in this room to keep me from sticking my foot too far in my mouth and bringing something up like this.

If there are valid reasons to consider it a minority opinion or if there is a valid reason not to mention it. Just

out of my ignorance.

DR. SINGER: Randy Singer, University of Illinois. I just wanted to make a quick comment on this indicator bug. In that I think it has a great deal of importance, even if it is not the target pathogen. I think as we learn more about the ecology of antibiotic resistance, we are going to find many examples where some commensal or some organism doesn't seem relevant that is carrying these resistance determinants, is actually the mechanism by which these determinants make it into the human population.

You are not following a food-borne pathogen. What you are following is a determinant, just some gene, that ends up inside of a human and is transferred then to the normal flora inside of that human host and becomes then a source of disease for that person.

I think there is examples of that with the, I believe with even vancomycin. And so as we learn more about the ecology of resistance, this indicator bug, I think, serves more than just as an indication of a rising resistance. But does serve as some indicator of risk.

MR. LADELY: Scott Ladely, USDA. Again, on the indicator bugs. I think that the target pathogen has to be monitored. As far as screening all and finding the most sensitive bug to pick up resistance, you may be shooting

yourself in the foot if you have the product finally developed and there is 65 percent resistance in that particular organism.

Fred's going to raise hell with you. As far as monitoring food-borne pathogens, I think that should be left to Fred and Dr. Cray. Looking at a couple of sentinel microbes plus your pathogen of interest, I think E. coli and enterococci are just generic species would be a couple of, in my mind, good ones to look at.

DR. GOOTZ: That was a good comment. I am glad you went before I did. I guess the idea of a sentinel organism in human health, the best example would be pseudomonas riginosa for all classes. Maybe staph --- or enterococcus, but pseudomonas always seems to be the one in human health that the new drugs fall down first on.

That includes carbapenems, beta-lactams, certainly quinolones, and on and on. While I agree, I tried to be positive and tried to reach consensus, I agree that it could have some value. Pseudomonas overpredicts in human health riginosa, the failure of fluoroquinolones due to resistance.

It is a sentinel. It is the first one to become resistant and it is certainly good to know that and to monitor it compared to the other target pathogens like E. coli, klebsiella, etc.

And scientifically, I think it might be very

interesting to look at pseudomonas --

DR. WALKER: You are going to ---

DR. GOOTZ: Oh, I know. No, I am just giving you an example. I am agreeing with you from the human health perspective. Trying to give an example, probably too long. But I agree with you that in the sense that once you begin to generate that data, while a scientist would probably feel comfortable with it, once it gets out there and is bantered about, and not understood or put in perspective, I am just wondering how negative people could make that information?

But getting back to animal health, sentinel organisms. Campylobacter jejuni is a very good one for flouroquinolones. Which is probably why we are all here. Back in 1991 or something people were trying to characterize the mechanism of fluoroquinolone resistance in campylobacter jejuni and our lab even isolated the gyrases out of that organism.

I think we were the first lab to publish and show how you get single and double step resistance mutations in DNA gyrases in campylobacter jejuni. We isolated the proteins and did in vitro biochemistry. Later on people did much more eloquent studies of actually sequencing the gyrase genes in campylobacter jejuni to show the first step of resistance and the second step.

It turns out that that is one of the least of course

susceptible organisms of human concern from the gut that we are discussing. It turns out it has an odd gyrase. Even a wild type in the sense that it has a --- in place of serene in the active site of gyrase.

Now that sounds like who cares? That is not important. But it sets the stage for why, when you expose it to fluoroquinolones that first step of resistance took the MIC to .25 and the wild type to I think 8. So, as a sentinel organism it has been very rough on animal health.

I think by giving fluoroquinolones for chickens, poultry, in water while from a managerial point of view that is the only way to do it, but from a selection or a resistance point of view or a sentinel organism point of view.

It wasn't really good because the levels in the stool of quinolone because you are giving the drug in water and the chickens are obviously variable in how much they'll be taking and how much drug will get into the fecal matter provided a nice selective condition, just like an auger plate for that first step of resistance in gyrase it took raising the MIC to 8.

Thus in Europe and places they were getting field isolates of campylobacter from animal health sources that were resistant and saying wow, what a horrible thing. This is the only way this could have happened by the animal's health use of

fluoroquinolone.

So, a sentinel bug can provide information, but it can be dangerous as well. And it has been shown that you can get selection of resistance in people with campylobacteriosis who take fluoroquinolones for therapy. There are clinical failures.

We were on one of those studies years ago, too. It can happen, but it is pretty rare. Therefore, the conclusion by everybody: regulatory agencies, the CDC, the lay press, is that the use of fluoroquinolones in poultry for animal health is really the only real mechanism by which campylobacter becomes resistant to fluoroquinolones.

So, that is not a very positive thing. I am trying to reach a consensus or reinforcement, but sentinel idea of a bug could be good, but it is a double-edge sword. We have to make sure that we are able to as scientists and clinicians get the upper hand in explaining the clinical or field relevance of that type of data.

And while I think we could here, I don't have any concern about that, I am really concerned more about the lay press and other groups getting a hold of some of that sentinel data and making hay with it.

But the last quick comment, which hopefully is positive, I think some of these pre-approval studies,

susceptibility monitoring of use pathogens is a good idea. We probably need to do more of it. And also I think in Tom's block this morning he mentioned there are other ways of looking at MICs, of field isolates, larger groups that just MIC 50 and 90.

And I think he mentioned cumulative percent plots. And that seems like a minor, but it is a very, very important point in the sense that when you plot your data out for MICs, let's say for 50 field isolates against a given drug or individually for 100 drugs, it doesn't matter.

You begin to see subtle shifts in the MICs, of these individual isolates that you can plot out on a curve, which you may miss at the MIC 50 or 90. And that costs nothing. We should always be doing that, we don't. I tend to be very sloppy.

Sometimes you know to get things quickly for a meeting you just get the MIC 50 and 90 and you know put it in the Powerpoint and away you go. But some of these simple, straightforward things actually are pretty important.

Where we can analyze subtle shifts in susceptibility of field isolates pre-approval and also post-approval and then maybe take some of those bugs that are shifting up, look at their genetics, ask on a very individual basis what is the mutation? And is that mutation characteristic of what happens

in other organisms for that class of compounds such as gyrase A for quinolones or you said for macrolides, MLS type the resistance for deflux.

So, I think what I am saying is that some of the pre-approval studies could be very useful. But they need not be so incredibly complex and open-ended as at least has been mentioned, I know in good faith, at this meeting so far.

Some of the things we are already doing could be pretty important.

CO-CHAIRPERSON HESLIN: We are coming up on 3:30 and we are scheduled to have a break. Is this a good break point?

DR. RIDDEL: I think it is. Unless somebody else has a --

DR. SINGER: Can I just make a quick comment?

DR. RIDDEL: Sure.

