

Is there enough evidence to draw a conclusion of that as to a positive benefit, a negative benefit, or no effect, based on the type of studies employed?

So, and certainly you are free to discuss other issues as well. So I will open the floor at this particular point relative to discussions on pathogen load issues and trials.

DR. KOCHEVAR: So, Cory, are we going to just go around like we did on these other questions? Is this how the format of this is going to work?

DR. LANGSTON: I was hoping that perhaps members that had questions would pose them. Now, when we actually come to making our opinion known, we will go around.

(No response)

DR. LANGSTON: Okay. I will just throw out an opinion. Again, this is our chance to deliberate so that we have listened to the information, and we are trying to synthesize that, and we probably each have our views of this is worthwhile, this is not worthwhile, this is junk. And this is your chance to influence the other members of this committee, or get your opinion changed.

So, for example, I have some significant reservations about many of the trials relative to the

fact that they are not looking at withdrawal times, taking into account what the pathogen load will be at the time that the animal is actually slaughtered. It is a worse case scenario. I understand that.

I also have significant concerns relative to the limitations of the assay methodology. We heard that it is quite dependent on the number of grams of feces, the enrichment processes, and can you really quantitate it to the point that the trial design can reliably detect those differences.

So I have significant concerns about whether the trial designs we have, which is the only thing we have at present, are accomplishing what we want it to.

Also, relative to what we do have, kind of my interpretation of things has been that if the antibiotic has a susceptibility profile such that the pathogens could be susceptible, if they are in fact susceptible to pathogen load decreases, which is good from a public health standpoint.

If, on the other hand, the organisms are resistant to that, or become resistant, the pathogen load increases. I think what has been surprising to me is the issue of when the drug has a different susceptibility profile, in other words, it has a gram positive or anaerobic profile, instead of the gram

negative profile associated with salmonella in our usual food borne pathogens.

The usual dogma has been that you are altering the flora of the GI tract such that selection pressure comes into play and you do not have the competitive inhibition, so the pathogen would reproduce and cause problems.

I say surprised in that, from what I have seen presented, I do not see a consistent trend in that regard. There are studies that have reported that granted, but there are also studies that showed it a wash or a decrease. So I cannot say that there is a consistent trend to support that dogma.

So I had some very significant concerns as to whether or not antibiotic uses significantly affects pathogen load. So those were the sorts of discussions I would like to encourage.

DR. WAGES: I will go next I guess with my feelings on the issue. You know, if you look at the information that has been presented to us, and that includes the Exponent literature review, which may not be as complete as we would like to have saw it.

But, basically, that resulted in basically a wash, if you will. I mean, there was I guess avoparcin might have had some positive effects, but anything -- at

least using the United States -- was either a wash or no effect.

That literature search also included therapeutic concentrations. And I think one study I even read going through the whole documented eight or nine days of therapy which would be a therapeutic, and again no affect on pathogen load.

I find over the past day that there has been no information presented to this committee that I can interpret that would be positive that would show that pathogen load studies would be an appropriate measure to be involved in the approval process for new animal drug for therapeutic reasons.

If you look at the sub-therapeutic I think -- even though I think they have served the purpose, which they have been intended to, you can call into question whether the sub-therapeutic use of antimicrobials has any effect on, at least, specifically, salmonella shedding. And, in fact, some of the data, if you actually look at the individual, you know, some of them had protective effects.

If we look at the Canadian experience and what was presented from both epidemiological studies, I will quote that most studies there was found to be no evidence of a pathogen load effect, coupled by looking

at international harmonization, Canada does not impose that. And, of course, an opinion said they would not suggest that, but that is an opinion.

But if you look at the European commonwealth, a very conservative country, a conglomerate, if you will, with respect to the use of antimicrobials to the point of withdrawing many growth promotants from the market, in a conservative area like that, or at least a mindset from a government standpoint, they do not require a preapproval pathogen load.

