

Veterinary Medicine
Advisory Committee Meeting

Pathogen Load

January 23 - 24, 2002

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I N D E X**VMAC Meeting - Pathogen Load****January 24, 2002**

	<u>Page</u>
General Comments by Aleta Sindelar	3
Public Comment Session/Scheduled Presentations by Dr. Kelly Lechtenberg Questions & Answers	11 20
Considerations on the Regulatory Policy of Pathogen Load by Dr. Richard Carnevale Questions & Answers	23 35
Animal Drug Approval: Should Pathogen Load Be Considered? by Dr. A.G. Mathews Questions & Answers	39 50
Observations of Salmonella Shedding Following Antibiotic Use by Dr. William Sisco Questions & Answers	56 66
Open Floor Public Comment Session by Dr. Jim Heslin, Moderator	72
Presentation of Questions by Dr. Stephen Sundlof, Moderator	78
Committee Deliberations on Pathogen Load by Dr. Cory Langston, Moderator	100
Summarize and Adjourn Meeting	153

Keynote: --- indicates inaudible in transcript.

PATHOGEN LOAD**General Comments****by Aleta Sindelar**

(8:42 a.m.)

MS. SINDELAR: Good morning, last day. Thank you, everyone. Last day of our meeting, a couple of process comments here. One, that we have a change for our scheduled presenters at the open public hearing portion. We will be having Dr. Lechtenberg first; Rich carnevale, second; Dr. Mathews, third; and Dr. Sisco, fourth.

So that is the only process comment I have. As far as check out for everyone, please remember to be checked out of your room by 12 noon.

So, without any further ado, Dr. Langston, if we can proceed, any additional questions that might have been pending from yesterday's discussion.

DR. LANGSTON: Does anyone have questions, either in terms of procedures or follow ups to the speakers yesterday?

DR. WAGES: Do we have any copies of any -- are there any handouts from the public presentations? Aleta, is there any handouts that we --

MS. SINDELAR: (Away from mike) Handouts, I will provide to you ---.

DR. HASCHEK-HOCK: I have a follow up question to Dr. Shryock. He has been involved in quite a number of studies for industry. And I was wondering if any of that information had been public, and also if he -- since he would obviously would have had to do a literature review, if he felt that the literature review presented to us was complete.

DR. SHRYOCK: With regard to the first question, there have been some reports published in the literature of the 558.15 type studies. Sponsors sometimes choose not to publish that sort of data for a variety of reasons, so that there is only a smattering of that type of information available.

The Exponent report literature search terms that were presented yesterday were somewhat narrow in my opinion, and that the word "antibiotics" may have included, but it was hard to tell, some of the specific types of antibiotics that were being tested.

For example, why not use a mynocin, or tylosin, bambermycin, or something like that, which may not be picked up with a general term such as antibiotic. Pathogen load probably would not pick up necessarily a salmonella campylobacter on E.coli.

So I do not know if that was truly captured in the general search term strategy or not. It was

difficult for me to assess the databases that were searched, because I am not an information scientist.

But I am aware that there were papers that are in my files that were not in their report. And I will mention one of these because I authored it, and that was on tylosin swine 558.15 studies. So they did not pick that one up.

There was a similar one that showed the same basic kind of data that came from Denmark, and that was not picked up in their report. Those were published in 1998 and '99, I believe.

So those should have been captured, but I did not see them in their bibliography. That causes me to wonder if, in fact, they have missed other papers that were out there.

So does that answer your question sufficiently?

DR. HASCHEK-HOCK: Yes. As a follow up question then, the two papers that you are aware of, what did the data show in those papers?

DR. SHRYOCK: Actually, you saw it yesterday, at least for the one study that I was affiliated with yesterday. So that is the kind of data that is out there. If you want a reprint of those papers, I can make those available to Aleta for your further review if

you would like.

DR. HASCHEK-HOCK: Basically, then it did not show any long-term effect on pathogen load, if I remember correctly?

DR. SHRYOCK: It would have been during the eight week observation period, and that was with medication throughout that eight week observation period. It is important to note that in these studies medication was continued until the end of the study.

There was not a point where the medication was stopped, and then the animals continued to be sampled. So you really do not have an idea of what would happen post-withdrawal.

DR. WADDELL: Tom, do you have any knowledge of any of the 558.15 trials that failed?

DR. SHRYOCK: I cannot speak for all of the sponsors, because I am not aware of what may or may not have happened there, and a lot of this would proprietary information from that perspective.

I can say that I know that there are studies that were done that did fail that I am aware of from a company perspective that it was a question more on the interpretation of the data, as I tried to share yesterday, where I refer to that as a borderline situation.

So any one of those three parameters, quantitation, prevalence, or duration, could have been just a bit over what was considered to be a pass. And, in that case, there would have been an option to repeat the study and try again.

So it is not a question where these studies that failed were of such a magnitude of increased salmonella shedding that it was totally obvious you could not -- you would just forget it and go away. It was much tighter than that, and it was more a matter of you might pass if you tried again. Do you want to make that investment?

DR. GLENN: A similar question. We had principal investigators, Dr. Gray, Dr. Isaacson, and Dr. McEwen refer to data in research trials. Were those picked up in the Exponent literature search? Are those represented there?

DR. SHRYOCK: I do not recall seeing them. I would have to go back and check the bibliography on that report.

DR. WOOD: In your experience in research, are there any -- is there a class of antibiotic that is more likely to shed than another class?

DR. SHRYOCK: Not that I am aware of. And, again, being from one company you do not have the

luxury, as say somebody reviewing for CVM would have, to look across all of these different studies.

So my information would be pretty much the same as what you have in the table that was presented. I would say that from my perspective there was no class that could be singled out that consistently failed.

There were some failures across the board, but there were passes across the board as well. So I guess my take home from my vantage point would be that I did not see that there was one particular molecule or class of antibiotic that was more likely to fail than another.

DR. HASCHEK-HOCK: I would like to address that same question to Dr. Gilbert.

DR. ROBINSON: Dr. Gilbert is not here this morning. He has child duties. He will be in probably about 9 or 9:30.

DR. LANGSTON: Any other questions for prior speakers?

DR. WOOD: Yes, I was wondering if I could ask Dr. Jeff Gray, who laid out for us a pathogen study, design considerations, confounding factors, and other kinds of principles.

What I do not think I did hear, and was wondering if he might comment on, kind of the question at hand is, is it possible to build a model that would

measure therapeutic applications of antibiotics -- I mean, that would measure the pathogen load created by those uses in an effective way?

I mean what we have in the 558.15 are measures of sub-therapeutic uses and with mixed results. But is it possible to build a model that would be usable for addressing therapeutic uses?

DR. GRAY: In my opinion, I think building that model is possible. It is a complicated process, and it would require the input from a number of different expertise areas. But I believe it is possible to build that model, yes.

DR. GLENN: I have another question regarding a new animal drug application. Is there any other point in the package of the data that is required to be presented from research that relates to microbial concentrations in feces or digesta, or total quantity of microbes, or is it just in the 558.15 studies where this concept comes into play?

DR. SUNDLOF: I believe it is only in the 558.15 studies that we require that information.

DR. GLENN: Okay. And under conditions of use of the antimicrobial -- in other words, I guess what is being sought on the label, and in the 558.15 studies there is probably one treatment that is representative

of that perhaps.

In other words, the antimicrobial is being fed, and they are estimating total pathogen, or total quantity of microbe in feces, or they are estimating total concentration colony forming units per gram of feces. Isn't that correct that only maybe one of the treatments is representative of, in fact, the condition of use sought on the label? Is that correct?

DR. SUNDLOF: I am going to have to refer back to our folks in HF 150 to answer that. If there are more than one dosage in that sub-therapeutic range that is fed for more than 14 days, do each of those have to be -- have to go through these pathogen load studies?

DR. ROBINSON: I am not sure there is anyone still around who could answer that explicitly. With respect to these studies, what our tendency is in any type of dosing range, is to either ask the sponsor to approximate the worse case scenario, the upper end of the range, so that would be either in terms of concentration or in duration of feeding.

DR. GLENN: Okay. And my point is that in my simple mind the challenge studies, in essence, creating a diseased animal, is an abnormal situation and does not reflect the condition of use of the antimicrobial in a feedlot or in a poultry facility or something.

Am I off-base on that? I think that is the way I interpret it.

DR. ROBINSON: I think that the data presented yesterday addressed two different situations: observational data, in which animals were already colonized, or already infected with the organisms; and then also challenge data.

And I may be misspeaking here, but I believe that the challenge data derives from two different scenarios: One, where animals are challenged, and then treated with antimicrobials; and another where they are treated with antimicrobials, and then challenged. All three scenarios would create different answers to different questions.

DR. GLENN: Okay, thank you.

DR. LANGSTON: Again, additional questions?

(No response)

DR. LANGSTON: In that case, I would invite our first public speaker to come forward and get started.

Public Comment Session/Scheduled Presentations

by Dr. Kelly Lechtenberg

DR. LECHTENBERG: Good morning. Thank you to members of the VMAC, and thank you to the Center for Veteran Medicine for facilitating this meeting and

allowing public comment on the process.

Just to give you a bit of a feel for my background, my name is Kelly Lechtenberg. I am a practitioner from northeast Nebraska. We have a commercial feedlot operation. We consult with 22 commercial feedlots in the upper midwest -- thank you, Aleta -- in a four doctor practice.

And I personally spend a significant part of my time doing safety and efficacy package development on vaccines or other biologics in non-pharmaceuticals, be it feed grate, types of products, injectables, water solubles, that type of thing.

So, it is with that backdrop that I come to you today to visit about the FDA's interpretation of pathogen load as it relates to the framework document. My trip today here is sponsored by the Animal Health Institute. And I think it is appropriate to let you know, be aware of that.

If can find the right button. I am sorry. We do have computers in Nebraska now, but we are expected self-service soon. I am sorry. Did you get this right here? Okay.

(Slide)

Past regulatory policy has been discussed in quite a bit of detail yesterday. And I apologize,

(a) that I was here yesterday, so that I now realize that part of this presentation is review for everyone. But it is important to put those things in context with respect to the framework document.

But past regulatory policy, based on the Antibiotic and Animal Feed Task Force, concluded that therapeutic use presented a small risk to public health, and therefore no preapproval study requirements will be imposed on products intended for therapeutic in point-by-point, therapeutic antibiotics are typically used at high dose for short durations of time and in young animals.

The benefits to these animals are thought to outweigh the potential for human risk. We believe it is necessary to have antibiotics available to prevent pain and suffering in these animals, and that FDA has recognized that healthy animals are in fact -- do result in safer food supply.

Therefore, the task force concluded that the significant effect of therapeutic antibiotic use on pathogen load and antibiotic resistance among pathogens present at the time of slaughter would be a relatively low probability event.

(Slide)

With respect to the framework document, which

is a risk-based approach, what we have been doing seems consistent in the past with risk-based regulatory policy.