DR. SINGER: I just wanted to make a quick clarification on that sentinel bug idea. When I brought up that issue as a potential predictor of risk, I was thinking in terms of gene transfer. So clearly, as most of you probably realize, fluoroquinolone doesn't really fit that bill.

We are talking point mutation in a chromosomal gene, unlike some plasmid or conjugate of transposon which has this risk. So in picking a sentinel bug, if we are thinking about a genetic mechanism that can be transferred, that is where I was

thinking of as a predictor of risk and not in the case of like a fluoroquinolone.

DR. RIDDEL: Yes, I think when we come back I am probably going to get a few comments directed towards pathogen load to help me out. Then we are going to start looking at the inherent questions of what we were assigned to do.

CO-CHAIRPERSON HESLIN: I think you can probably lead off since you wanted to say something, but at 4:00 o'clock we can reconvene. That is about a half an hour.

(Break)

CO-CHAIRPERSON HESLIN: Okay. We will go ahead and get started. The ending point for today is 5:30, so we have got about an hour and -- almost an hour and one-half.

Let's start off this session with a comment.

MR. CONVEY: Ed Convey, Limerick Strategies. I have had a chance during the break to talk to some people and I might be redundant on these points, but I wanted to make them anyhow.

First, Tom isn't here, but the point that Tom made about upper management making decisions against an uncertain regulatory background I think is important. And presumably that is well recognized. That presents a certain difficulty in terms of management decisions by industry.

The other point I would make I think is also pretty

obvious, but I am going to make it anyhow. That, in my mind as a non-microbiologist, and I want to make it clear that I am not an expert.

But, listening to the experts, it is pretty clear that the overwhelming message was that the state-of-the-art is such that it is unlikely that you are going to be able to do studies that are definitive in terms of predicting resistance development and worse, making some determination from those studies on impact on human health.

I think the Chair was on a reasonable tact though in asking the question about what does industry do to get comfortable. And this is preliminary to putting very sizable investments into a new antibiotic.

What would they do to get confident that the emergence of resistance would not be quick? And that is a reasonable line of questioning. Because these are the people who are going to commit hundreds of millions of dollars into a new program.

And, if the specter is that resistance development is quick, and the product then is a liability, then they are not going to make that decision. So, within the expert community and industry, it seems like the answer to those questions are worth ferreting out.

What would give you confidence as a pioneer drug

developer that resistance will not be an issue for an antibiotic? And I think the experts that spoke to that acknowledged that that kind of background studies are done in industry exactly for that purpose. To try to make a decision about what is reasonable to take forward.

So, those are my comments.

DR. RIDDEL: Go ahead.

MR. WATTS: Jeff Watts. I want to speak a little bit to use patterns. Besides also agreeing that one of the things that we should know and one of the things that we do is know your compound well. Know the classes that it is in and understand its various activities.

But I think it is also important to speak towards use patterns. And also understand that there are patterns that contend to lend towards resistance, but also use patterns and management practices that may help moderate resistance.

We just completed a study. We looked at 811 staphorius strains for mastitis. Ten different countries. We really went into this expecting to be able to see differences in resistance patterns based upon the products that were approved in the various countries.

One of the things that was remarkable was that the MIC 90 values, for practically every antibiotic that we tested was flat. You could see no differences from country to

country.

Now, if you start thinking about how we handle staphorius cows, for 30 years we told dairy farmers, we told veterinarians there are no syringeable solutions to your mastitis problems. It is a management problem.

So, what do we do? With staphorius cows they get treated a couple of times. If they don't respond they are called from the herd. And we remove those animals, they are not treated for multiple times, and so this moderates resistance.

Tom, we have used cloxacillin for 30 years to treat mastitis. And in that particular study and in other studies that I have done, I have yet to find a single --- Most of our staphorius strains are actually still susceptible to penicillin.

So these are practices that help to moderate resistance. We should understand those use patterns. And, if we can understand those use patterns that may moderate resistance, then as a sponsor we can respond to that in a post-approval manner to help farmers manage resistance in their herds.

DR. RIDDEL: While you are up there Jeff, as you are bringing a product through R&D, is it feasible to be able to project what the use patterns will be? Is it feasible to

delineate use patterns which would select for decreased susceptibility and maybe even project mitigation strategies before approval as a part of your pre-approval study or document? Or would that be inappropriate?

MR. WATTS: The simplest thing, I think there are some very general things that you can do. And Tom, I will ask you to help me out here. The simplest thing you can do is when you design your drug profile, the first thing you do when you start looking for a compound say to treat BRD, or to treat swine respiratory disease or whatever, the first thing you are going to understand is how you are going to use that drug?

Are you going to use it as an injectable? Is it going to be an intra-mammary for mastitis? Is it going to be a P additive. Those sorts of things. And you know that certain types of those sort of applications are going to have more of a tendency to give you more problems with resistance because a sick animals don't eat well, they don't drink water well versus an injectable.

So, there are some very general things that you can do.

DR. RIDDEL: What -- of course I have been involved with DCPR and Anduka who are fighting for extra label use. How is that going to impact or complicate some of these things?

Right now, for fluoroquinolones, you can use it in

beef cattle. You can even use it in the relatively worthless dairy bull calf, but not the valuable dairy heifer calf that is in the pen right next to it.

But that is legislative. Unless more regulations come along, a product could come to market that wouldn't have that restriction. How would extra label use by the profession impact some of these considerations? Extra label but legal under DCPR and Anduka.

I guess I was asking you to predict potential use patterns.

MR. WATTS: It depends upon the use pattern. It depends upon the extra label use. If you have a -- let's say you are trying to treat a pneumonia by an organism that is not on the label. Say you have got a diagnosis, it is H-parasuis. And you know this compound has activity against H-parasuis and you know that you still want to use the same basic treatment pattern that you would use for treating any other -- for treating the label bugs for SRD.

That to me is not a high risk situation in terms of extra label use. If you are going to open that bottle and lavage animals to treat diarrhea, that to me is a much higher risk in the extra label venue. So, it depends -- again, it would go to the use patterns. And how that compound is being used.

DR. SHRYOCK: Tom Shryock. I guess, just to follow-up on some of those points with the use. You know, it almost puts the practitioner in the perspective how should I choose what drug to use? Should I base it on efficacy and expected clinical outcome? Or, should I choose this drug on implications based on implications to public health, which is a lot further away from the immediate needs.

And that is a quandary I think that we may find ourselves in, in certain cases. How does that all relate to pre-approval studies? I guess the questions that we find that practitioner asking "How do I choose my drug?" revolve back to what sort of studies should we or could we do to enable that practitioner to make a worthy decision.

And I wonder if there is an opportunity to perhaps use some of these pre-approval studies that are already being done, that we have already mentioned: pharmacokinetics and some of the MIC studies, to maybe embellish the label a bit more to perhaps consider some of the things that were discussed several years ago in the flexible labeling workshop for example.

The big old labels got a lot of information that would enable practioners, who now have prudent use guidelines to subscribe to, to try to really make their best clinical judgment on as much information as we can give them to try to

satisfy both goals.