We were given the February 2000 Powerpoint presentations. And I do not know if you can call that a consensus because being on that, a moderator, we were told to give as much information as we could, and then from all of the discussions.

But if you look at the back part, and even individual Powerpoint presentations, there was considerable information and statements made that, not only preapproval studies predicting antimicrobial resistance were problematic, but pathogen load studies should not be involved in the approval process.

So, and then we really did not get a very good concrete data presented of looking at carcass contamination in pathogen load, as it even has the potential to affect human health. And I think this is

the bottom line.

If we look at carcass contamination, and from the first question, it boils down to HACCP and those types of practices not altering antimicrobial use that effects -- at least I know that in poultry, but it appears that, according to USDA, the same thing occurs in other species.

So I guess I just did not see any information presented to me, as I evaluated it, that had any semblance of supporting a pathogen load for an approval of the therapeutic drug, and, if anything, questioned whether the sub-therapeutic regimen for pathogen load is appropriate.

DR. HASCHEK-HOCK: I agree with all of the comments that have been made so far. But I would like to also add in the deliberation that if we are talking about public health, the carcass contamination is really what we are most concerned about.

And, as pointed out by a number of speakers, there are so many other stresses and procedures that go on between the farm situation and the slaughter house, which have major effects on the pathogen contamination that they really overshadow the effects of antimicrobials which are, if it is therapeutic, they are usually used in young animals.

If they are sub-therapeutic, we have seen the pathogen load increases transiently, and then goes back to low levels. And also, the withdrawal time is another factor that is included there as well.

So it seems that none of those factors are taken into consideration when the studies are done, and therefore the relevance and predictability of pathogen load to the public health issue is very low.

DR. KOCHEVAR: I think in the phrasing of the first question where it predicates everything on "as it relates to public health," if you look at that, and you look at the things we have seen -- and I am agreeing with the two previous speakers here, we basically were not presented with any evidence that even addressed that issue.

The hypothesis that as pathogen load increases, incidents or risks of food borne disease also increases seems intuitive. But, in fact, we do not have any information that addressed that. And so, it is very hard to consider this in light of that.

Totally independent of that question, you know, I would agree with previous speakers that we did not see information based on all of the experts that we listened to that suggests that the design and conduct of these pathogen shedding studies is anything but

problematic, and that there is many, many confounding issues associated with them.

Even as you ignore all of the confounding issues, there were still no data that was compelling, that there was a correlation between antimicrobial use and increased shedding. So, it is sort of a series of negatives for me anyway.

DR. GLENN: I would also like to concur with my colleagues here. I think we are all in the same message. But we certainly all agree that human health here is paramount. We would like to reduce the incidence of food borne illness. And we know that when we are using antimicrobials, even at sub-therapeutic levels, that we are effecting this development of resistance in microbes.

But what we are trying to determine on the human health issue is, what is this, a dotted line? Or what is the relationship between pathogen load and human health? And the way I kind of look at it is, is pathogen load a critical control point?

I think our last speaker yesterday mentioned we are really using a HACCP approach. Is it a critical point? And so, I agree with what Dennis said and everyone. The data that we have been presented -- first of all, I started with the data in the guidance 78 and

the framework.

As someone publicly commenting today, we had two, an FSIS and USDA cited literature for the guidance, which I understand has been updated. And so, those were dated '96, and '92 to '96, but just two; and then the framework document includes a 1977 and a 1969 citation.

So, in the last two days, we have been presented I think probably the world's literatures as best we could compile it. So I appreciate that, and want to make note of that.

And, in doing that, however, regarding therapeutic use, we really saw almost no data. Except for the Exponent studies that were these extremely high levels in the feed, I do not remember a curve on some therapeutic use. So there is nothing there to evaluate.

And then, on sub-therapeutic use, the data were variable and did not support a relationship between this use and the feed, and pathogen load. So, in the portfolio of what is affecting microbes on meat and poultry, I do not see that pathogen load is important relative to either therapeutic or sub-therapeutic at this point and time.