(Slide)

Because, according to the framework document, changes in pathogen load are generally related to the pathogen, the antimicrobial that is involved, the duration of antimicrobial therapy, and the time between cessation of therapy and the anticipated slaughter time of the animal.

Take those factors and include in that discussion the difference in management practices, slaughter techniques and food processing, the proposed species to be treated, and the frequency, and the extent to which that species is colonized by organisms that will become animal -- have the potential to become human pathogens.

(Slide)

And it is the interpretation of the framework document in the intent of that regarding pathogen load, certainly appears to be reasonable, inasmuch as the exposure correlates with the potential concern.

And it would appear to change past regulatory policy very little with respect to Section 558.15, which required pathogen load type studies for antimicrobial

growth promoters, but not requiring them for most therapeutic antimicrobial usage.

However, the implementation of that document, it appears to be less straightforward than that. Recent guidance to sponsors demonstrates that the FDA policy, with respect to implementation of the framework has changed markedly.

(Slide)

As it relates to exposure and within exposure, the duration of therapy component, the framework documents refers to six, the time period of 6 to 21 days, as medium exposure. Therefore, duration of therapy less than six days would be considered low exposure, hence, pathogen load studies, one might say, would not be required.

In reality, sponsors have been asked to conduct pathogen load studies even when duration of therapy with a product is as short as three days.

(Slide)

Another exposure issue with respect to withdrawal period, the framework document has not explicitly defined that withdrawal period. However, if we presume greater than 14 days, withdrawal would be a low exposure based on current products, and use that as a benchmark.

Again, sponsors are being asked to conduct pathogen load studies for products who have a stated withdrawal period of 30 days. When, in reality, those effective withdrawal periods can be much longer than that because of other products administered in the case of a product that there might be vaccines or other products going into those animals, or to treat diseases that occur in the age of an animal where it is not likely to be anywhere near a slaughter way.

The effective withdrawal period, as used on these antimicrobial treatments, are oftentimes much longer than the specified withdrawal period, hence, adding more safety into the system.

(Slide)

Pathogen shedding subsides even in the face of continued drug administration by a selective drug. If we look at Dr. Williams example with challenging pigs with a tetracycline-resistant organism in the face of tetracycline shedding -- or, excuse me, in the face of tetracycline feeding, even in a strong scenario like that by 10 days post-challenge there has been a greater than 99 percent reduction in salmonella shedding by both the treated and the untreated animals.

And at 14 days, although still present, no notable difference between those that have received

tetracycline and those that have not received tetracycline, with respect to those that are shedding.

Again, extended withdrawal periods will help minimize this risk that resistant organisms are found at slaughter.

(Slide)

Another, with respect to exposure issue, is how many animals in the total population are actually treated?

The framework document would reference that growth promoters are potentially used on all animals of a target species, or at least all animals within a specific production setting.

As far as therapeutics, the products would only be used on animals that are diagnosed as being diseased or at-risk. Once again, in reality, sponsors are being required to conduct pathogen load studies even when the indication is for disease for reflects on a small percent of the animals.

(Slide)

The target species, again, to take an example, target species that are not important to enteric zoonotic pathogens are less concerning. And I appreciate that this is an interpretation issue.

But, in reality, sponsors are being required

to conduct pathogen load studies. Even when used as a species has apparently little association with food borne illness.

(Slide)

And, as one example of that, food borne pathogens are commonly found in swine. However, several epidemiologic studies in the U.S. demonstrate a low association with food borne illness. And the CDC does not consider swine-derived products to be a common source of food borne pathogens. Although swine products can be a source of food borne illness, the risk is low.

At risk of jumping out of context of pathogen load for just a moment, this was one of the points that several of us made at the WHO meeting several years ago on resistance, that the family pet may in fact have a higher impact on whether my daughters develop a resistant antimicrobial infection than the piece of meat we had at dinner this evening.

There is new evidence coming out with respect to both salmonella and campylobacter as it relates to calves, that that may in fact prove to be the case.

(Slide)

Experiences with therapeutic drugs. FDA guidance requested a salmonella challenge study. These studies have been requesting those. These studies have

questionable relevance for predicting pathogen load in commercial settings as per the Exponent report that we heard a review of yesterday.

In addition to that, some current comments would suggest that the bar be raised or lowered depending upon your perception to increase to detect as little as a 20 percent in the quantity of shedding. And to put that in microbiologic perspective, a 20 percent change can be affected by numerous culture characteristics and sample handling criteria.

That might be as little as five minutes at the improper temperature for sampling an organism, which is not to diminish the importance of the statement, but it is to recognize that very small changes in technique can have that type of result, hence, constitute what might appear to be real, and, in fact, be noise in the system, if you will.

(Slide)

In summary, the FDA is requiring pathogen load studies for product uses of short duration, withdrawal periods are long enough to allow resolution of the effects if present, a small proportion of the target species population will be exposed, the target species have little association with human illness. In addition, the results of the requested studies will be

of questionable value for assessing risks to human health.

(Slide)

It is my recommendation that past policy on pathogen load, as it relates to therapeutic drugs, is adequate and should be continued unless or until substantive data are available to justify a change and appropriately redirect the regulatory focus.

Thank you again for the opportunity.

MS. SINDELAR: Thanks, Dr. Lechtenberg. Our next speaker is Rich Carnevale. I will be passing out the copies of his talk. These were received today, so we will have them posted on the CVM website as soon as possible.

DR. WAGES: We are not allowed to ask questions after a public comment, or is that in the open?

MS. SINDELAR: No, no, you can go ahead and ask questions.

Questions and Answers

DR. WAGES: A question, Kelly. What therapeutics are now required? Do you know what therapeutic antibiotics are required to have a salmonella shedding study off-hand?

DR. LECHTENBERG: That is a great question.

Not only is it proprietary, but I do not know the answer.

DR. WAGES: Okay.

DR. LECHTENBERG: And that is humorous, I understand. However, in pulling this presentation together, it is important that I was able to access the fact that that is occurring, and yet sponsors have not been forthcoming, as far as say this product has had this study.

When projects come to me -- and the first part that I will see is for a bid process, all of the regulatory hurdles have been reached already. And I can say that we have not been asked to conduct a pathogen load study on a therapeutic.

But I have been assured as recently as 8:30 this morning, that, in fact, there are sponsors here that will say to you that they have products that have been held up in the registration process, with this being the single remaining hurdle, and the cost in sales is probably in the millions.

Not that this is a dollars and cents issue, from my perspective as a veterinarian, if, in fact, there are therapeutics available that will do those things that we want therapeutics for, that is my reason for saying we should not impede that process without

data to tell us that we should.

DR. WAGES: Yes, just to clarify, they are held up in the review process because of pathogen load studies, not the salmonella shedding studies?

DR. LECHTENBERG: That is my understanding, and I am very happy to have other folks refute that if that is --

DR. WAGES: On that same venue, and I understand you probably cannot answer this. But if there is a requirement or a suggestion that -- well, I guess a requirement if it is holding up patho -- or the approval of the drug.

If there is a requirement for pathogen load studies, studies that to date, except for a comment this morning that the modeling of such studies might be possible, could somebody in this room tell this committee how these studies are run, or are supposed to be run to predict pathogen load?

It was commented yesterday twice that companies are required. If this is true, there has got to be some sort of thought process going into how those studies are to be modeled, and how the answers, the data is to be interpreted. And I guess the sum is not quite right in my mind.

DR. LECHTENBERG: Again, I think a good and a

fair question. And I would also agree with Jeff's comment. I think such a model could be developed. But my first question is also your first, I think, why we are here is, is there a need to have it developed?

Is that mechanism already not in place, given that we are not here to talk about resistance, per se? But there are already, in my opinion, other irregularity and approval steps in place to address this issue other than what we think of as a low level antibiotic feeding the traditional 558.15 type of pathogen load study.

DR. LANGSTON: Other questions for Dr. Lechtenberg?

(No response)

DR. LECHTENBERG: Thank you.

Considerations on the Regulatory Policy of Pathogen Load

by Dr. Richard Carnevale

DR. CARNEVALE: Well, good morning to VMAC members, invited guests, and members of the audience. I am here representing the Animal Health Institute. We are a trade association with members of the pharmaceutical and biological industry that manufacture animal health products.

And a little bit of my background before I joined the Animal Health Institute. I spent about 13 years in Food and Drug Administration, actually, the

Center for Veterinary Medicine, New Drug Evaluation. I do not take any credit for designing 558.15 studies, however, although I was there at the time. And then I spent another six years at the USDA FSIS Inspection Service.

I do take some credit for the designing salmonella performance standard, however, that you heard about yesterday. I do not want you to think I am single-minded on this issue. I do have an appreciation for the regulatory side of the business.

What I would like to do is present to you some comments from the Animal Health Institute, basically, from a policy perspective. You heard a lot of science yesterday regarding pathogen shedding studies and the effect of antimicrobials on salmonella.

What I would like to do is really talk about the policy at stake here, and what CVM is attempting to do with regard to establishing requirements.

(Slide)

So the question is: Should FDA policy for evaluating pathogen load effects be revised to apply to all antimicrobial drugs?

And I think you clearly understand the issue at hand, is that they have applied to sub-therapeutic feed additives, and now the question is should they be

applied to therapeutic drugs?

(Slide)

And I won't spend much time with historical perspective. You have seen these slides before. This is from the framework document about how long the issue has been before us, since the 1950's.

(Slide)

And the scientific investigation has proceeded over the next two decades, and it arrived at the 558.15 studies. Again, these were studies that were required for feed, antimicrobials for continuous use, continuous use being defined as greater than 14 days.

Now, two components again were resistance selection, and numbers of salmonella shedding, feces, otherwise known as pathogen load. And we are not talking about resistance today.

We are talking about pathogen load. And I am not sure it was really made clear to you yesterday that this is just one element of what CVM is proposing to try to do with antimicrobial safety.

There are other elements to this approach that they are taking. There are thresholds that are being proposed. There is categorization issues. So I want to make it clear, this is not the only data requirements that are being put on the industry. We are only talking

about salmonella pathogen load in this particular forum.

(Slide)

The 1970 Antibiotic Task Force again concluded that there was a small risk to public health, and therefore no preapproval study requirements should be imposed on products intended for certain uses.

(Slide)

And, again, you have seen that slide. Kelly just put that up there. The conclusion was that therapeutic antibiotics presented a low probability event.

(Slide)

So thinking about the historical perspective, let's skip to 1996. In 1996, probably, maybe the only feed additive, feed antimicrobial that was approved in the '90s -- I am not completely sure about that, but I know it is one of the few -- a drug called Pulmotil, which is tilmicosin, was approved in 1996.

This drug is for the control of swine respiratory disease, and it is used at a duration of 21 days in feed to control respiratory disease in young pigs. Because it was over 14 days, theoretically, the 558.15 requirements could have applied to this product.