That is certainly not addressing pathogen load or resistance selection studies necessarily, but I am just wondering if maybe that is one of those out-of-the-box kind of exceptions that you have got a Powerpoint slide in reserve for.

I don't know. It is just something to think about.

MR. BOETTNER: Alexander Boettner from Intervet International. I would like to come back to a question you asked before we had the break. You said well, what would be the worst possible scenario for pre-approval study? Let me make a rather provocative statement to this regard.

I would say not a study design could give us this scenario, the worst scenario probably is the process we are dealing with at the moment. And what I am mean by this is that for pre-approval studies and all of these issues, for the last two years no new antibiotics has been licensed.

Every single compound in the regulatory process is more or less stuck. Where at the same time, with the use of existing compounds we may continue to contribute to resistance development and to put things into perspective.

Wouldn't it be important to look at resistance development of all compounds being used and not only concentrating now very, very much on the new compounds which are in the licensing process.

DR. RIDDEL: So, you are not asking for CVM to begin to require post-approval modeling on this that have been approved for years, are you?

MR. BOETTNER: Say that again?

DR. RIDDEL: You are not asking for somebody to require monitoring programs for a product that has been approved for years, are you?

MR. BOETTNER: Yes. Well, I think we have to sort of -- if we are looking at resistance development and the potential impact on human health, we should not limit this to new approvals. We have to sort of assess these risks with existing compounds as well.

And we may be looking at the use pattern of existing compounds and looking at potential development of existing compounds would be -- I put it -- English is not my native tongue, but -- maybe a more useful exercise than just sort of now discussing in length how processes how new animal drugs approvals could be regulated while looking at -- the studies of pre-approval studies where there are still a lot of question marks.

And, in the mean time none of these drugs do get approved and it gives a sign to industry that they probably, because this process becomes very unpredictable, that they seize with their research programs or --- programs to develop

new drugs for animal health.

DR. RIDDEL: So I guess for my edification. Do not some of the ongoing monitoring programs evaluate this information? And if an antibiotic was approved, became an obvious contributor to reduce susceptibility in a zoonotic pathogen, wouldn't there be a likelihood that CVM or some other regulatory agency could force some type of mitigation of that?

Right now, aren't they collecting data on susceptibility to antibiotics that are currently on the market? It is not formalized. I mean, it is formalized, but it is not within any mitigation goal.

MR. BOETTNER: Not that I know of. I know that there is NARMS, there is monetary. But whether there are any mitigations from the results provided by NARMS, I don't think so.

DR. RIDDEL: Again, out of my ignorance, have there been -- I know the studies have not been performed uniformly, there has been a change of protocol through the four years that NARMS has been in effect, right? So you may be comparing apples to oranges.

But, there hasn't been any currently labeled antimicrobial that has been pinpointed as being a hot point or being a serious problem, right or wrong?

MS. : That is right.

DR. WALKER: --- we just went back and looked at staph and --- isolates from 1987 to 1999 against four fluoroquinolones that were commonly used in --- veterinary medicine.

We found that the MIC 50 and MIC 90 over that 11-year period or 12-year period really didn't change at all for any of the fluoroquinolones. The MIC 100 changed, beginning about 1986. We started picking up some resistant organisms.

So, for the most part it is a small sample of organisms, but the bottom line is that for the most part we are not seeing a lot of change with that particular organism.

MS. : I hesitate to actually whether I should actually say anything, because I am just supposed to be listening.

But, in terms of your comment on the existing products versus new approvals, that is always been kind of a point of confusion with what we put out on the framework document.

We have always intended that the overall approach in terms of the framework once that is finalized, would be applicable to products that are already on the market. But realistically, we would need to prioritize which products we looked at because of limitations and resources.

And so, we would most likely use whatever

categorization system that is finally agreed on to help us focus on the products that are of most concern.

So, in terms of whether -- the NARMS data I think is definitely something that would be very helpful in identifying where products may pose a public health concern. And I think we would potentially use that in the future, but we have not at this point in time made any decisions to take any particular action or work with any companies on mitigation, specifically in relation to the NARMS data at this point in time.

So, I think we are going to address that. We are getting there. But, all of this is not finalized yet. But we feel that for the new products we also need to look at the issue in terms of microbial safety and we feel that the pre-approval studies are an important component of that.

DR. PETRICK: My name is Dave Petrick and I work with Schering-Plough Animal Health. My background isn't in microbiology. My job now is in regulatory affairs.

I just wanted to put some of the comments and some of the thoughts I have had over the last couple of days in that environment. I think, listening to the presentations, it just strikes me that every time someone draws a straight line and says here's a good path, there is seven more divergent paths that follow.

Whether it is looking at Oh, yeah. This is what we

need to do pre-approval, it is important to have this information. Then we come up to but what is the context in which we collect it? Should it be in an in vitro study? Should it be with a live animal? Should it be from the field? Should it be here? Should it be there?

Then we go well, what is the environment that it needs to be tested in? Should it be like the rumin, the secum? It just strikes me that there are a lot of things that we don't know and there is a lot of things that we are very unsure of.

I guess what causes me to have a great deal of concern over just the concept of pre-approval studies, is if we generate data, we can't lose sight of the fact that it won't just be here with us. I think one of the other speakers had that remark that they are not concerned if it is within this scientific community because we can understand it, we can put it into context.

Well, that may be true, but CVM doesn't work within the scientific community and neither do I as a regulatory person. We have to work within the confines of is the product safe and effective and if it is, therefore should it be approved or not?

And I guess the fear I have is with data being generated, there is a requirement that all pertinent data from

the regulations are submitted. So that means that CVM then has to deal with that data in some way, shape or form. And I just have a fear we are walking ourselves down a road where we will spend money, we will collect information, data will be submitted, data will be reviewed.

And, at the end of the day we are not going to be any further along at being able to predict rate and extent of existence or extent of resistance development for any product, whether it is new or whether it is old.

Part of the reason this issue has hung on for as long as it has, from the Swan Report forward, is we can't put a finger or we can't put our thumb directly on the problem. We can't define it precisely.

And I think we are kidding ourselves if we think we can walk away from here with a definitive study design that is going to give us those answers. If we can find a means of putting it in a context of baseline information or information that will start a process, then I think that is wonderful.

And putting my management hat on at the company that I work for, if I could run a study I wouldn't care if it cost $100,000. I wouldn't care if it cost a million dollars. If it would give me the guidance to say that I know my products going to be good for 10 years, that is money in the bank.

But, from what I am getting unless someone can tell

me I am wrong, I don't think were at that point now. I just worry about trying to either codify or put into guidelines or put as a requirement for approval, a study or studies that generate data that no one is really clear what its meaning is.

I guess that is where I come from a regulatory standpoint.

MR. HALLBERG: John Hallberg from Pharmacia & Upjohn Animal Health. I am going to work on a working-delusion here. I have been sitting here listening to all of the comments and I have come up with several, I don't know if you'd call them revelations, or not.