DR. WOOD: Before we get a steamroller going here, I sat on this group as -- we all of course are consumers. We are all concerned about public health,

but that is my particular role here.

And so, I want to really heighten the concern for public health and the expectations that I carry with me coming to this committee from my own organization and from other consumer organizations that, as the FDA, CVM addresses antimicrobial issues, that the concern for public health is fully addressed from every aspect, and that no stone is left unturned.

My organization over the years -- I mean, I cut my teeth working on HACCP, which was back in '95, I guess, from my first meeting sitting at the USDA around the table, looking at many of you across the table.

And, prior to that, the question of pathogen load and shedding, as a result of all different kinds of factors on farm, has been a very primary concern for many of us, as we have addressed public health issues. And, certainly, we have seen that reflected in what was presented yesterday from the USDA in the HACCP plans that were there.

Having said that, I, too, have been frustrated by the lack of hard data that we have been provided at every turn. Apparently, this is so new that much of the data is not there yet.

We have the E.coli 0157:H7 study that is still not public to provide the documentation that we are

looking for, in terms of the numbers of people made ill by carcass contamination related to what comes in on that carcass in the front door of the slaughter house.

We do have, though it is not new, because we have also learned with the 558.15 studies, that, you know, from the 1970's there have been studies on this. And I have been, in learning this, wondering why there has not been more intensive study, and why the literature is not a fuller plate for us to review.

But, all that aside, we have not been presented with sufficient data to make a complete decision, I do not believe. That I guess is, in part, answer to number one.

But I guess, just so that I am clear where that leads me, the assumption that follows is not then that we do nothing. I think we need to gather the data, so that a decision can be made, as opposed to not make a decision because there is no data.

And, perhaps, that is a mandate that we may want to ask CVM to accomplish by contract or by doing it themselves of constructing a study that will identify the information that needs to put in place to fully determine whether or not and when pathogen load studies need to be put in place.

Also, so you will know where I am coming from,

if we do not have the data, because of the expectations of the public regarding what CVM and how FDA should be responding, I do think there needs to be some form of a response at this point until we have a whole package together.

I think to throw out, or to not include one part of a very complex condition without having the whole package to look at and to address is a very dangerous situation to be in.

DR. KOCHVAR: I would agree. We would all agree that antimicrobial resistance is a critical issue, and everyone is concerned about it, and that is really why we are here.

I guess I am very concerned though that the resources that are being brought to the table to address this problem be directed to the things that are likely to yield the most information, and you mentioned one of them, that in the front door or out the back door of the slaughter plant.

And, Alicia, you made this remark and it is, I know, not part of our purview today. But the other studies that address resistance in those microbes, you know, seems to be such a critical feature of what FDA is putting their resources into that, like you, I think all efforts need to be continue and be supplemented, but

they need to be directed in a useful way to those things that seem like they really are going to yield revealing information.

DR. LANGSTON: Along those same lines, I did note that it appears on really almost just one study that if the organism is resistant the pathogen load would increase. That is not proven. There is not enough study to say that. But even if I do believe that, I do not know that a pathogen load study accomplishes anything.

My view is that the emphasis there has to be on detecting resistance when it develops for those organisms, and intervening at that point. So, to echo those comments that have been made, I think the resources need to go toward resistance monitoring and to ability organisms in that drug spectrum to develop resistance, and much less so toward pathogen load.

DR. GLENN: Now, Richard, I wanted to comment regarding your assessment that we cannot make a decision today. I think one of the beauties of science is that we have the resources of all of the scientific community in front of us at this given point and time, but this is a moving dynamic. Science is a moving dynamic, so a decision could be made relative to today's science.

But I think everyone here would agree that the

concept of continuance and trying to determine what is the most appropriate way to view this particular point, whether it is a critical control point, maybe we learned that it is, but maybe it is not. But I think that does need to continue. So, I just would like to support that a decision could likely be addressed.