However, CVM exempted studies on this particular product based on the following reasons:

Because the drug was available by a veterinary feed directive; veterinary feed directive was a new form of regulatory categorization for a product. We had prescription drugs. We had over-the-counter drugs. We now have veterinary feed directive drugs.

Pulmotil is the only drug that has gone through that VFD process to date. The claim is for control of disease. As I said, respiratory disease in swine, it was *pasteurella multocida*, and *actinobacillosis*.

The claim was supported by data demonstrating the product is effective; the product was intended for a limited portion of the indicated species or production class; and there was a rational and demonstrated benefit associated with administering the product for more than 14 days.

So, again, in 1996, a consistent application of the previous decision to exempt therapeutic antimicrobials -- and in this case, it was a special case because it was actually fell into the category of possibly requiring 558.15 studies, but because it was considered therapeutic CVM exempted it.

(Slide)

So looking at that regulatory history, why should we now change our policy to require both

preapproval resistance studies and pathogen load studies for therapeutic antimicrobial drugs, in other words, apply the same requirements that 558.15 required of feed additives?

(Slide)

Well, with resistance, at least one could say that in the framework document, CVM referenced 17 research articles that addressed concerns with antimicrobial resistance of veterinary antimicrobials including therapeutic drugs.

(Slide)

With pathogen load, there were no references provided by CVM for any evidence that therapeutic veterinary antimicrobials should be evaluated for this pathogen load issue.

If you go back to guidance document 78, which was issued just prior to the framework document, there were really only two references, and they were pretty dated, 1969, 1977, they really had little to do with the issue at hand. One was a feed additive study, and the other was a study in humans with a clinical salmonellosis.

So, again, no information to support the case that now pathogen load studies should be applied more broadly to a larger class of antimicrobials.

(Slide)

The studies that have been published since 1990 -- I won't go over these -- a number of these studies were in the Exponent report. You will recognize some of them. In fact, Dr. Mathew is here today, and he can probably talk about that last study.

But these studies that were done in the 1990's, that were related to pathogen load, some of which were done with feed additives, others were done sub-therapeutic uses, others were done with therapeutic uses, such as apermycin, and rifloxacin is in there, do not really justify concern that pathogen load is an issue.

And I think this supports what we heard yesterday. In fact, maybe antimicrobials, particularly, the broad spectrum ones that are effective against gram positive and gram negative, might in fact decrease shedding.

(Slide)

So we would contend that there is no evidence that post regulatory policy should be changed to address pathogen load now, with regard to antimicrobials, other than animal feed.

(Slide)

Most studies were available to the agency when

Section 558.15 were implemented. I do not think there is very much new, frankly, since those requirements were first put into place. Therapeutic antimicrobials are in a number of antimicrobial classes. They have been used in veterinary medicine for decades.

I do not know that there is a whole lot of evidence that they have caused a problem with salmonella shedding to the extent that it has really jeopardized public health. Use patterns really have not changed much.

Antibiotics are still used in younger animals well before slaughter, so that it would seem to be, in many cases, a long opportunity for reduction or for reversion to previous pathogen levels.

We also need to remember that the 558.15 pathogen load studies were really concerned with gram positive antibiotics. And sub-therapeutic antibiotics, for the most part, tended to be gram positive in activity. And, therefore, the rationale was that if you killed off the gram positive organisms, the gram negatives would flourish. And so, the salmonella shedding idea came about.

I think with therapeutic antibiotics, in most cases, we are talking about broad spectrum products. They, in fact, kill the gram negative organisms. So

there would be a less likelihood that you would have a continuation of the organism in the intestinal tract.

And we were also discussing back in the 558.15 days chronic administration versus short-term. You have heard other people say this. I mean, exposure is important here. How many animals treated for how long?

Feed additives were tend to be used in large numbers of animals for the life of the animal, or a large portion of their production life. Whereas, therapeutic antibiotics obviously are short-term, small numbers of animals in and out in five to seven days, maybe two weeks at a maximum.

(Slide)

So, we would ask, is this change being made arbitrarily?

Well, it is certainly motherhood and apple pie to say that changes in policy should be based on scientific rationale. I think everybody would agree with that. But I think maybe in this case, CVM might be regulating on the exception rather than the rule.

What I mean by that is we heard yesterday varying reports of the prevalence of salmonella in animals. And up until yesterday, I assumed that there was a fairly low prevalence overall of salmonella in most production animals with the exception of chickens

being higher. But now I hear that there is probably a ubiquitous prevalence of low levels of salmonella in a lot of animals.

But we also heard that the species and serotypes are very important, and to require these pathogen load studies on the off chance that the animal may be carrying a particular species serotype at a high virulence rate that it really could effect public health, it seemed to be to regulating on the exception rather the rule.

I would guess that most animals that are treated therapeutically are not carrying a pathogen of detriment to public health. More importantly, and Dr. Lechtenberg brought this up just a few minutes ago, there really is no validated model to know whether the changes are significant or have any impact on food safety.

I would add that I have been told these studies costs about a quarter of a million dollars, the pathogen shedding study under 558.15. And I also have been told by Dr. Fagerberg, Diane Fagerberg, that she hated to do these studies. They were rather inhumane in her feeling, because these animals had to be kept under strict isolation, and they were given high levels of salmonella.

So, one must question whether there is an animal welfare component here as well.

(Slide)

Changes in regulatory policy may have unintended consequences. And what Dr. Lechtenberg said, it is my understanding that there have been products denied approval because of pathogen load studies, and companies simply will not get into the development process if they face the kinds of regulatory hurdles that these kinds of studies may cause.

The other important thing that has not been brought up is that the scope of 558.15 was established by notice and comment rulemaking. This is important. When the government wants to require something, they usually do it by notice and comment rulemaking.

They publish it in the federal register, and they tell everyone what the rationale for their new requirements are, and then it gets finalized, and the companies have to comply.

In this case, it has really been put on the industry without notice and comment rulemaking; 558.15 specifically talked about feed additives. If we are now going to expand this to therapeutic drugs, it seems to me that it ought to be a comparable notice and comment rule put out, so the public can comment on it, and the

public can see what the agency's rationale for doing what they want to do.

(Slide)

So we think that historical perspective ought to be revisited. Again, I won't go through the principles that were laid out back in the '70s. But, the bottom line is that the effect of pathogen from therapeutic antibiotics would appear again to be a low probability event, and these conclusions I think were made valid today.

(Slide)

So our conclusions. We do not think pathogen load studies should be required for therapeutic antimicrobials, as there is yet to be a scientific or policy reason that supports the change.

And, at a minimum, if the agency intends to move ahead with requiring such studies, they must publish a proposed rule to amend the current regulation, to now expand the scope of 558.15. Because, in my view, the guidance document 78 that came out, that put these requirements on the industry, was premature, and it may not have had regulatory underpinnings to do it on.

(Slide)

Let me just finish with one thing. And many of you know Dr. Angulo. Many of you know Dr. Angulo is

very energized on this issue. And I have a lot of respect for Fred, although AHI certainly does not agree with everything Fred says about antimicrobial resistance.

However, I think this is one thing we can agree with Dr. Angulo on, and he made this statement at the pathogen load workshop last year. And, basically, his conclusion from CDC perspective was that pathogen load studies are of limited value.

So, I will close with that. And, again, thank you, CVM, for allowing me to make these comments.

DR. LANGSTON: Questions for Dr. Carnevale?

Questions and Answers

DR. WAGES: Dr. Carnevale, prior to the framework document being proposed, are you aware of therapeutic antibiotics feed grade having to go through 558.15 studies?

DR. CARNEVALE: Prior to the framework?

DR. WAGES: Prior to the framework.

DR. CARNEVALE: Do you mean within the last five to seven years, or ten years?

DR. WAGES: Yes, prior to whenever in '99, I guess, is when the framework started coming in.

DR. CARNEVALE: I am not aware of any antibiotic having to go through the 558.15 studies for

quite some time, because there have not been any feed additives proposed. I think the only one I know of is the one I mentioned, Pulmotil, which was exempted.

But I do not think there has been another feed additive that has gone through the process, possibly, some of the inophores. I would not know that because this data is generally not available publicly. So I do not know whether there have been studies.

Obviously, if there was a continuous feed additive for non-therapeutic use, it would have had to go through the studies. I do not know of specific cases.

DR. WAGES: And a follow up is -- and it just might be terminology -- but in the comments that I have said earlier about products being held up because of "pathogen load studies," are those in reality a 558.15 type of a study that is being held and really not a pathogen load in this abstract space that we are talking about? Would that be a fair assessment?

DR. CARNEVALE: My understanding is it is protocol that 558.15 was based on, yes.

DR. WAGES: Thank you.

DR. CARNEVALE: And I think they are using pathogen load and salmonella shedding interchangeably.

DR. WAGES: And is that appropriate?

DR. CARNEVALE: Well, I understand it to be the same issue.

DR. WAGES: Okay.

DR. CARNEVALE: Yes, you know, maybe there is semantics here. But I understand pathogen load and salmonella shedding to be basically the same concept from a regulatory standpoint. Now, whether that is the same concept from a scientific standpoint, I do not know.

DR. HASCHEK-HOCK: Am I incorrect in thinking that we are supposed to be addressing the sub-therapeutic use of antimicrobials rather than therapeutic use in relation to pathogen load?

DR. LANGSTON: I think that is a question that we can address to Dr. Sundlof when he presents the questions to us at a later point.

DR. GLENN: Rich, what is the reason that were given by the agency for the need for these pathogen load studies when we are using a therapeutic antimicrobial?

DR. CARNEVALE: There was no reason other than what was captured in guidance document 78, that to ensure the antimicrobial safety you needed to do that, but there was really not a good reason given.

DR. GLENN: Okay. So I assume that it is not related to perhaps negligence in the use of

therapeutics, and that we are trying to identify this lack of compliance? That is not an issue?

DR. CARNEVALE: No, I do not think that has anything to do with it. I think it was simply the idea that in order to assure antimicrobial safety with regard to pathogens, this was another component that needed to be looked at, that had not been looked at previously.

Now, I do not know what drove the center to believe that pathogen load studies now needed to be done on therapeutics. That is one of the problems as you see in my talk that we have had. There has not been very good documentation for this thing.

That is why I would request if the intent is to require this, instead of doing it on an ad hoc basis, which is being done now, as you put it into a regulation, at least the regulation has some force of law.

DR. LANGSTON: I would just simply comment that the framework document does mention need for pathogen load studies. And I think that is one of the things we do need clarification on relative to the questions we are addressing.

I suspect that is where FDA is coming from in trying to -- or in suggesting these studies, but that is speculation on my part, and we will try to get that

cleared up from Dr. Sundlof later on.

Any other questions to Dr. Carnevale?

(No response)

DR. LANGSTON: Thank you.

DR. CARNEVALE: Thank you.

DR. LANGSTON: Next speaker.

Animal Drug Approval: Should Pathogen Load Be Considered?

by Dr. A.G. Mathews

DR. MATHEWS: Well, I also would like to thank the VMAC panel and CVM for the invitation to, or at least allowing me to speak here. I would like to say that I am speaking on behalf of AHI.