But I think we could probably say that for a pre-approval study or any study, one-size will not fit all. There are too many compounds, too many different classes, too many different metabolisisms to say that this is the study that will get us these results.

But I would propose that in the process of approving an drug, and I basically come from clinical development and recently made the transmission to regulatory. So I am new at regulatory and a little more experienced there.

But if in the process of the submission of an NADA, you are using a phased-reviewed submission scenario where you go in and request an IDD first time in. In theory you should be able to go into the government at that point and for your

compound give a brief identification of mechanism action: how does this think work?

From the laboratory you should be able to generate what are potential resistance mechanisms? So if I take a bacteria and force it with this drug a bunch of times, what are the different types of resistance that we could generate and bank those. That is a piece of information for the future.

I should be able from the literature, potentially if this is a family issue, I should say what is the potential of cross-resistance? Put that up there. Typically, before I go to the government with an I80D I need to have some preliminary idea of metabolism. What happens when I put this compound in a cup? Or put it in a paper or put it in whatever? How active are the metabolites versus the parent, okay?

Then what I should be able to do from that is I need to get an I80D approval to go out into the field and do studies. Now, at that point I am probably also going to go in and talk to Steve's group, or Cindy, or Sue, and put a developmental plan forward on how to get this product approved: efficacy studies, human food safety, target animal safety.

I am going to submit those protocols to get that work done. Now, as Marc Papich told us, in the design of the efficacy studies we should use our PK/PD information to identify a good effective dose and potentially not a minimumly

effective dose. But something that is going to give us good efficacy in the field when we are treating our disease.

In the process of doing that, that gets us into our clinical efficacy studies. From those studies we gather a whole bunch of pathogens typically on pre-treatment sampling that we can use to establish a baseline of what are the MICs for these pathogens early in the game.

Because in theory, these drugs, this is the first time this drug has been in the field for this indication. If you are doing I80D studies. Then, that should be submitted to the agency as here's something else we put on the shelf.

Then, as part of the approval we should consider establishing "what is susceptible". Okay? We have this problem right now, of well is it macro-susceptible, is it this base susceptible? What is susceptible? And a lot of compounds we don't know that.

Then, when you get all this database done and you submit your NADA as potentially part of the last discussions with the agency for approval, is how to you set up the post-approval surveillance? What are we going to monitor? Where are we going to monitor?

I would suggest to the group that this monitoring be on target pathogens and that we should let the NARMS folks worry about the zoonotics. That our compound would be added to

the NARMS observation at that point, on approval.

Then, for the next few years take that as the database to start that. Resistance is going to happen. When it is going to happen nobody really knows, but until we set up something to get us in the ball game with new compounds, we won't know how that is going.

That is my working delusion, and I don't know if that helps or not.

CO-CHAIRPERSON HESLIN: Anyone want to respond to his delusions?

DR. VAUGHN: That is the best idea I have heard yet. I am Steven Vaughn with CVM. I just want to throw out a few other ideas just to consider, not that I have any answers.

First of all, I am looking at it from the perspective that we are a public health agency. So what is our job? Our job is basically to prevent human pathogens that have resistance factors to important therapeutic compounds in human medicine from reaching humans and causing disease.

From that standpoint, if we work backwards we have to be able to approve drugs that are safe by some standard. We don't know what that standard is, for sure. Some folks are using reasonable certainty of no harm as a standard that is pulled over from the pesticide part of the Food, Drug and Cosmetic Act.

Some people are saying we should use a food standard which is not deleterious or injurious to people. What preponderance or amount of evidence do we need to be able to say a product is safe?

The other part of that is it is also safe in the context in the conditions of use. And I think that gives us a tremendous amount of flexibility to be able to say that we have a pre- and post-approval strategy or construction under which we can take certain information pre-approval and utilize it in a post-approval mode to ultimately accomplish our mission. And that is to prevent those pathogens that are resistant to important therapeutic compounds from causing disease in people.

I am concerned a little bit about -- and this is where Steve Vaughn's personal opinion, I will take off my CVM hat -- I am a little concerned about the framework document in that regard. I am not so sure that the framework document is a pre-approval document.

I think really the logic behind the framework document is that the categories are really categories of priorities for mitigation. And whether that occurs in a pre-approval or post-approval mode, I am not sure at this point in time, myself.

I would think if we saw an increase in resistance occurring, or a loss of susceptibility that our priority for

mitigation would be based on the categories. I am not so sure that we can make a blanket statement in a pre-approval mode that if it is a Category I drug it should never be put on the market.

I am still inclined to think that regardless of whether it is a therapeutic drug or a therapeutic antimicrobial or a production antimicrobial, it might be valid to approve those products. I am concerned from the standpoint that when we do something, everything we do has the ripple effect.

What is going to happen when we remove production uses? One of the proposed mechanisms by which production drugs work is they lower disease incidence in cattle. I think we need to keep that in mind. We know we have dealt with that in the residue arena, where we have had a big effort to push a particular drug from being used because of a residue concern.

And then the next drug of choice that became popular was worse than the drug that we had in the first place. We need to think about what we are doing and the impact of what we are doing when we look at making categorical statements.

So that is one point to consider. Another thing that I am thinking about is that we need to be able to identify when a product that we have approved actually is the cause of the loss of susceptibility. And I am not quite sure how to do it.

I was trying to think of a good word to say and I am not a microbiologist. Maybe Tom can get up to the mic here, or Jeff, and tell me, but if there is some way to be able to fingerprint for a trace back post-approval system to be able to identify that a product was implicated or not implicated.

I am concerned we are dealing with resistance that is a global issue. We heard several speakers speak to that. I don't know in a feed lot situation if I get isolates from a feed lot, what the source of that particular resistance might be if I started to see it in feed lot samples.

We have four million feed lot cattle coming from Mexico every year into U.S. feed lots. I don't know what prior treatment exposure they had in Mexican ecosystems and what problems that may have caused and been introduced into a U.S. feed lot. I have no way of knowing that unless I have some trace back capability.

So, that is one of the things we may want to think about in terms of pre-approval. Can we develop information that allows us to either say it was caused by a particular product or not caused by a particular product? Some of that may be defensive research on the part of the pharmaceutical companies.

We also, most importantly, need to know how to mitigate. If we do see the development of resistance, what are

the tools we have available to mitigate? I am concerned about what we can do with the on-label indications and I am concerned about what we can do with the off-label indications. The regulatory tools that we have available are somewhat limited.

We can modify labels. We can take enforcement actions against certain extra label uses, prohibit extra label uses or withdraw products. But, there is a very finite arena of things that we can do.

I think, about situations that Jeff talked about, we have done a real good job of educating dairy farmers about staph mastitis. But, as soon as they walk out the exit door of the parlor they walk through an oxytetracycline footpath. And I wonder if we are doing the right kind of things in those kinds of situations?