The other thing I wanted to mention was that one of the things I found frustrating in hearing about the entire food safety system here was that CVM, we have had this emphasis on pathogen load since the '70s, and this task force, and studies were initiated.

And then, in '92 to '96, we have had a final rule on HACCP, and we have begun to quantitate, as best we can, through monitoring of pathogen reduction. And it seems to me that post-approval that additional monitoring to NARMS could be included.

If a pathogen load over here from this agency is important -- again, I am questioning is it at a critical control point. But if it is, why aren't we assessing pathogen load shedding, or concentration in feces, or some aspect of that, even in animals that are delivered to slaughter plants?

I mean, is that not doable? And why haven't we been doing that?

So, it seems like we have CVM concentrating

here on pathogen. And it seems like, in an absence, we have initiated slaughter plant control which is great. But if we think there is a link, why haven't we filled the void with some method to monitor that? You know, I would love to see that data I guess is what I am saying.

DR. WOOD: Can I just clarify? I am expecting us to act. And, although, what we act on we may disagree about.

DR. MACDONALD: You know, as a chemist, this has been a very enlightening discussion. And, basically, what I would like to just ask about, or comment on, is that what I do is I determine what happens to a drug in an animal. And I do that in a fashion that will totally predict what will happen, what metabolism occurs, what are the elimination conditions.

And from that we can totally predict for the future use of that drug what will happen in actual practice, and we do this to a very, very high standard, 100 percent accountability, two to three significant figures on everything.

I have sat in meetings and defended why a one part per trillion assay is only plus or minus 15 percent, which is the world that I live in. But the preapproval studies that are used are totally predictive of what that compound will do in actual practice, and

from that decisions are made on marker compounds, withdrawal times, et cetera.

I think the thing that, after listening to all of the real life conditions that go into this process of pathogen load or salmonella shedding, is the question that I have to ask is, have all of the studies that we have done in the past, all of these 558.15 studies, did you learn anything about what is going to happen in actual practice?

Because, you know, the number of factors that confound here are just enormous. And my feeling is, as an experimental scientist, when you do a study, what do you learn from it, and where can that data be taken?

And I do not know at this point whether I can say that from those 558.15 studies, yes or no, you could predict anything concerning the real life application.

DR. GLENN: Clearly, limitations in those 558.15's are -- I mean, we are using SPF animals. We are doing challenge studies at doses which some of the animals die from. The assay for the quantitation concern that Cory mentioned earlier, there is a lot of limitations, big, big questions.

DR. LANGSTON: Any additional comments?  
Alicia.

DR. ANDERSON: Yes, I would just agree that I

think the data presented here has not been particularly convincing that that pathogen load studies are necessary, but I also do not think we have got enough evidence to say that they should just be thrown out, or that they are an unnecessary part of the preapproval process.

I do think that the framework document, which very clearly outlines how preapproval and post-approval testing should be conducted, it is probably going to be the best way to approach these kinds of things.

And also, supporting what you said, Cory, about directing the efforts of FDA towards antibiotic resistance testing instead of pathogen load testing, Europe does not require pathogen load testing, that is true. But they already have these mitigation plans in place, which we do not have in place yet.

The framework document is not in place yet. So, I think if we would say, well, we do not think the pathogen load is necessary, then what are we going to replace it with?

I think if we do not have the framework document in place yet, it should not be thrown out until we have something to replace it with that would be useful.

The other thing that I was a little concerned

about is I noticed that when you looked at the table of the drug studies of the 558.15, they were almost exclusively gram positive except for two broad spectrum drugs, one of which failed, and one of which passed.

And, certainly, it has been shown in humans which are given gram negative drugs with salmonella, they will invariably shed salmonella. They will become carriers, at least in some people that are given almost any gram negative drug.

So my concern would be, well, if we say it is not necessary, well, then what if other broad spectrum drugs are then developed, and then they are not -- you know, they are not required to do pathogen shedding?