But I would also like to say that given my research in antibiotic resistance, which has been my primary focus area, I am not always endeared myself to either side, if there are in fact two sides to this issue. And I was a bit surprised when I was asked to come and speak at this meeting.

So I come to you as an academic researcher. I have not had the background in regulatory issues that most of you have had, and the political sides, and so forth. But I am here as most scientists would like to be, just presenting data. If it helps answer some questions, that is great. That is what we have been trying to do for years.

So I will offer some humble opinions, but I may not be as definitive as some of you who work in more regulatory issues.

(Slide)

As far as my background, for those of you who do not know me, I do work at the Tennessee Agriculture Experiments Station in Knoxville, Tennessee; primary responsibility is in research, a little bit in teaching in the college of ag, and college of vet med; was institutionalized at Perdue for many, many years, took some time out in between to do other things. I was not a slow learner there. I had other things going.

(Slide)

My primary research area originally included intestinal microflora work, a lot of enumeration work, that advanced to enteric pathogens, and food borne pathogens, primarily in swine; some herd health issues, some herd nutrition issues.

And I present some of our peer reviewed publications there for each of those; and then now, much, much work in the antibiotic resistance area. And while I am here, because my focus with age has been decreasing, I want to mention a few things that had been brought up earlier.

As we have worked in the areas of enumeration

enteric microflora, and in the areas of identification of food borne bacteria, what I have come up against, as a researcher in both of these areas, is I am continually amazed at how well we can identify organisms and type them to clonal types, trace the sources of those organisms, and determine whether an animal is positive or negative.

What I am frustrated by is our ability to enumerate, and we are still using archaic methods, plate counts, most probable numbers. And when you contrast these two types of studies, and both of those studies will be needed in pathogen load, I am very fearful for what types of data would come out of those studies because I have much less confidence in our ability to actually count organisms.

So, having said that, I hope that that might address some other questions that had come up.

(Slide)

Okay. Should pathogen load be considered?

That came to me as a question about three weeks ago. I tried to just develop my own views on that. And the primary questions that I had was:

(1) Does scientific evidence exist to support that change? (2) Will the proposed challenge studies answer appropriate questions? Those will be the first two

items on my agenda.

(Slide)

And here I have presented some of our data in that regard.

(Slide)

One of the studies that was noted in the Exponent review was this particular study, Paul Edner and myself conducted, where we actually went at the question of pathogen shedding and antibiotic resistance, given a challenge model, and given specific types of antibiotics, so the challenge study very similar to others.

Pigs were challenged post-weanling. We used an NADC strain that Paula Cray had worked with for a number of years. We ensured that those animals were positive following that challenge; and then we treated groups of animals with aminoglycoside, apermycin, with the cephalosporin, ceptosequet, carbon diox, oxytet, and we had a control very typical of the types of antibiotics that would be used in swine herds.

We housed these animals in typical commercial-type setting. These were not isolation chambers. They were, in fact, groups of pigs separated by pens in a finishing facility, curtain slided, slide in floor, very typical of what you see in the industry.

We recovered challenged isolates from fecal material -- again, noted whether the animals were positive or negative. We did not try to count the numbers of salmonella that were being excreted.

And these were the data that came forth for us. The control group that did not receive antibiotics as indicated in that orangy yellow kind of line. And what we are looking at are the percentage of pigs that are shedding over time. And these are days post-challenge from 0 to 84.

We see typical trends, as has been seen in other data. As far as the decrease in shedding, positive animals, if you look at the control, we had consistent shedding for a longer period of time in 100 percent of the pigs, as opposed to all other groups of antibiotics. And that includes a combination apermycin, oxytet, carbon diox oxytet, and ---.

And there was a difference noted, a statistical difference noted between the apermycin OTC, and the control, whereby, the control was greater overall, as far as persistence and resistance. So that was one challenge study that was, I think, conducted in a manner of on farm situation.

(Slide)

Now, we have conducted a number of other

challenge studies, again, really focusing on antibiotic resistance, not so much on numbers shed, but we do have those data and we were able to pull those out to give some idea of what we saw.

Again, these animals were challenged with the same isotype of salmonella. In these cases, we have used various antimicrobials. We have used various dosing schemes including rotations, pulse dosing, gradient dosing.

A lot of this work was sponsored by the National Pork Board or NPPC in earlier times. So we tried to adapt the studies to be very applied and very on farm. And we also included interactions with different managements, high sanitation, low sanitation, high animal density, low animal density, and so forth, looked at those interactions again with antibiotic resistance and number of pigs shedding.

In these cases, animals were kept in separate isolation facilities. Although they were nursery units and finisher units, they were housed in separate rooms. Again, fecal isolations, and so forth, recovered the challenge organisms and other organisms.

(Slide)

Our results in those studies -- and I think we have conducted somewhere around 16, and that includes

replicates in I think five different trials -- in no case was shedding of salmonella increased by antimicrobial use. In some cases, shedding of salmonella was decreased by antimicrobial use.

(Slide)

And I will show some, just a couple of data, two different studies. One is, again, typical animal shedding after challenge, percentage of pig shedding, days post-challenge, control, again, in yellow-orange. In this case, 100 percent of the pigs were not shedding after challenge, and we do not know what happened here.

But, in any case, ranged from 50 to 70 percent of pigs were shedding in all treatments. There were no differences between the antibiotic treated pigs and the control pigs, and all shedding as far as numbers of pigs positive declined as would be expected over time.

(Slide)

Now, this particular study we were looking at effects of antibiotic use over generations of swine. We had sows that had been treated with antibiotics and looked at their pigs under various regimens compared to control groups that had not received antibiotics for generations.

This was a case where numerically we saw a decrease in salmonella shedding with antibiotics, so

control was different. We did not have a lot of pigs in the study, and we were looking at three days. So we had to come back to a Chi Square categorical type analyses.

There really were not differences, although numerically it looks like something going on there. But, in any case, we are confident that we did not see an increase of salmonella shedding by use of antibiotics.

(Slide)

Now, as far as another on farm study, we had conducted one a number of years ago where we were interested in determining resistance patterns, and occurrence of food borne pathogens on farm types. One type was considered to be organic farms, non-antibiotic; the other type of farm were typical commercial units.

We tried to choose farms that were equal in size and equal in management, so we did not have interactions going on there, animal density, and so forth. In our area of the word there, the southeast, we could identify four farms -- I take that back, some of these were in the midwest and southeast -- four farms that used antibiotics commercially.

That included therapeutic antibiotics and three farms that were of the size that we needed that did not use antibiotics. And, again, we collected fecal

samples. This time from sows and pigs at various age groups for recovery of isolates.

(Slide)

Our results, salmonella was recovered from a few pens from both farm types, both farms that used antibiotics, and both farms that did not. There were no differences observed in shedding between those farm types. In all cases, we had to recover salmonella by pre-enrichment, typical bam type analyses.

In order to get enough positive samples to report, we had to pool animals within pens to get enough evidence that salmonella was occurring. And there was no evidence in our minds that commercial farms that used antibiotics had higher pathogen load, as far as salmonella was concerned.

(Slide)

So, from our works, challenge studies did not show a problem; wild-type studies, on farm studies did not show a problem.

(Slide)

Now, as a scientist, you are always concerned that maybe you are the group that everyone is always reporting. Well, in contrast to Dr. Mathews' group, we found this and we found that. So, going to the literature, and you have seen some of these studies

before, we wanted to know is this consistent with other people have found?

And if we look at the poultry industry with flavomycin, salinomycin, we had seen no effect; sales group in Athens, no effect, and Shryock, Baggenson, and so forth, again, no effect. In fact, I am familiar with the types of searches that were conducted by the Exponent review.

We constantly searched databases. I can tell you that there are many -- not many -- there are a number of studies that were reported by Exponent, some that were missed by Exponent. They have all said the same thing. I am not aware of any that were missed that say something different. Hopefully, that may answer the question.

The challenge model has already been discussed, and some of these I am sure were discussed yesterday. I missed some of those discussions.

(Slide)

But I do want to add something that you have not seen, and that again comes back to trying to count organisms for challenge studies or for pathogen load studies. We may have the ability to detect one log ten difference between numbers of organisms maybe. I am not confident that we can.

But, certainly, if you are talking about a smaller difference, a 50 percent difference, 20 percent difference, I am not very comfortable talking about those types of studies. Because I do not have confidence that we can do that, that anybody can do that yet.

(Slide)

I also want to note that most of the recovery methods that we use for salmonella are based on the enrichment sort of recovery. And I am curious and a bit concerned that those organisms that show up when we enrich, fast growing clonal isolates, are those the same ones that colonize and persist on our ag products? Are those the same isotypes?

I am not so sure that is the case. And, again, that makes me wonder if we are answering pertinent questions through the use of these challenge studies.

(Slide)

So, to summarize considerations that I would have, would the proposed changes break a longstanding FDA principle by establishing requirements without scientific justification?

And, given all of the media, and so forth, discussions that are going on, I am always concerned

that things are being said, or issues are being handled in a way without scientific justification.

Particularly, we have seen this with the European countries as of recently. And that is kind of frightening from a scientific point of view.

The data presented here, along with the findings of the Exponent and others, really do not show scientific evidence in my mind that there is a problem out there. So, with that, I think mine is done. I appreciate your time and attention. Thank you.

Questions and Answers

DR. WOOD: We have had several studies now on swine, and some references to broilers. We have not had any studies presented looking at shedding related to antibiotic use therapeutically with cattle. Are you aware of studies that would address that question?

DR. MATHEWS: Dr. Pope, I believe, maybe has worked in that area. I was at a conference earlier this summer. We discussed some of that work. So, yes, I am aware of some going on.

DR. WOOD: And what were those findings, do you know?

DR. MATHEWS: He had mixed reports, very few number of animals, not a lot of significance. There were cases were again if you choose a resistant organism

and colonize the animal with a resistant organism, and then select using that particular antibiotic, not surprisingly you see persistent colonization by that organism.

DR. HASCHEK-HOCK: I noticed that in the data you presented that you used the percentage of pigs shedding, and you also alluded to the fact that it was difficult to enumerate our organisms.

Can you expand on that a little bit, why you use percent pig shedding? And have you at all attempted to count the number of organisms shed?

DR. MATHEWS: Yes, certainly, a number of species of bacteria we have tried to enumerate, not only in feces, but most often we do intestinal colonization work, and we deal with different types of E.coli. We deal with gram positive organisms, streptococci. We have dealt some with trying to enumerate salmonella.

And, again, we typically resort to doing serial dilutions of the sample, and then direct plating, and counting colonies. As you do serial dilutions, anyone else who has done those studies, you might be frustrated by the fact that you do not get a nice linear change in the number of colonies on plates, as you dilute by ten-fold, or do two-fold, because of problems with, for example, groups of organisms that may clump,

and you might have a thousand organisms in that clump they show up as one colony on a plate.