I do think we need to have some pre-approval screening to have some kind of baseline information, but I don't think we need to tweak it down where we have to say this is the number. This is the dose, the optimum dose at which we cause the minimal amount of resistance. I don't think that is a real number.

I can certainly speak to effectiveness trials and we look at dose titration. That is why we abandoned dose titration, we don't think that it has the inferential value to a population to be able to say that is the optimum dose for all

clinical situations for a particular indication.

That is why we are more inclined to think of dose ranges where we modify dose intervals and duration, and routes of administration for varying clinical situations.

So, I think if we talk about trying to optimize this I think we need to talk about in terms of ranges rather than trying to pinpoint single fix doses. That is it.

DR. RIDDEL: Any comments from other people in industry on the working delusion?

(No response.)

DR. RIDDEL: Okay. Well, I think those were all really good ideas. I think they may begin to form some grounds for our response tomorrow. If there are no other comments, let me force you to get back to helping me out just a little bit.

I had a mole slip around through a couple of other rooms to see what comments were going in those directions. And there were similar negative comments relative to pathogen load. And while I think I am going to hold you to not throwing everything out saying we don't need these things, we are going to have to do something.

But I think, and again this is my area of lack of expertise, I need somebody to help me to come up with some well-founded comments on if pathogen load studies are irrelevant, especially for some of our use patterns then.

Or, if some of the studies that have been described in some of these models, such as knowing the metabolism and knowing some activity that metabolites, if those that have informational impact that could at least secondarily address pathogen loads. I need some information along those lines.

I have not heard anything except negatives about pathogen load studies. And while I think we are going to have to approach CVM from a ruminants standpoint with some type of pre-approval format, I think maybe there is segmented parts that we can say this really isn't relevant to what we are dealing with.

But, I need some help on understanding pathogen loads because that is one area where I have no basis in at all.

DR. SHRYOCK: That is consensus. Look at Tom and you want him to talk and be the strawman.

With pathogen load, I guess some of the positive aspects? I can lay out a few of those. And a few of the limitations, the list might be a little bit longer.

I think probably you could really excerpt a lot of these questions or comments from the talk that Kathy gave, the talk that Paula gave. There is a lot of considerations.

And if you were to ask me to design a study that I had a lot of confidence in that I could take to my management and say: If we did this, we would have this thing aced. We

would have a bona fide predictable study.

Given all of these variables in here with regard to animals, the dosing, the duration, is it challenge? is it seeder? type of situations. When in the process would you want to sample for your zoonotic pathogens? Which pathogens do you want to sample?

All of these kinds of things are posed as questions and you can design these studies and do them and get information, but it is only as relevant as that one study under the conditions of use in that particular experiment. There is no guaranty that you will have data generated that is predictive in a total, national type of situation.

There is no measure of validity relative to perhaps other drugs, at least the 55815 studies you are only testing a medicated, non-medicated, and environmental-type control. The extrapolation from all of this based on some arbitrary measures for pass/fail, how does that really relate to human health? I have some difficulties trying to get to that endpoint.

I guess I really spent a lot more time on the limitations than on the positive aspects. Those positive aspects would be that you actually do have an animal model of some sort. So you have this black box of gut ecology factors in place. It is not just an in vitro setting where you have optimal growth conditions for a bug or two.

The studies can be controlled, very much so. You can pen your animals individually, control their environment, diet, dose, everything. It is easy to control those.

There is is some precedence for doing some of these kinds of studies. We could design based on what has been done in the past. So there might be some history that one could follow, is a positive aspect of at least a pathogen load study.

I think I will just stop at that point and see if there is anybody else that would like to chip in, but those are a few thoughts that I have off the top of my head.

MR. LADELY: Scott Ladely, USDA-ARS. I don't think they are relevant, I am sorry. If you are looking at salmonella, it depends on what serotype you isolate that has more to do with resistance pattern than anything else.

If you tried to save some money, bought a bunch of Holstein calves, you are really screwed because the prevalence of salmonella's going to be higher. It doesn't have much to do with what you are treating the cows with.

Resistance patterns for salmonella it just seems like some serotypes are more prone to resistance than others.

DR. PETRICK: Dave Petrick again and I will just hitchhike right on that to go back to my comment that I think relevance is incredibly important in a regulatory environment. And we want to make scientific-based decisions, but if we are

going to make a regulatory decision based on science, the science has to have a good foundation as well.

Because, if we don't have a good foundation in the science, the regulation can't be sound, and I don't think that is where we want to go either.

So I think one of the really important things is to make sure whatever studies we are doing, they are always relevant to the question at hand.

DR. RHODES: Linda Rhodes from Merial. I think the slide that really put this in perspective for me was Paula's slide where she showed all the different types of salmonella sampled in the same population over time and how incredibly variable those isolates were, depending on the age of the animals.

I mean this is very impressive data. I think what it shows is that you can imagine a large number of variables that are going to effect your pathogen load isolate data that have no relationship to the treatment of the drug.

And so when you have so much variability in the endpoint that you are measuring, you know it may be a good thing because it will just mask any drug effect you have and then you can say well there was no effect and everybody will be happy and you did something.

But, it goes back to that whole point of relevance.

What are we really asking? I think because the mechanisms are so unclear, what causes this variability in shedding over time in the same animal and in animals that are growing? How does the way you collect the sample impact your data?

I think until we can show some test system in an academic setting or in a government lab-sponsored setting, where we can do the same experiment with the same drug over and over again in different populations of animals in different laboratories and get the same endpoints. I don't think anybody is going to have a lot of confidence in whatever data we generate.

It is kind of like doing the confirmatory method, you know you have to take it around to several different labs and they all have to be able to perform that method reproducibly and get the same data from the same types of tissues before the government has confidence that we have got a good confirmatory method.

In a way, I would like to see those kinds of data. I would like to see the same drug in the same population of animals performed at six different academic labs or government labs, showing a similar effect on pathogen load and then maybe we'd have some confidence that these data, these studies that we are planning to do would mean anything.

I think that is what is lacking, is an ability of

consistently and reproducibly being able to show a similar effect in any kind of defined test system.

And then beyond that, if you were able to come up with that, which I think would be very difficult to do, then it comes back to Dave's question of what is the relevance of those data? Is it really predictive of what is going to happen in the slaughter house and how much contamination are we going to get on a carcass that is then going to have a human health implication?

But I don't even see the beginning of reproducibility of data here. I mean maybe people who are much more experienced than I am in this area can comment on can you reproduce these types of data in a consistent way across labs and have any confidence in the predictive result of these types of experiments?

DR. RIDDEL: I will take that to be a no.

MR. MUSER: Rainer Muser, representing myself. Maybe it helps to add some other argument to what you are asking for. Dr. Angulo brought up the idea of that there is a limited number, he didn't say limited number of resources, but he did say we might be able to use our resources better in another area that pathogen load because it doesn't really mean that much.