Well, then, you know, I think that pathogen salmonella shedding would occur if they were using broad spectrum drugs, or drugs with a gram negative spectrum. But it is just that those drugs have not been even -- they have not even been put up for testing because I think they would invariably fail.

Although, tylosin did get passed, we have not seen really any that I can think of in the past few years that passed, or have even been put up to be tested. So I would just be concerned also to think that there may be new drugs that may be passed, may be put up to be tested that would be more likely to cause shedding

in the future.

DR. HASCHEK-HOCK: In relation to those comments, the current preapproval studies required, I think we all agree, are not predictive. And there are many other confounding factors that affect pathogen load. It seems to me, as pointed out, that we have many gaps in our scientific knowledge about those issues.

I think those need to be addressed. I believe that research funding needs to be allocated to the specific areas that are lacking, and a model that could be considered predictive be developed that could be utilized instead of these studies. But I do not see any reasons to continue studies that do not give us information that is useful.

It would seem perhaps that a directive be made that additional research be done and a predictive model developed, and then an evaluation would be made at that time whether and/or how to incorporate that into preapproval studies.

DR. WAGES: Alicia, just on one of your comments, based on the literature survey that Exponent gave us, there was neomycin, streptomycin, and oxytetracycline, and cortetracycline involved in some of those that still had either no effect or protective effects on salmonella shedding.

DR. ANDERSON: Right, yes, I agree that there have been a few. But if you look at the studies that have been, I think, since the requirement for FDA to do the pathogen shedding load, I think overwhelmingly they have been gram positive.

DR. WAGES: Yes, I would agree. And from our standpoint in the poultry industry, our greatest concern is clustered in --- and necrotic enteritis.

So, our push for, you know, back in the '70s, when cox CD stats and proline was no longer the issue, and the ionophores came on the market the push was for, at least in our standpoint, to control the gram positive necrotic enteritis to supplement the cox CD control or lack of, because it still causes coxitis. So that is probably a big factor.

DR. GLENN: I wanted to address what Alicia mentioned. What else would be useful if this is not? And I think that is a real good question. And from what we have heard the last two days, it is fairly difficult to answer.

But one of the things that I just think about is that under the conditions of use of -- as per label of the antimicrobial, that is normal animal fed these, as per on farm use. It seems that that gets about as close as you want to get to what actually is going on in

the gut and defecated by the animal.

So, in my simple mind, that is the kind of data that I want. So, in the studies we saw, I was trying to pull out, you know, the treatment, which was that one that was related, and still there are not enough data, and it is not definitive that we have a relationship, even to those conditions of use, where the animal is healthy, and so forth.

In addition, the new animal drug applications study so many aspects of that animal. The animal is healthy. I guess there is toxicology work, and a whole package of information, so very well researched and studied.

So I am not sure that knowing a little bit more about the gut microbiology is even necessary at this point in my mind, but might be the most useful.

DR. WOOD: Could I just pursue what you were offering as a predictive study? I mean, would that be something that might be developed by the center, or they are in contract that would be then -- I mean, how would that be used?

I mean, I really find that intriguing and was thinking in those lines as well, but was not sure how to develop that.

DR. HASCHEK-HOCK: Well, I think, first of

all, there is a need to develop the specific questions that would need to be addressed through research to develop data before you could actually determine how a predictive model could be developed.

But who would develop that? I guess it probably would need to be under the auspices of CVM. Some of the initial research data could also be through National Research Initiatives Competitive Grants Program. There have been allocations made to certain areas in the past, and perhaps this might be one that could be included in subsequent calls for proposals.

DR. LANGSTON: You know, my view is that the hypothesis behind it, that antibiotic usage would increase pathogen load or could, is a legitimate one. If I had been on that '70s workshop, I would have recommended these studies.