If you vortex a little bit longer, that clump breaks up, and suddenly you have a thousand colonies on that plate. Very sensitive, technical aspects can come into play there, and not only as people have been doing these plate counts for years, and years, and using them as a guide for the numbers of organisms, but again I do not have a lot of confidence that we are counting organisms. Salmonella is no different in that regard.

DR. KOCHEVAR: It was mentioned yesterday, or there was a question raised about more molecular methods like quantitative PCR. And the answer given yesterday was, well, you still had to enrich when you did that.

Do you share that opinion, there is no method available that you can --

DR. MATHEWS: I do share that opinion. And, again, we are dealing with a timed assay with quantitative PCR. I do not think it has been verified very well that these are actual counts that are occurring, and they are done in vitro, in an in vitro situation rather than the actual growth within in vivo type of work.

Until I see something definitive that this is the type of enumeration procedures we should move to, I

would have no confidence. I have much greater confidence in what we have done to identify organisms to isotype, and identify a positive animal, much more.

DR. HOLLAND: Could you go back to your slide that is titled "Effects of Antibiotics on Shedding Patterns?"

DR. MATHEWS: Let me see if I can figure out -- okay.

DR. HOLLAND: Would you take a minute and describe to us on your second bullet there where you have --

DR. MATHEWS: Okay.

DR. HOLLAND: I am sorry.

DR. MATHEWS: Which slide?

DR. HOLLAND: Seventh or eighth.

DR. MATHEWS: Sorry for all of these bullets here.

DR. HOLLAND: No, the next one that has -- one more.

DR. MATHEWS: One more up -- oops, this one?

DR. HOLLAND: That one, that one, yes, your second bullet there. Would you explain to us your concentrations or dose and why you selected those?

DR. MATHEWS: We tried to use what is commercially acceptable. In most cases, these were the

label used recommendations, 150 grams per ton of apermycin. Cephtiafura was a therapeutic dose. It was a three-day high dose IM injection of cephtiafura; oxytet was 100 grams per ton; Carbadox was 50 grams per ton.

Again, these are types of regimens that are typically used in the swine industry.

DR. WADDELL: I noticed you use these in combination, all those four within combination with tetracycline.

DR. MATHEWS: Yes.

DR. WADDELL: Why was that?

DR. MATHEWS: Because where I came from in the midwest that was a common usage. OTC was used following as a growth promotant antibiotic in that herd as a growth finisher. And for that particular study, we only had so many treatment rooms available. And so, to make it I guess relevant we tried to use what was most commonly used at that time. This was conducted in the early to mid-'90s, if I remember right.

DR. WADDELL: So tetracycline was in at the same time, or it followed it?

DR. MATHEWS: It followed.

DR. WADDELL: Followed.

DR. MATHEWS: It followed the other uses, yes.

The apermycin, for example, cephtifura, commonly used, as you know, John, in the younger animal, the nursery animal, and then that is followed by a growth promotant type use of oxytet. Carbadox may be a little bit different in that regard, because it may often be used in the post-nursery stage as well.

DR. GLENN: Were the animals sick in these -- in this study?

DR. MATHEWS: No, typically, when we dose the animals, we will see an increase in body temperature, and for maybe two to three days after the dose we will see loose stools. But the animals had typical average daily gain, and typical feed conversion for our part of the country. And that has been very common in our challenge. With that particular isotype, that has been our common experience.

DR. GLENN: I also have a question regarding the issue of counting the quantity of microbes, as opposed to, you know, a plus or minus. Someone mentioned is this semantics?

But I have tried to read the documentation and stick to the definition of pathogen load, and that strict definition is a quantity.

DR. MATHEWS: Yes, it is.

DR. GLENN: So in a mass balance approach, we

look at quantity in, and here we are interested in quantity out on meat. And it seems like that is very critical.

DR. MATHEWS: Yes.

DR. GLENN: So I am interested that you say we have trouble counting, just in terms of the overall system, food system, so that seems very problematic.

DR. MATHEWS: You may want to talk to food scientists in that regard. I work closely with Dr. Andron, who you may be familiar with, on the ag product side. And we do a lot of work together. We share the same frustrations with enumeration procedures. Thank you.

DR. LANGSTON: Thank you, Dr. Mathews.

We will have one more scheduled speaker before we take our break.

Observations of Salmonella Shedding Following Antibiotic Use

by Dr. William Sischo

DR. SISCHO: Okay. Thank you very much for the opportunity to speak to you. My name is Bill Sischo. I work at the University of California - Davis, at the Veterinary Medicine Teaching Research Center. AHI asked me to present some of the data that we have been collecting, and they paid for my trip here.

I will just give you just a little bit of a

background. Primarily, right now I am working at the Vet Med Teaching Research Center, which is about 280 miles south of the main campus; primarily, working with veterinary students in their senior year teaching clinics, as well as doing research.

My research historically has always been in dairy production, things that improve the economics of it, as well as improving productivity. Current work has been on product quality and food safety issues, and, particularly, recently on antibiotics.

What I am going to do is present just a piece of the data that we have been collecting. Most of our work is observational studies. I do not do some of the studies that you have heard where they are experimental challenge studies. Mostly, we are going out in the field and working with dairy farms and calf ranches.

The study that I am going to talk about today is that first one on prudent use, which was sponsored by CDC. And just to give you a little bit of an understanding, the project was really directed at developing some strategies for the calf ranches that raise replacement heifers, as well as calves that are going for beef, to develop record systems, and within that structure we were collecting data on what are the changes, the dynamics of resistance associated with

antibiotic exposure.

The farms that participated in this study really were volunteers. So it was not really intended to get at prevalence. It was really intended to use these herds as demonstrations.

(Slide)

A little bit of background about the region where we are. We are located somewhere right here in the middle of the San Joaquin Valley. About 50 years ago, the dairy industry in California was spread throughout the whole state.

There was a thriving industry from San Diego up to the northern part of the state. And as the state has grown though, agriculture, and not just dairies, but all of agriculture has constricted down, and now we are looking at fairly large operations in fairly small regions.

(Slide)

This is the counties that I work in. You can see there is a scale on the bottom there. There is 80 miles -- I mean, yes, 80 miles. It sort of stretches across the whole county. There is 500 dairies that are in this region right here. We are located right there.

There is about 1200 animals on each of those dairies. Those are milking cows, double that for the

number of animals that are replacement stock, and you will end up with somewhere around 500,000 to 600,000 cattle.

We also have about that number of people, and plus a fairly extensive agricultural region. And, as those dairies have grown, one of the things that has happened is that there is more specialization.

The dairies have tended to send out calves to ranches to raise, although some of them maintain them on the ranch around the home farm. There has been developed two different styles of management of those animals. One of them involves a fair amount of antibiotics, and another does not.

(Slide)

So, what I am going to show you is a study that looked at salmonella shedding, not specifically as a main objective, but it was one of the subobjectives. We wanted to look at the age-related dynamics of antibiotic resistance patterns in calves that were raised in these two different systems. The objective is to use that as an outcome for an intervention trial.

So what I have got now are calves that were housed on a mixture of dairies and calf ranches in this study presenting three dairies and three calf ranches, because those are the ones that we summarized. At this

time, that is 297 calves that we enrolled.

What we did is we enrolled them at the day of birth and we followed them through. The heifers actually out to their next parturition, but most of the data I am presenting today is just the first six weeks of information.

We sampled them on two week intervals, and we took fecal swabs, took health and treatment histories, and then also evaluated the milk replacers that were going to these cows.

(Slide)

And just as, again, as an observational study in the data that I am presenting, you would sort of think of this more as an ecologic study. I have got two groups; one that is raised on a home dairy. When you look at calves that are raised on home dairies, they tend to be single sourced animals.

Occasionally, somebody might take in animals. But these groups they all come from that home dairy, and are all raised in a site, slightly geographically separate, though still on the home ranch. So they are separate from the cows.

There is fairly reasonable costs for management, which means that the failure of pass of transfer in this group is somewhere between 5 and

40 percent, still fairly high at that 40 percent for pass or transfer.

They generally are fed whole milk or milk that might come from the hospital strains. Very rarely are they actually fed a milk replacer. That is a powder that comes from a commercial source. There tends to be less overall morbidity and mortality and less treatment.

So calves are exposed to much fewer antibiotics, although the opportunity in this part right here for discarded milk to have some antibiotics in it exist. In our calf ranches though, they tend to be multiple source groups. They come from many ranches. Some of them travel as far from California maybe from Idaho. So they can travel quite far.

The colostrum status is just assumed to be 100 percent failure pass of transfer, not that it is true when we have evaluated that. It is higher, maybe in the 40 to 70 percent range. And that is also because there is bull calves involved in that, but the owners presume it is 100 percent pass of transfer and manage it that way.

As a consequence, they get milk replacer and discard milk, same discard milk as the dairies get, much more likely in the milk replacer to be getting antibiotics. In fact, 100 percent of the herds that we

get feed antibiotics as part of the milk replacer. Treatments are more common, it is a first. The rate of morbidity is much higher and calves get treated.

So, again, as an ecologic study, that is the pattern that we see. That does not mean that every calf got a treatment; on the dairies they did not. It just means that in general there is a lot more antibiotic exposure on these calf ranches than there is in the dairies.

DR. GLENN: And it is from date of birth to eight weeks post?

DR. SISCHO: Yes.

DR. GLENN: For sampling?

DR. SISCHO: Yes, six weeks actually.

(Slide)

So the lab procedures, just for those who were paying attention yesterday, the intensity that you look for salmonella varies. And, in this case, if you look at the procedure -- I think yesterday you heard people were taking up to ten grams of fecal material.

We take very small volumes of fecal material, and we do not do the pre-enrichment, only a single enrichment. So we are not looking as hard as some of the other places.

We have made that decision that we really want

to measure animals that are shedding, rather than just animals that may have an exposure to salmonella maybe having a few colonies that are shedding. We were actually measuring a fairly substantial shedding rate.

(Slide)

On what I am going to present is prevalence data, so proportion of animals that are shedding. It is going to be stratified by calf age and the operation type, and then some odds ratio for shedding.

And here is the chart that I have down here, or the four sampling periods. Day zero is zero day on arrival. So they may be anywhere between zero days, to the day of birth, to about two days old.

Two weeks, four weeks, six weeks, these are the dairy reared, and these are the calf reared groups. What you can see is that the rate of salmonella shedding that we detected was 118 isolates that we found. Animals would be showing up in all of these groups. There is a few animals that shed across some of the age periods, but not that many surprisingly.

Over here in the calf reared groups where there is quite a lot of antibiotics being fed and administered to these animals, we have a relatively low rate of salmonella recovery on those farms.

Probably the most significant thing here is to

look at the very top part. There is a very strong age dependency on day zero, the very early animals arrival on the farm had a fairly high rate of salmonella shedding compared to the animals once they have stabilized on the farm. And I think that goes back to some of the things that you have heard yesterday about the stresses.