And what it means to me is that when we put an

antibiotic on the market, the resistance situations are an exception to the rule. It is a small number of things that are happening. The pathogen load are a subsector of that again. So we are beginning to chase the infinitesimal with doing that type of study.

The question is really then how meaningful it is, particularly considering that a true role of pathogens in food derived from animals could probably be controlled better by other means than trying to figure out how an antibiotic down the road might cause it.

It might be better by hygiene in the slaughter plant or whatever, you name it. There are good measures to take care of pathogens in food derived from animals.

CO-CHAIRPERSON HESLIN: Well, before everybody runs out. We still have a blank number three up here that needs to be filled in.

DR. RIDDEL: To look at a couple of specific questions that Dr. Quinn has asked us to look at, I think some of these we have covered.

The pathogens which should be the focus of pre-approval studies. Consensus to me seems to say that target pathogens, known zoonotic pathogens, and now we have the concept of the sentinel organism. Are those all things that we could or should agree to? Things that we should present coming

from ruminants?

DR. EWERT: Kathy Ewert, Bayer Animal Health. I just want to -- I wasn't in the room for that discussion, but I just want to clarify what I, in industry, understand the framework document to address and that is public health or food safety issues.

Target pathogens, those pathogens being the organisms targeted for the drugs we are using, for example nuflura, bactril, or micatil. We target pasteurella and hemophilus and those sorts of bugs.

Those target pathogens really have no implication at all in food safety. And those are the responsibility of the sponsor of the industry to monitor and most companies do monitor that in some way or another.

So I would see what the rest of the group thinks. I would not suggest that as a pathogen to be monitored in pre-approval studies. That is done as part of our efficacy work. If our drug is inefficacious against a target pathogen then we don't have a product and there is no reason to move ahead.

As far as sentinel organisms go, I mentioned yesterday in my presentation that I can find nothing relevant in the literature to indicate that monitoring the sentinel organisms gives us any kind of indication of what is going on in the food-borne pathogens.

So I think that discussion took place earlier, but I just wanted to go on record as saying that.

DR. RIDDEL: Okay. And you understand, I think Dr. Walker presented the thought that you would culture all of the enteric organisms out of an animal, a group of animals, and check them all for susceptibility changes.

The one which shows the greatest change would become the sentinel organism and use that as a predictor of a worst case scenario, more or less. Am I paraphrasing what Dr. Walker said correctly?

DR. EWERT: But how would that then correlate to the true food-borne pathogen with changes in susceptibility in the food-borne pathogen? Unless we know that that particular organism has the capability of transferring a resistance component to the food-borne pathogen.

I mean we can do that now. We can do that now, but I just question what the relevance is of that to looking at issues with food safety.

MR. BIENHOFF: Steve Bienhoff with Intervet and I would like to reiterate some points about this sentinel organism.

I think that it opens up more questions than what you are going to get on answers in that. If you are looking at sentinel organisms and you can increase in a resistance, what

does this mean as far as your pathogens are concerned? What point do you intervene on your drug?

When you go to an agency you are proposing an organism as a sentinel organism, which one do you pick? You look at a number of them and there is going to be various ones that will show resistance. And you take the one with the most resistance, the one that is maybe further down the line, maybe more predictive.

But which one do you pick? So you have those questions to answer and then once the drug is on the market then you have to come back, you get this resistance showing up out in the field. Again, what does that mean for your zoonotic pathogens?

Is it really that predictive of what is happening? And at what point do you intervene? So you get all of these questions there that you haven't answered. What do you do now? So you are collecting data, and data is nice, but a lot of time data produces more questions than answers.

I think what we are trying to get to is the point where we are coming up with some answers on how to approach it, but going in that direction opens up a whole other area.

MR. SCHMID: Peter Schmid, Intervet. In my opinion, during the early drug development we get a lot of information on the susceptibility of different bacteria against the new

compound.

Not only the target bacteria but also gut flora. And if you take the most susceptible population from the gut, for example E. coli and look into the MIC distribution, we can do together with our first pharmacokinetic studies, we can test the influence of the intended use of the compound on the MIC distribution of the gut flora.

I think this is a more sensible and more sensitive measurement of the possible influence of the intended use of the product on resistance development or resistance selection.

MR. LADELY: Scott Ladely, USDA, again. For sentinel organisms, it is a tough deal. I don't know what the best ones to pick will be.

But, what they'll probably do, this is my hunch, in the future is they'll be looking at stuff like the NARMS data and CDC's data, human and animal isolates. And as resistance levels come up they are going to take some action.

If they are looking at salmonella, campylobacter, those organisms, maybe that should be our sentinel organisms. I don't know.

That is why we need to follow resistance. Because at some point in time they are going to say, and from looking at that data, government data, the human and the animal isolates, they are going to say this is getting out of hand and

they are going to want to pull some drugs from some uses.

So maybe we should just go with the particular species that they are monitoring, the government's monitoring.

DR. EWERT: Kathy Ewert from Bayer Animal Health. That just brings up an interesting question here. We might have different definitions of what sentinel here.

What you are talking about that they are monitoring for NARMS is already a salmonella and campylobacter, those are potential food-borne pathogens. Potential being the key word.

However, what the agency is talked to us as a company about, a sentinel organisms that are not particularly pathogens, for example E. coli. The whole population of E. coli.

MR. LADELY: Right. But how good does that tell you about the food-borne pathogens --

DR. EWERT: Well, exactly. That is the question that we are asking. But I mean there are thousands and thousands of strains of E. coli.

MR. LADELY: We will be checking E. coli. We will be looking at the generic ones. That should give us a better idea with salmonella because looking at salmonella depending on the serotype resistance is just all over the --

DR. EWERT: We have got quite a bit of information generated with our post-approval monitoring program and with

pre-approval studies that we did. Looking at E. coli as a sentinel organism compared with salmonella as a food-borne pathogens, and found that there is no correlation.

MR. LADELY: Right.

DR. EWERT: There is no correlation. And based on studies that we did, we had salmonella with higher MICs and E. coli that we got out of the same sample with very low MICs. Conversely, we saw E. coli with high MICs and salmonella with very low MICs.

So we found no correlation in baseline work that we did. This is in cattle. And with our post-approval monitoring, while we saw a transient rise in a few E. coli isolates, we never saw a single isolate elevate with its MIC for salmonella, never.

So that makes me wonder what relevance do those E. coli isolates have to the overall food-borne illness picture.

DR. RIDDEL: For my information, being concerned about antimicrobial susceptibility and some of the invasive salmonella and campylobacters having very important therapeutic tools in human medicine, can the same be said for E. coli? For example 0157? Antibiotics are they a mainstay of treatment for that disease in people? If not, then they probably should be specifically excluded because of lack of relevance to the issue, right?

DR. EWERT: That is correct. And that is what we did, at least in our post-approval monitoring. We specifically said that we would not look for anaerotoxigenic E. coli of any sort. They would just be the generic coliforms.