But, again, based on what we have seen here, either we cannot make a determination, or the preponderance to me indicates that it is not an issue. And I do not know that -- well, let me say. I, too, would encourage the development of a model that is truly predictive.

But I do not know that it is worthwhile continuing the existing ones, as Wanda said, when they are not really giving us the information that we want,

and nor do I feel like we should be withholding or slowing the drug approval process while we are waiting on this evaluation model, or this new model to be developed.

So, I agree, we need more data. We need a better model. I would encourage that to be done. But I do not feel like right now we have information that supports the continued use of what we have.

DR. PARKHURST: To follow along those lines, I have agreed with just about everybody that we just really do not have enough evidence. We do not really know what is going on. Science is a dynamic process. We keep moving along, and people are feeling the need to have these drugs available.

It is kind of a feeling that in the past -- we are not showing that any detrimental effects right now. There is not a big red flag up there. So the idea is, yes, we need a new model. And do we want to stop the process while a model is developed?

I do not really understand this post-approval monitoring. But would that be able to play a role in developing new data as we went along?

DR. LANGSTON: I would think so would be my response.

DR. WOOD: It could, but the problem is that

if new drugs are developed, or even current ones, those that are in the pipeline, I mean, once a drug is approved, at least as I have looked at the history of the FDA, it is very difficult for it to be withdrawn.

So, to me says you front load as much of the data gathering and decision making process as is possible, because once the approval is done, you can then have extensive post-monitoring and surveillance, which we do have.

NARMS is doing a very good job at that point, and becoming even better; and we have Food Net, and all kinds of surveillance that is going on post-approval. But that will impact, at least as I view it, mitigating strategies, but not necessarily affect the approval of that antibiotic.

DR. KOCHEVAR: Didn't we hear from Dr. Sisco though that, even in the context of studies that were designed to look at pathogen load, that you could derive some data on the incidents of resistant strains.

And, perhaps, those kinds of studies can be designed more appropriately to target that question, as opposed to just trying to count bugs, which we have heard from everybody is a very hard thing to do well.

So, I think there is potential to do useful preapproval studies coupled with very useful post-

approval studies, but I just do not think pathogen load studies are the preapproval studies that are going to be the most appropriate.

DR. GLENN: I think the model concept is good. It is one that scientist move toward in order to strengthen collectively all of the knowledge we have and predict. But we have articulated that we have a limited knowledge and we wish we had more.

And so, any model that we would develop, let's say, today, is going to be as weak as the material -- you know, as uninformative as what we have probably been presented today. So, a model development will take awhile. We are going to have to really work on that.

DR. LANGSTON: Take a long while.

DR. PARKHURST: Then, you know, then I think Richard has raised a valid concern.

Can we put a stipulation in that as science becomes more progressive, then you can open the process up again, and you would expect to open the process up as technology improved, and you were able to get better counts, say, or able to make a better analysis, a better model? Is there a way to do that?

DR. LANGSTON: I would argue that that is a desirable thing, that if you can develop a model that is fairly predictive that you would revisit the issue.

Now, grant it, from a regulatory standpoint, I think that would be very difficult, but that is not our decision. We simply should base it on science as to what is optimum in my view.

DR. WAGES: I guess I think the framework document as it is written gives the, you know, the opening of CVM to review all existing antibiotic approvals. And I do not know if in our deliberations we can ask for a clarification.

But it is my understanding that it all can be opened up when the subject of human health concern has been raised. So, you know, I think that avenue exists to open the package back up if human health concerns are raised, based on that approval.

DR. LANGSTON: And I understand both issues as to post-marketing surveillance. I think that is somewhat of a safety net for us, in that you can detect, both through NARMS and on farm surveillance, both increasing resistance and increasing pathogen load.

I understand Richard's comment that it is after the fact, after the drug is approved, and it becomes difficult to remove the drug, but is not impossible to remove the drug.

As you know, that is a current issue right now on one particular product. So there is that possibility

of removing the drug if pathogens do increase post-marketing.