(Slide)

And just to sort of emphasize that sort of effect that we saw for dairies compared to calf ranches, the odd ratio for shedding was anywhere from 4 to 12 calves on dairies where more likely to be shedding than calves on the calf ranches.

(Slide)

Now I am just going to go over a couple of studies. You have heard these. And I guess the point is that there is a lot of factors that affect salmonella shedding. Antibiotics is one of the ones you are considering, but the preliminary data from our study says that age is an incredibly important factor as to whether an animal sheds salmonella.

I am going to go to this one which you have not seen, which is the National Survey of Data Cattle, part of the NARMS survey that was done in 1996. The interesting pieces from that, if you looked at across

the U.S., 5.4 percent of the dairy cattle were shedding salmonella at the time that they came in and did a cross-sectional study, one point in time that they took these data from.

If they looked at animals that were scheduled for calling, that rate went up to 18.1 percent. And when you took animals actually out to market, then 15 percent were shedding. So, overall, on a farm, 5.4 percent, but as things were happening to animals in groups shedding was going up.

This one just emphasizes the things that you heard yesterday about pigs and transportation stress. Transportation stress increases shedding in an experimental model.

(Slide)

And I will just go to sort of this last one. We have heard some of these other ones about the effects on swine facilities. But in poultry facilities, that shedding is very much premise dependant. And, you know, I have talked about salmonella shedding.

But as soon as you start asking questions about what sero groups are there, what serotypes are there, and taking it down, you start finding very specific farm effects that are very difficult to sort of separate out and explain independently, and that is what

they are finding there, that depending on the integrator, the rates that you saw of salmonella shedding.

So management factors associated with the premise actually will dictate some of the rates of salmonella shedding. There were age dependant effects, just like we observed, as well as seasonal effects.

(Slide)

So, just to reiterate the things and sort of wind up here, is that in our study we had a very strong age-related effect. There was -- you know, it depends on how you decide to interpret it, but certainly exposure to antibiotics did not increase shedding. And, in fact, in our study it looks like calves are less likely to be shedding if they have some level antibiotics.

In the peer review data, there is a very strong transportation influence from cattle, swine. I have not really seen the poultry work, but I suspect that might be there as well, as well as age effects.

So I will stop there, and I will be happy to answer any questions. And I appreciate again the opportunity to speak.

Questions and Answers

DR. LANGSTON: I had a question. The

antibiotics I am most familiar with in milk replacers are usually tetracyclines, perhaps, neomycin.

DR. SISCHO: Right.

DR. LANGSTON: And it was quite interesting that the ones receiving the milk replacer, the ranch reared calves, had lower salmonella. Do you know if those salmonella were in fact sensitive or resistant in general to those antibiotics?

DR. SISCHO: The majority of the salmonellas that we observed were sero groups C1's. The majority of those were monodados, and all of those are susceptible to all of those antibiotics, both of those.

DR. KOCHEVAR: Between the two types of rearing conditions, what is the density of animals in those two different venues?

DR. SISCHO: Yes, they are very similar -- density, the housing situations are nearly identical. They are housed in hutches, three banks, three animals in a bank. Usually, more total animals on the calf ranches than on the dairies, because the dairies are only supplying maybe five animals a day compared to maybe a hundred that may come into a calf ranch.

DR. PARKHURST: Just as a point of interest, could you comment on the seasonal effects, what do you think causes them?

DR. SISCHO: I think there is a geographic seasonal effect, you know, summers, and places where winters are more harsh tend to have higher rates. In our region, we often are turned around. We have very hot, dry summers, and our winters are warmer, environmentally more conducive for survival of the organisms. We have more wet, cool days.

And so, the ability of it to move around on whatever vehicle you choose, whether it is people, animals, wildlife, the manure, it is just more likely to have viable counts than in the summer for us.

DR. GLENN: You mentioned you took some of these studies out to first parturition in the heifers. Could you comment on those data?

DR. SISCHO: Yes, it is much sparser. It is not nearly as rich as the data as the data that I presented. But as you follow animals all the way out for the first 18 months, salmonella virtually disappears. We have a very difficult time identifying it.

Again, I will go back to our culture and method in looking for that one CFU in a ten gram sample. But, at the same time, as they move into parturition, there tends to be an increase in shedding around that time, which I think is also reflected in what has

happened with the cows.

DR. WADDELL: Do you know of any studies where they have looked at animal caretakers or handlers of those calves and incidents of salmonella?

DR. SISCHO: Not explicitly incidents of salmonella. Dale Hancock has done some work on outbreaks of diseases. And one of the things that he has done is he cultured esophageal feeders, which, you know, one of the things that we try to do is get people to feed colostrum.

One of the ways to get that is to force feed it, and he found that that was one of the elements that moved it around between -- within the operation. So there are studies that say that people, and, as well as the things that people are using will move it.

DR. GLENN: I have another question regarding the non-survey work. Although I am familiar with the numbers that come out on all of the species, could you describe to me how they actually sampled dairy cattle in these various environments of on farm culling and that market, do you know?

DR. SISCHO: I guess maybe I need a different -- the question is how did they sample?

DR. GLENN: What are they sampling specifically?

DR. SISCHO: As a fecal sample?

DR. GLENN: Feces.

DR. SISCHO: Yes.

DR. GLENN: Okay. And it is a grab sample, and they go to a random allotment of farms, and they go to a random number of cows, and they take a sample, and they leave?

DR. SISCHO: Right, yes. They have a limited number. Depending on the size of the herd, they may sample a high proportion of the herd. But in a large herd they still will only stop at, I think, it is 20 or 30 samples.

DR. GLENN: Okay. And same I guess for culling, they must go the point of --

DR. SISCHO: At culling they have identified it on the farm. So the question would be, who is leaving the farm? And then they would go in and sample, and then they followed animals off to market, not necessarily from the same herds, but followed them out to markets.

DR. GLENN: Okay. I appreciate it.

DR. KOCHEVAR: I know we are not considering this today, but it is a point of interest. In these studies, was there any attempt made to look at the presence of resistance factors in the isolates or

anything else that would address the issue of resistant bacteria?

DR. SISCHO: Well, the salmonella isolates that we predominantly recovered -- well, all of the salmonella isolates fell into three -- we have been using some things where we have been clustering the data, so we had three clusters of isolates.

The majority, the vast majority of the isolates were susceptible to all of the antibiotics. There was a small minority at either end. And, again, as you look at them more carefully, and type them more carefully, you start seeing more farm-relating things. So, isolates would start showing up on farms rather than as to class.

But we found high DT104 type pattern in one group of resistance, and in another one is a new version of a new pork that is pretty highly resistance, but, again, tended to be fairly strongly farm clustered rather than across the farms.

DR. KOCHEVAR: So, as you looked at that data, there was no difference between the ranch reared versus the dairy reared in terms of --

DR. SISCHO: In this group, there was one ranch that had the salmonella typhimurium, and one dairy that had the salmonella.

DR. LANGSTON: Thank you.

DR. SISCHO: Okay. You are welcome.

DR. LANGSTON: At this time, we will take a break. Again, just noting check out time is 12, and our lunch break is at 12:30. So, if you wait for lunch, you will be past the check out time. You will either need an extension, or go ahead and check out. So, we will reconvene.

(Whereupon, the meeting was adjourned for a short break.)

Open Floor Public Comment Session

by Dr. Jim Heslin, Moderator

DR. HESLIN: My name is Jim Heslin. This is a continuation of the public comment session. Before break, there were four scheduled presenters. Now this is an opportunity for others who want to make comment to come forward and do that.

For those of you who were here on Tuesday, the game plan is the same. You should come forward to one of the microphones, identify yourself, and your organization. We have, not a whole lot of time, so I would ask that you keep your comments brief. But I do not want to set a time limit on them.

To stay on schedule, Dr. Sundlof is scheduled to present questions at 11 o'clock. So that gives us

about 25 minutes. So, except for people who may still be out in the hallway, anyone who wants to begin -- yes, sir.

MR. SUNBERG: Good morning. I am Paul Sunberg, and I am here representing the National Pork Board. Okay. Paul Sunberg, representing the National Pork Board. And I think I have got three points.

And, primarily, I see in the question 1, it talks about an overall scheme of current animal production practices. And I want to address that point of current overall animal production practices with three things.

The first thing is that for the producers, the availability of antimicrobials is an important factors. And the producers will look at that availability as one of the tools that they can use to provide a safe, healthy, and quality product to the packers.

So the availability of antimicrobials, cost-effective availability is an important thing. And, again, like I said, one of the variety of tools that they need to have, as well as the types of, you have heard, vaccines, hygiene, nutrition, all of those other things play into that.

The second point that I think could be clarified some that I want to reinforce at least is the

role of HACCP and how the packers HACCP plans effect the producer, and talking about pork production here.

I do not have data, but you have got a lot of data about the number of confounding factors that effect pathogen load and effect pathogens in the animals on the farm, and it is a confusing issue.

The packer HACCP plans, I believe, as we heard, call for the packer to be responsible for the product, and to address hazards as they come into the plant, as well as the level that go out.

Currently, they recognize that because of that confusion, and because of the confounding factors, that the producer on the farm has very limited, if any, ability to affect microbial or pathogen load.

The chemical residues and antibiotic residues that could come in with the animal is something the packer cannot take out. Therefore, the producer is responsible, and the producer meets that responsibility through a pork quality assurance program, and those types of activities, as well as physical hazards with broken needles, and other things that come in.

But, at this point, there is a recognition that the most cost-effective place for mitigation, as well as the most effective as far as pathogens go, is in the plant itself rather than on the farm.

So I want to make sure that I reinforce the point that the producer has limited, if any, ability right now to affect pathogen load as it comes into the plant even with or without antibiotics.

And that leads to the third point, and that is the research that is going on with the National Pork Board. I am heartened to hear at least a couple of references to our research efforts, and our research funding that we have been going through for many years now in the area of antibiotic resistance, as well as in the area of actually pathogen load, if you put it that way, but it is specifically, especially, salmonella and pork safety.

In 1996, we initiated an international symposium on salmonella in pigs, and it is specifically in pigs. And it was a small group that got together at NADC and AMES. It was probably about as many people as on the committee to talk about collaboration and what we can do and how, if we can affect pathogen load on the farm; that has grown.

Last year in 2000, it was in Germany. We had 169 papers presented or submitted with I believe 49 oral presentations, a lot of interest in this. And the reason there is a lot of interest in it, and the reason that the National Pork Board started this, was because

of the HACCP question: And will that effect producers on the farm? And, if so, how can they cost-effectively interact with that?

So, those three points, very quickly, I wanted to make you aware of: (1) the importance of the issue for the producer in antimicrobials; (2) clarify the HACCP relationships; and (3) some of the things that we are trying to do.

DR. HESLIN: Okay, thank you. Before you step away, any questions from the committee?