But, there are other people that can speak to this better than I can. But it is my opinion that 015787 is not an organism for which antimicrobial therapy is indicated in humans. That is correct?

DR. SHRYOCK: (Nods yes.)

DR. EWERT: Okay.

DR. RIDDEL: Thanks.

DR. WALKER: Bob Walker, CVM. When I was talking about the sentinel organism, say we have a new drug, miraclemycin. We don't know where miraclemycin is going to fall in this scheme and so one of the things that we want to do is to do some preliminary tests.

So we are concerned about the potential of selecting for resistant organisms that may be human pathogens or could transfer resistant genes to human pathogens.

And so we take this drug and we take a number of enteric organisms from the target animals' feces of the animal species that we are going to go for approval with, and we test this miraclemycin against all of these different bacterial species to get a baseline MIC and then we look at what happens

with repeated exposures at various concentrations.

Now we know with staphorius, it has been shown in the literature that if staphorius is exposed to ciprofloxin in concentrations at two times the MIC, resistance occurs every 10^{-7}. If it occurs at four times the MIC, it occurs every 10^{-10}. And both of those are relatively common.

If it is 10 times the MIC, resistance doesn't occur. So we would expose these different intestinal organisms from this target animal species to varying concentrations of this test drug or new drug, over a period of time. And we are not going to see a change of MICs in all of these organisms. It is just not going to happen.

Strep-piogenese has been exposed to penicillin for 50 years and the MIC hasn't changed. It is still the same. I talked to you about what we saw with the staph-intermedius. It has been exposed to anaerofloxin for 12 years and we are really not seeing a change in the MIC 50s, MIC 90s.

But, one of those organisms may, as the proteus did, show an increase in MICs. Look at that organism, see why this occurred. Is there a resistant gene associated with it? Identify that. Identify the factors that contributed to this increase in MIC and then look at that as your potential sentinel organism.

Because any time that organism or that species of

organism is exposed to this drug, under clinical conditions, it may have a decrease in susceptibility. And that is what you want to look for. Not waiting for it to get resistant or to become resistant, but to look for a change in susceptibility.

Like I indicated before, if you started out at a .06 and it jumps up to .25 or .5, it may still be susceptible but it has changed. And then you can become, start looking at mitigating factors or factors that could have contributed to this.

In the mean time, because this was the most sensitive organism in terms of this potential change of all the ones you tested, you can kind of rest assured that while it has gone from .06 to .25, the pathogen in this environment probably is still back at .06 or .12 or whatever it started out because it is not as sensitive to change.

DR. RIDDEL: Dr. Walker, let me ask a question before you leave. That is understandable and that is a good educational concept for me. But, the information you described as far as sentinel organisms, should it be information which is the property of the company upon which they would base decisions for further development for going through the process?

Or, should it be information that if it goes to CVM then it is going to become a part of the regulations and

requirements. And if it is not relevant to the point at hand, which is human food safety, then should that even be offered up as a potential comment in this process?

Things need to be safe and they need to be appropriate, but you don't want to throw out things that are not as relevant as they could be that may make the process more difficult.

DR. WALKER: And I think that is a very good question, a very good point. I think that we are in a field or a time of discovery right now and I would like to think that this is something that can be worked out with CVM.

That this organism, say it is a proteus, is not a human pathogen. Say we are talking about a fluoroquinolone resistance. This new miraclemycin is a fluoroquinolone and we know that fluoroquinolone is not plasma transferrable. At least at this stage of the game.

So, the chances of transferring resistance to a human pathogen are slim and none. So, what we would propose then, if I were in the drug companies' shoes, what I would propose to CVM is that we are looking at this as a sentinel organism, recognizing that it is not a human pathogen, but also recognizing that it is most likely of all of the enteric organisms from this animal species to change in susceptibility profile.

And having CVM then recognize that maybe that is a good sentinel organism to use. I don't know where it goes from there. I am too new on the scene to make any further judgments then that.

DR. RIDDEL: Well, from what I understand what Dr. Ewert was saying, susceptibility for this "sentinel organism" could climb sky high and the pathogens with which we have to concern ourselves with being totally not linked to that.

So, yeah, we know we have a pathogen that can develop resistance very readily, but where does that factor in to decisions by the company, decisions by the agency, or the overall approval process?

DR. WALKER: Yeah, I think that is another very good point and we may have to look at that. If this is a sentinel organism, but it is totally unrealistic, and we go back to staphorius. We know with staphorius it is a problem with penicillin. Strep-piogenes is not a problem with penicillin.

So if staphorius were the sentinel organism for penicillin resistance, it was a poor indicator of strep-piogenes and maybe that is a very good point.

But I think this is an indicator organism that we could at least watch and monitor and if it has no relevance down the road then within the discovery period or the

development period, maybe that data will come out that we are not seeing any change in the susceptibilities of salmonella.

If we go back and look at the salmonella that they are getting in the NARMS study. What is the MIC 50 or the MIC 90 in the salmonella that they collected last year? Did it change any from the year before? Or how close is it to say for ciprofloxusin? How close is it to the susceptible breakpoint?

We don't have the answers to those. But we do for the proteus and we know that it is moved. And so that is all I am saying that it may just be an organism that we can look at mechanisms of resistance, we can look at changes in susceptibility due to exposure to the drug.

It is an organism that most animals would carry if this were the sentinel organism so it would be readily detectable in the fecal samples from most animal species, or at least the target animal species.

So, do you see what I am saying? It is just an indicator organism.

DR. RIDDEL: Yes. And then I think I guess the last question, and I can't remember who made the comment, but everybody always uses the phrase perception is reality. And what if 60 minutes gets a hold of this information about this sentinel organism that is going through the roof.

To me, having been involved in some lawsuits, the

scariest phrase I ever hear is "I will be judged by a jury of my peers." There are people out there I don't want judging me because they are not smart enough to integrate the facts. And this is a very complex situation.

And that is something. I know you can't be scared of the press, but that is important --

DR. WALKER: But the other part of this was, is once you have identified this you have a monitoring system that allows you to detect minor changes in MICs. And this is a very stat system.

If your dilution scheme is appropriate and you can detect these minor changes in MICs, you can determine when you are losing it with this organism long before -- unless it is like an aminoglycoside which is a day and night thing like Dave White talked about.

But you could get an indication that you need to initiate mitigating factors because this organism is changing in its susceptibilities and if you continue down this path it may become resistant.

But then you go back to the press and you say well, this is a non-pathogen and is incapable, again for the fluoroquinolones, incapable of transferring resistant genes to human, so it is not really of concern.

Granted, there is always going to be some people

that are concerned, but from my perspective I think we would get a lot further in pre-approval studies looking at that type of situation than the tremendous variabilities there are in E. coli or other organisms that may colonize in the intestinal tract.

Just like it was brought up today, do we do E. coli and if so which one? And what is the MIC? Or do we look at anaerobes? You know, that is just a plethora of organisms and I am not sure that any drug company could ever afford to get involved in.