DR. HOLLAND: Excuse me. But we have a question before us relating to pathogen load. While a lot of this discussion is good, and I am not saying stop the discussion, it is really not germane to pathogen load.

DR. LANGSTON: The resistance issue?

DR. HOLLAND: Yes, as it relates to pathogen load.

DR. LANGSTON: I agree. I agree. I think several of the members including, perhaps, myself, want to make the point that perhaps that is a greater issue of consideration for the FDA than the pathogen load issue, but I understand your point. Thank you.

DR. PARKHURST: Expand upon that a little bit for us that are not as alert.

DR. HOLLAND: No, I am just viewing this kind of dogmatically. We were asked to address a question dealing with pathogen load, and to me that is the issue that we should be addressing.

Resistance and other factors are other issues that may be down the road important, but it does not affect the question we have been asked of pathogen load.

DR. LANGSTON: Just be glad that I have not

brought up gamma sterilization.

DR. WOOD: But it does have an impact, in that, the way I think the discussion has developed. And I just raised this, so that we can see the connection, and that is that we are dealing with the whole here. And if we pull out one piece of that, what does that do to the rest of the package? And I think that really is a very germane question.

DR. KOCHEVAR: So, for example, if you look at the framework document, and you go through and remove all of the pathogen load studies from that, your concern is that that makes that package narrow, that system for trying to deal with the problem of antimicrobial resistance insufficient?

DR. WOOD: My concern is that none of the tools are in place yet. And, yet, we are still -- we are tinkering with that package. I would like to see that package put together and put forward in the best way possible, and then let's make some adjustments.

But, as we sat around this table, I think the table was down there two or three years ago. You know, the relationship, as guidance document 78 lays out, between pathogen load and antimicrobial resistance concerns really is a package.

I think there is some, as I view it, there is

validity for both to be a part of that package. The question before us today is how do we shape this part of that package, the pathogen load part?

And for me an option is not removing it, because we have nothing to put in its place. We have been talking about a study, but there is nothing to put in its place. I think, given the tenuousness of this process, and the concern about antimicrobial resistance that we all share, that simply removing and not moving forward in one area is a dangerous place to be.

DR. KOICHEVAR: But if we are going to do science-based discovery here, then it is very difficult to ignore what has become a rather compelling pile of evidence that the money could be spent better somewhere else.

I mean, that would be my concern is that, you know, it not only maybe not yield something good, but it takes away from an effort that might in fact yield something better.

DR. WOOD: I understand that. And the concern that I have though is that I view this as an increasing pile of non-evidence. I mean, you know, there are very minimal studies. You take a look at the Exponent review study-by-study, and one conflicts with another, and we still really do not have the data by which to make a

decision.

DR. LANGSTON: So, Richard, am I correct in saying that you view the existing studies as being useful and should be continued?

DR. WOOD: I view the existing studies as being inconclusive, not providing the information that we need.

DR. LANGSTON: When you say though that you are reluctant to remove the pathogen load issue, but you do not like the studies as they now exist, what are you going to put in their place?

DR. WOOD: What I am trying to say is that, you know, we do not have the information we need to make that decision. And so, we should then continue with some form of pathogen load study related to the best information that we do have, as opposed to not moving forward on that because of these insufficient studies.

DR. WAGES: We cannot wait for studies. You know, let's start looking at the numbers of studies that we have been presented to us, okay, so they are not in the thousands. Just because that study does not support what I wanted to say, you know, I think this committee has to accept the information that we have got and do make a decision based on it.

And the other thing addressing Richard,

remember that the framework was the best current thinking that CVM put in front of us. Richard is basically concluding that that document, as a whole, had no baggage to it. I do not think you can say that.

I think when you look at the February 2000 workshops, and what has been presented here, there is at least the pathogen load preapproval studies that appears to be baggage. That is not needed for that whole framework to be a part of a good document to go on with drug approvals. So I guess I would disagree with a little bit of that.