DR. GLENN: I have a question, Paul, regarding the interrelationship between the producer and the slaughter plant. There are a lot of systems now, or several being put in place which relate to on farm practices and that product. And labels or things are being put on the products as a result of what they certify as being done on the farm.

You have indicated that regarding the use of antimicrobials, that is included in some of these processes, right, where we are getting a label at the end of the day on pork, or on poultry?

And, usually, it is that they do not want them to be used at all, correct?

Is there anything in between going on where there is an economic benefit that is related to the use

of antimicrobials, anything in between?

MR. SUNBERG: You are right. There are programs that would put labels on. For the industry, those are minority. They are more looked upon at this time as niche markets.

Certainly, they are important niche markets, and there is not any discounting that, but the majority of the industry does not do that. They use all of the tools that are available to them.

I do not know of any programs that would say specifically, we do not use this antibiotic or that antibiotic, specifically, in naming that. It is either an all or none type of thing. Either we do, or if it is labeled that way, it is probably labeled as we do not use any.

DR. GLENN: And I would also say that, in any event, these niche areas are not related to their wish to reduce pathogen load necessarily. It is the organic label that they are seeking in the end.

MR. SUNBERG: Well, yes, as a niche market, it is a market availability thing. It is do I have an opportunity to gain an advantage, a cost advantage by producing a product in some way?

If there is not an advantage to doing that, to producing a product in some way, then there is not a

whole lot of incentive to get into that a niche market.

DR. HESLIN: Any other questions?

(No response)

DR. HESLIN: Okay. Anyone else want to comment?

(No response)

DR. HESLIN: Okay. Well, with that, if there are no further comments, we will close out this session, and Dr. Sundlof will take it over for the presentation of questions.

Presentation of Questions/Procedural and Clarification

by Dr. Stephen Sundlof, Moderator

DR. SUNDLOF: Okay. Thank you, Jim. While we are waiting for the computer to wake up, let me just ask. There were some questions, I think, Mr. Chairman, that you said you would like to propose to the FDA during this time. So maybe we should start with that before we actually get into the discussion of the questions.

DR. LANGSTON: I think one issue that has come up repetitively is that it appears that industry is being asked to do pathogen load studies on therapeutic drugs, as opposed to just sub-therapeutic, which the 558.15 were designed or were supposed to address.

So my question to you, is this committee

supposed to address pathogen load issues for both sub-therapeutic and therapeutic?

DR. SUNDLOF: Okay. Well, the focus of this obviously is therapeutic drugs. We have required by regulation that sub-therapeutic antimicrobial drugs that are fed for a period of 14 days or longer, should undergo these studies, these pathogen load studies, as indicated in Section 558.15, as well as the bacterial resistance studies.

I think though some of the questions that we are going to ask is -- the way that the questions are asked is that it leaves a lot of latitude for the committee to respond on all aspects. But what we are primarily concerned about right now is the issue of whether or not these studies should be required for therapeutic drugs.

And let me provide you with a little bit of background as to why we are having this meeting in the first place, and as it relates to the issue of us requiring certain therapeutic drug submissions to submit 558.15 type studies.

Let me just say, first of all, we have not required any companies to submit the pathogen load studies for therapeutic drugs, but there are two submissions. And I am not allowed to say what those

are, same drug, two different species, for which we have gone back to the sponsor and said to them, we do not know where we are going to come out on pathogen load at this particular time.

If you want to wait until we make our decision, fine. But if you are concerned that it will hold up your time to market, then we would suggest that you have the option of conducting studies that are in very much similar to the pathogen load studies under 558.15.

We have not gone back and thought through the entire, how would this be different from therapeutic drugs? And so, why are we having this meeting?

And you recognize that we did have the preapproval study meeting back in 2000, which we tried to address this issue. And we did get a lot of good information out of that.

But when it came to the point where we were actually faced with an application, there was some concern that we had not come to final closure on whether or not pathogen load studies should be required for therapeutic antibiotics.

And, in discussing that internally within CVM, there were some honest differences of opinion on that. We could not reach resolution. And so, one of the

reasons that we are holding this, probably the primary reason that we are holding this meeting, is to get an outside perspective, to help guide CVM in making that final deliberation.

And so, the decisions that you make, and the advice that you give us today will be very important in our ability to move forward and resolve this issue once and for all.

DR. HASCHEK-HOCK: One question that came recently to mind is, are similar studies required by the European Union or through the CODEX on therapeutic and/or sub-therapeutic drugs?

DR. SUNDLOF: No.

DR. WOOD: The definition of CVM, of what a therapeutic drug is, and what a non-therapeutic drug is, is based on 14 days. Does that mean then that -- where is the use of drugs for "disease prevention" fall?

I mean, some would view that as a therapeutic use. But in your definition it does not fall in that category or does it?

DR. SUNDLOF: I would have to ask somebody for the exact definition, but I think there are some. If it is used for more than 14 days, and I think there may be some disease prevention claims in there, that might fall under that rubric, I do not know for sure. Maybe

somebody from CVM can answer that question as to exactly what is encompassed by 558.15. I know there is a 14 day thing, but --

DR. WOOD: Well, conceivably, then when we are talking about therapeutic drugs, we are talking about a much larger use than simply a very limited use of that antibiotic?

DR. SUNDLOF: That is entirely possible. I think it was mentioned earlier by Dr. Carnevale that there has only been one drug which has a 21 day dosage regimen. And, in that case, we consider that to be a therapeutic drug, and did not require 558.15 studies.

DR. WOOD: Okay.

DR. SUNDLOF: But, to my knowledge, that is the only one of those that would go beyond the 14 days period.

DR. WOOD: Can I ask one more question?

The intent with the framework document overall, once all of the pieces are put together, is that going to be put forward as a guidance document, or is it going to be put forward as a pending rule? What is the procedure on the framework document once it is at the final stage?

DR. SUNDLOF: We expect there to be notice and comment rulemaking. Okay. Let me just also say that

guidance document 78 says that we would consider these studies, these pathogen load studies in our review. But it did not say that we would absolutely require pathogen load studies for a therapeutic drug. So, I think that distinction needs to be made.

DR. GLENN: I want to ask another question. First of all, I want to reiterate that you are saying our primary focus in the last two days is whether studies should be required on therapeutic use. I think I got that.

However, does that mean we cannot comment on the current use of these studies for sub-therapeutic use?

So I think I am talking about these 558.15. You want no comment on that?

DR. SUNDLOF: I would leave it up to the committee to advise us on that. I think that is very much open. The issue that we have before is, is one where we, as has been expressed before, we are not able to make decisions on therapeutic antibiotic drugs that we have under review.

And so, that is the most immediate concern for us. But we would certainly appreciate if the committee wishes to discuss sub-therapeutic drugs or other uses of drugs as well. I mean, that is --

DR. GLENN: Because we do spend a lot of time on that.

DR. SUNDLOF: Well, that is where all of the data are.

DR. LANGSTON: And, just for clarification, Richard, I think the majority of the drugs I am aware of that are for disease prevention are technically classified as sub-therapeutic.

For example, in the southeast, there is no really good vaccine for anaplasmosis, so beef cattle are placed on tetracycline throughout the insect season, which is substantial in the southeast. And that is fed chronically for that.

So I would presume that is considered a sub-therapeutic use by FDA definition. Yet, it is strictly a disease prevention issue. There are no growth promotion aspects of it in adult beef cattle that I am aware of.

DR. WOOD: Well, the reason for the question is I have seen, and perhaps we all have, you know, some categorization of antibiotics, and they have not been simply in terms of growth promotion or therapeutic. But they have growth promotion, disease prevention therapeutic, and that disease prevention category becomes rather large.

And so, I was wondering what was before us then as we were talking about therapeutic drugs?

DR. LANGSTON: My interpretation would be that these prevention mostly would be considered sub-therapeutic. If anyone wants to disagree with me or clarify that, I would certainly welcome that.

(No response)

DR. SUNDLOF: All right. Then I will read the questions. I think everybody can read the questions, but we will ask the questions of the committee. And I think you have a flowchart in your package that will help you navigate through these.

The first question is: What is the contribution as it relates to public health of antimicrobial drugs to pathogen shedding and contamination of carcasses in the overall scheme of the current animal production practices?

DR. LANGSTON: Let me put forward to the committee how we might proceed with this.

Rather than taking it a question at a time, as we did in the import tolerance issue, these seem so interrelated, and whether you move to the next question, depends on how you answer the first question, I am going to propose that we allow each member to comment on the whole range of questions at once, and then move to the

next person, who will comment on all of the questions, move to the next person, on all of the questions.

Is that acceptable to the committee?

(Nodding of heads)

DR. PARKHURST: Could we possibly handle the first two questions separately, and then proceed to your organization?

DR. LANGSTON: That would be fine with me. So, Steve, if perhaps you could go through all of the questions at this point, and then there are a couple of issues as to how to link through that flowchart on the questions I have. But if you would go through all of them at present that would be helpful.

DR. SUNDLOF: Okay. All right. The first one I have already read. It is, basically, "Of all of the things that can result in changes in pathogen numbers in animals, how important is antimicrobial use?" I think is the first one.

The second one is: Which antimicrobial drug use conditions in food animals, if any, are more or less likely to affect pathogen carriage and shedding?

The third question is: Do the committee members think that the potential for antimicrobial drug use to affect pathogen load is sufficient to warrant evaluation as part of the drug approval process?

And, if not, why not?

And if the answer is no, then I think that is the end.

If the answer is yes, then we move on to question number four which is: If the committee members think that antimicrobial drug effects on pathogen load are sufficient to warrant the evaluation, should specific prospective pathogen load studies be designed and interpreted to address the following concerns?

If, yes, what might that approach for conducting such prospective studies be?

And if, no, what other approaches should be considered to address these issues? Mr. Chairman.

DR. LANGSTON: And, just one point of clarification relative to that versus the flow chart, you mentioned if you stop at question 3, if you answer no, then that would be the end of it. Yet, question 4 says, "If, no, what other approaches should be considered?"

So what is the difference in --

DR. SUNDLOF: My sense, as i read it, and maybe the people that wrote this will be able to shed some light on it, but it looks as though the number four says that if we think the effects on pathogen load are sufficient to warrant evaluation, which is the yes to

question 3, then address the two questions under number four.

Have I interpreted that correctly?

(Nodding of heads)

DR. SUNDLOF: Yes, okay. So the interpretation -- I just got nods from the back of the room. If you answer the question, number three, to the negative that you do not believe that it is warranted, you stop there, and do not proceed on to question 4.

DR. LANGSTON: Along those same lines in the flowchart, question 1, of course, is a core question. I can see if you answer yes to question 1, or have concerns that you would move on, if your answer to question 1 is no, why do you move on to question 2?

DR. SUNDLOF: Yes, well, that is a valid question.

I think because, first of all, question 1 is, what is the relative importance of antimicrobial resistance to the overall issue of pathogen shedding in animals?