DR. RIDDEL: I appreciate the comments and I don't want to live my life scared of the press, all I remember is in 1989 the Wall Street Journal had headlines about finding 64 percent of samples of milk on the grocery store shelves having levels of sulfamethazine in them as defined by the Charm II test.

Now, that was a headline, one-inch letters. If it ever showed up in the classified that those parts were three to ten parts per billion, when at that time CVM considered 50 parts per billion a level of safety. And so, the perception and the ill-effect on our industry's consumer was there, the reparations were never made known.

DR. WALKER: That is why you use them as an indicator organisms and you look at changes in the degrees of

susceptibility, you don't look at resistance, long before resistance occurs.

DR. SHRYOCK: I guess I will have to disagree with you on this one, Bob. To choose a bug like a proteus or something to me is adding more complexity than we have already got which is considerable.

To me the relevant public health organisms, we have already discussed salmonella, campylobacter, enterococci. E. coli is of questionable value to me. If we were going to invest a lot of resources in other organisms, that requires a whole other mindset in order to do that.

And then try to make that relevant to perhaps a zoonotic pathogen which is there is already some question as to what that is relevant to.

So, we are only getting ourselves deeper and deeper into a quagmire by going off on sentinel organisms that are, from my perspective, not very valuable to look at. We can do these decrease susceptibility shifts with salmonella, with campylobacter for certain drugs.

Others, as David White indicated, once you get a resistance gene or plasmid in there, you go from zero to 60 right away. It is an all or none type phenomenon. You don't get this MIC shift. That is only with certain classes of antimicrobics.

So, from my perspective I would just rather go with something that we have already got a handle on. There is some data in the literature and see where we can go with that.

DR. PETRICK: Just very quickly. To go on with what Dr. Walker was saying, if indeed you can detect subtle shifts in monitoring post-approval by doing your dilutions correctly. Then I would propose to the group that don't worry about it pre-approval, that the time to do it is post-approval when you can monitor something carefully.

When you'll increase your field to test from and you can, it sounds to me from what Dr. Walker was saying, you would be able to catch it at an early enough stage if you have enough power built-in and enough resources built-in to the post-approval studies.

So, I think that is something to keep in mind as well.

DR. SINGER: Randy Singer. I guess at the risk of shooting my just budding research program right here and now, the idea of cultivating a sentinel organism for monitoring may be moot because there are techniques that people are working on, for instance for genes that can be transferred.

Or if you can identify very specific primer sets you can do direct PCR directly into -- take your fecal sample and you are looking for genes in that fecal sample and you are not

worried about cultivation any more. You are just looking for whether or not that gene exists.

You don't care about what bug its in any more, you just want to know whether or not a resistance mechanism is present. So you begin to be able to monitor many more animals over many more time periods over much broader spatial scales without the worry of picking your target bug.

Now of course you get back to well, what is the risk? But if you are thinking away from fluoroquinolones and are just worried about gene transfer, it again, and what I hope to be doing is looking at it as an indicator of risk. So, the idea of picking a single bug as an indicator may be hopefully moot in the future.

DR. RIDDEL: Randy, would use of that information, if that testing methodology becomes available where you could look at a fecal sample from the target animal species and say with confidence, yes or no, there are or are not genes with resistance in here anywhere, would that be something that you think should be implemented by the pharmaceuticals as the develop the product? Or would that be something that should be in a -- and therefore be in their pre-approval strategy? Or should it be in the regulatory process?

I guess, I am assuming, again operating from a high level of ignorance, that when we talk about these pre-approval

studies we are talking about something that is going to become a regulatory document that you are going to have to deal with, right?

DR. SINGER: Right. The only way you can do an assay like this is if you know precisely the sequence of the gene you are targeting and that it is a specific primer set. So it is not cross-reacting with other resistance mechanisms, genetic mechanisms.

I don't see its place in pre-approval studies because you won't yet know which genes are possibly conferring resistance. Unless you are using closely related antibiotic genetic mechanisms as indicators of what you might expect, once this product is used.

This I see as more of a post-approval monitoring system. I mean, and it is not going to be -- well, I can't foresee where molecular techniques are going to head, but it is not going to be something that is so easily implemented. Because again, you are going to have to be very certain that what you are probing is again very specific for the, you know, this specific gene for a specific antibiotic.

Because you won't have the organism to then go back later and look for an MIC. All you have got is DNA and you don't know from which organism it came. So, it is more post-approval unless you want to use related antibiotics pre-

approval as a screening.

CO-CHAIRPERSON HESLIN: Just a quick time check. According to the clock on the podium here it is 5:25. According to that it is 5:12. Either way we are down to our last five or ten minutes or so.

MR. SCHMID: Peter Schmid, Intervet. I think the gene assay is not very sensible and not very meaningful. The presence of a gene itself doesn't tell you anything. It is a question of expression of the genes and what happens to the genes under the selective pressure of an antibiotic?

MR. LADELY: Could you repeat? I didn't catch the first time of that question.

DR. RIDDEL: Would you repeat that please?

MR. SCHMID: I think the presence of a gene itself doesn't tell you anything. It is a question of the expression of the gene. And the second question is what happens to the gene under the presence of an antibiotic which puts selective pressure on it?

DR. RHODES: I actually think what you are proposing is really probably going to be the way of the future. I agree that just having the DNA doesn't mean that the protein is expressed, it doesn't mean it is doing anything in the cell.

But, there are now some really eloquent studies that are being done to look at the cassettes of vancomycin

resistance for example. And to really very carefully characterize the genetic drift involved.

I think if you go for DNA versus MICs, what you have done is you have made an end run around that whole list of questions that Paula put up about how big your sample is and what your culture conditions are and how often you sample and from what tissue you sample?

You really are getting right to the heart of the question, is the pressure, the selective pressure of your treatment in a larger population creating a larger number of resistant organisms at the DNA level?

And really that is the basic question. Because the fear is that the DNA is then going to transfer into a zoonotic pathogen at a higher rate which is then going to lead to a higher incidence of disease.

But, I think we are probably about 10 years away from being able to really have the resistance genes fully characterized. Their variation, in an epidemiological sense in the population fully characterized, and the PCR methodology reproducibly available to be used in a field situation.

So, I think it is really going to be a good direction to go in for the future, but it is probably at least a decade away from being some type of test off of which we could regulate.

DR. RIDDEL: Well, I think we have come to a -- if there is a good place to split and maybe allow me to get introduction role a little bit better and have a strategy with my professional facilitator over here.

I would like to ask you all to come back tomorrow morning and maybe we will have a set of comments that may at least be the framework for what we will talk about in our workshop review that you can supplement or delete.

Something a little bit more that we can work from. And it may not be just a set of answers to the questions. But these are comments we would like to make from a ruminant perspective as far as pre-approval studies.

Okay? I appreciate it.

(Breakout Discussion Concluded at 5:20 p.m. to Reconvene at 8:30 a.m. on Thursday, February 24, 2000)