And if you say it is small or it is big, I think that will help you in answering at least question number 3, which is based on what you consider to be the overall effect of antimicrobial use on increasing pathogen load.

Is that sufficient to warrant the kinds of studies that we are talking about with pathogen load? Is that helpful?

DR. LANGSTON: Any questions from the committee relative to the issues before us?

We will have a discussion in just a minute as to therapeutic and sub-therapeutic. But, in terms of the flow of how things will occur, any questions on that?

DR. HOLLAND: I just have a point of clarification for question 1. If we address pathogen shedding or pathogen load, carcass contamination could be affected by factors other than this in the slaughter house. How do we take a look at that perspective relative to question 1?

DR. SUNDLOF: I think the question 1 is asking, of all of the things including fecal contamination, including stress, including what happens in lairage, including what happens on the farm in terms of HACCP, and including what time of year it is, and the whole -- you know, out of all of those different things that can possibly have an impact on pathogen load, what is the relative contribution of the use of antimicrobials in that? Is it big, small, somewhere in between?

DR. WOOD: And this has to do with the definition of terms I guess. In some places, the term pathogen shedding is used; in other places, pathogen load is used. Pathogen load I would take to mean, you know, that which may be in the gut, and has not been excreted, and perhaps even in some tissue.

Pathogen shedding is what has been excreted and is counted. Are we to consider both as one? I mean, from what we heard yesterday in some of the presentations, there are some real differences if we are to consider pathogen load or pathogen shedding.

DR. SUNDLOF: I think when this was written, pathogen load and pathogen shedding, carriage and shedding, pathogen load includes carriage and shedding. That is in a combination. And so, those two words together in our definition I believe is what we call pathogen load.

DR. WOOD: The second thing on public health, that concept is coming from a consumer group, you know, food safety is a part of a public health concern, but public health also considers other things like, you know, the health of workers, environmental concerns, and all of that.

So this question number 1 is really dealing with even a broader area of concern than only food

safety. Is that correct?

DR. SUNDLOF: That is correct, but that is an issue that is separate. We generally handle user safety differently from human food safety. So if there are user safety concerns, generally, those are handled differently through proper labeling and that kind of issue.

So we are not asking the committee to look at user safety issues at this time. You may come back later and ask the committee. But, at this time, we are not asking for that information.

DR. LANGSTON: Any other procedural questions to Dr. Sundlof, definitions, et cetera?

(No response)

DR. LANGSTON: Okay. Hearing none, in that case, we will move into committee deliberations.

What I would like to do first is to address whether the committee wants to take up the issues of both therapeutic, which the FDA is asking us to look at, in addition to sub-therapeutic.

After that, I will ask if you have any additional questions of speakers for clarification of points, and then we will actually begin our discussions.

So we are being asked to look at pathogen load issues relative to therapeutic drug approvals. Do you

want to also address the issue of the historic -- the implemented 558.15 sub-therapeutic use?

DR. GLENN: Yes.

DR. ANDERSON: Yes.

DR. HASCHEK-HOCK: Yes.

DR. WADDELL: Yes.

DR. WAGES: Yes.

DR. CARSON: Yes.

DR. GLENN: Yes.

DR. WOOD: Yes.

DR. MACDONALD: Yes.

DR. LANGSTON: It is unanimous that we do want to address both therapeutic and sub-therapeutic use relative to pathogen load issues and the preapproval process.

So, in that case, do you have questions for any of the speakers, audience members, FDA?

DR. HASCHEK-HOCK: Is Dr. Gilbert here now?

(No response)

DR. HASCHEK-HOCK: No, okay. I am paraphrasing a question that Dr. MacDonald asked, or Dr. Wood asked -- Dr. Wood asked regarding in the studies that have been submitted to FDA, was there any evidence that a class of antibiotics affected pathogen -- that any class of antibiotics affected pathogen load more

than others?

I think that was the question that was asked.

DR. GILBERT: Again, without having that sort of comparison, I cannot tell you. I have not ranked them as far as that information goes. I guess that is something we could take a look a look at. But, to the best of my knowledge, I know I have not, and I do not think anybody else ranked them as far as one being worse than the other.

DR. ANDERSON: I had a question for I guess Dr. Sundlof or Dr. Robinson.

Can you explain why you do not require the sponsors to tell you what -- or maybe you do -- but what drug class the drug is?

Because I would think that would be very important to determine if it is an analogue or a class used in human medicine.

DR. SUNDLOF: Oh, absolutely. We require them to tell us exquisitely what that compound is, you know, down to the salt. We want to know about various, you know, isomers, and it is very specific.

I think in the information that Dr. Gilbert presented, certain antibiotics just did not fall into a general class like tetracyclines, or aminoglycosides, or sulfonamides. And so, they got caught up in this kind

of general group. But we know exactly, the exact identity of that particular drug was known.

So, is that correct, Jeff? Do you want to talk to that?

DR. GILBERT: Yes, Dr. Sundlof is exactly. I mean, we know what the gram spectrum is, and we know this chemical structure, and a lot of that other stuff going on. The ones that were in the unclassified gram positive, like he said, may have fallen into a category or a name, and not been adopted yet, or was to standard. It did not just fit in with the other ones.

DR. ANDERSON: Okay, great. And my second question is, if the two criteria that you are using to determine if a new drug is safe is the prevalence, and the duration, and the shedding of the drug, but also the resistant characteristics of the drug, if, for instance -- and I realize there is some question about how useful these preapproval studies are in pathogen shedding for even looking at resistance.

But prior to the framework document being put in place -- and I think the framework document will do an excellent job of addressing resistance by looking at post-approval and mitigation following that if there is a problem -- if, for instance, you did not do pathogen shedding or pathogen load, would FDA be doing anything

to look at resistance prior to approving a drug?

Is there any other way that FDA looks at resistance prior to approving a drug?

DR. SUNDLOF: Yes, in fact, we are putting a great deal of effort on that, in terms of trying to write guidance that will pretty much look at what we have said in the framework document and apply those to things like preapproval studies.

We will be coming out with a document, which we hope will come out in June, which will be a document that will lay out all of the preapproval studies that relate to both pathogen load, if we continue to be interested in that, and all of the resistance studies that may be appropriate. And we intend to have an open meeting as early as July to address that issue separately.

So, no, we have not abandoned preapproval studies for resistance. The pathogen load studies do not really address that issue. We do not think they specifically address that issue. That is why we have pathogen load as a separate issue, in separate studies, and the antimicrobial preapproval resistance studies will be designed probably very much differently than a pathogen load study.

DR. LANGSTON: Other questions? Okay.

DR. PARKHURST: There is a concept I do not understand is there is preapproval and post-approval?

DR. SUNDLOF: Right, right. Preapproval studies are required before we grant approval for a particular drug. the pathogen load studies would all be required before we would make the determination as to whether or not we considered the drug to be approvable.

Post-approval studies are studies that could take place after the drug is approved. For instance, if we are concerned about resistance development, one of the things that we want to do is after the drug -- if we decide that the drug is approvable, after we approve the drug, we want to be monitoring for the emergence of resistance in pathogens of concern.

That would be a continuous, ongoing process of looking at the resistance development, and we do this through our NARMS program, National Antimicrobial Resistance Monitoring System, in conjunction with CDC and FSIS.

So we have a continuous monitoring program once -- so that once the drug is approved, we can find out if things are occurring that we had not anticipated through our preapproval studies.

I think it is no secret that one of the things that we are not very good at, at this point, from a

scientific perspective, is being able to predict resistance -- where resistance where develop, in which species of bacteria, to what extent, how fast it will develop.

It is something that is scientifically too challenging to be able to predict that in advance. So we need post-approval, monitoring, and surveillance systems in place, in order to make sure that those drugs continue to be used in a manner that is safe for public health.

DR. HOLLAND: Dr. Sundlof, I apologize for putting you on the spot. But would you give me briefly your philosophy of pathogen load?

DR. SUNDLOF: Well, obviously, we have required it on these studies for years. I think this has been a great exercise and opportunity to kind of look back at the whole issue of pathogen load, and kind of take stock of where we are and what we have learned in the past.

I have gotten just about as much out of this as I think anybody has. And what we really want to know -- so I am being evasive, Bob -- but what we really want to know, you know, you have heard everything that we have heard.

We have gone through a great deal of effort

and expense in order to, first of all, put together a comprehensive -- what we consider to be a comprehensive review of the literature looking back at our old studies, bringing in all of the experts and the people who have worked in this area in the past, and just kind of look at the whole big picture.

And the reason that we wanted to have this committee look at it is so that we can -- everybody gets the same view of the situation. And I do not want to prejudice any of the committee's decisions by giving you my personal point of view, or the view of the Center, because the Center does not have a single view.

We are hoping that through this process, we will be able to reach some kind of consensus within the Center. So I am throwing it back on you.

DR. HOLLAND: Thank you.

DR. WOOD: I have some questions. And I am not sure exactly where to direct this, if it is to you, or to perhaps one of the presenters this morning about withdrawal times.

Because it seems like that is perhaps where some questions were raised about the relationship of when pathogen load studies should take place in the continuum of the life of the animal, in the therapeutic or non-therapeutic, in particular, we are talking about

therapeutic uses here.

Withdrawal times are developed based on residues, is that correct?

DR. SUNDLOF: That is correct.

DR. WOOD: All right. And are there cases where a -- I guess in non-therapeutic uses, there are no withdrawal times prescribed, is that right? Are there withdrawal times? There are withdrawal times applied for every antibiotic, is that correct?

DR. SUNDLOF: There are some antibiotics for which there is a zero withdrawal time, and that is based on the elimination characteristics of the drug. So, in other words, there are no residues of concern for some drugs that are excreted or metabolized extremely rapidly.

But, regardless of whether it is therapeutic or sub-therapeutic, there are withdrawal times for sub-therapeutic or non-therapeutic antibiotics, as well as the therapeutic ones.

DR. WOOD: Okay. What about the cases where the life of the animal may be very short -- like my favorite place to eat chicken, I think those broilers grow out to about five weeks or so. I mean, how is the withdrawal time related to therapeutic or non-therapeutic uses with broilers with a very short life

growing time?

DR. SUNDLOF: Well, they have to be removed from any medications for a specified period, the withdrawal period, such that those residues, any residues that might remain would be at such a low level that they would not pose a threat to public health.

So, even with chickens that are five, or six, or seven weeks old, they have to observe withdrawal times just like all of the other animals. And there are some drugs that you just cannot use in poultry because of that, that their lifetime is shorter than the withdrawal time. And so, therefore, we do not approve drugs for those.

DR. LANGSTON: Any other questions?

(No response)

DR. LANGSTON: Thank you.

Committee Deliberations

by Dr. Cory Langston, Moderator

DR. LANGSTON: At this point, we will move into committee discussions then. Again, this will address both therapeutic and sub-therapeutic use. I think the issues do overlap substantially.

But, in essence, the issues are, is there evidence to suggest that antibiotic usage influences pathogen load?