DR. GLENN: Richard was describing the whole system in a holistic way and giving relative value to all components of the framework. But I would strongly say that we can today comment on that one component entitled "Pathogen Load." If we cannot, maybe we should not have been here.

But I would strongly support that we can comment. And I am not in favor of supporting the notion that we would retain something like, because I think that is a non-science-based decision. We have been presented the state-of-the-art science on this issue.

And so, we have to make a decision today on what that indicates, and I think we can.

DR. KOCHEVAR: I think your concern, Richard,

that we have seen a lot of evidence, and your conclusion is not so much that pathogen load studies are not informative, it is that we have not done them the right way to answer the question we need to answer, and I am sympathetic to that concern.

But I guess I am also concerned that, again, that there are studies that could be designed that would be much more useful and would advance the ball, and that by leaving pathogen load as the focus, that you do detriment to the final outcome, more than just saying at this point.

I mean, we have heard from a number of people that, try as they might, and there has been a lot of effort made to try to make these studies better, to make them more predictable, to make them where the numbers of repeatable. And it seems that that is a very difficult thing. So, even if we wanted to, I am not sure we could fix pathogen load studies based on what we have heard.

DR. WOOD: Well, that is what I went to bed worrying about, if there was anything I was worrying about with this committee. And that is why I asked the question of Dr. Gray this morning. And, apparently, there is some feeling, and justified feeling, that good models can be put together that would accomplish what we want. That is all I have to go on.

DR. PARKHURST: In order to address that question, it seemed to me that there was this big gap in the literature, and only recently had people begun to focus on these pathogen load studies. And that is why I would like to see that kept open.

I have now the impression that by talking about post-approval monitoring, that gets into the resistance rather than keeping the pathogen loading open, question open. Is that what I am hearing?

DR. LANGSTON: My view would be that it would still address both. Anyone can correct me if they want. But I think the post-marketing surveillance could address both. I think it should address both.

DR. GLENN: I am not fearful that, you know, we will drop the concept of pathogen load off the face of the earth here, because I know that the principal investigators that we have heard from, I mean, they are dedicating large portions of their careers to continuing to look at this and help provide the information for this model we are talking about.

What is a better predictor? What is more useful? What is more relevant?

So I am really confident that things are going to continue to be looked at here. But we have got to get closer to that meat product, if we are going to ever

take that -- if any lines are going to be drawn, we have got to continue to do that research.

DR. PARKHURST: Would you support having this agency support those studies, those PI studies, or do their own studies?

DR. GLENN: I think the agency needs to answer that, but it appears to me they have excellent scientists. And when they see an issue, I know that they go out and either competitively provide funding for research, or they do their own research. So, I have confidence that that would occur too, and as well as the PIs that are out in the U.S.

DR. PARKHURST: The reason I bring it up is because I do hear people saying that is taking the money away from something that may be better spent elsewhere.

DR. LANGSTON: Other comments?

(No response)

DR. LANGSTON: We have a choice now then if no one has anymore discussion of either moving directly into voting, for lack of a better term, expression of your opinions.

However, we are only 20 minutes away from lunch, and I understand that lunch is ready at this particular time, and would allow you to develop those opinions if you want. I will defer to the committee as

to which they would prefer to do.

DR. WAGES: Not me, but we have got some people I think that are pushed for time on flights, the early afternoon, that would probably vote to continue. I know two people that are looking for a plane.

DR. LANGSTON: Continue?

DR. HASCHEK-HOCK: Continue.

DR. LANGSTON: All right. At this particular point then, I will ask you to render your opinions on these issues of pathogen load.

DR. WOOD: Are we dealing only with question 1, or we are dealing with the whole --

DR. LANGSTON: No, we are going to deal with all of them. I do not know that I will particularly want to start it. So, Dennis, volunteer, thank you; and then we will move to Tom this way, and then move around.

DR. WAGES: In what is a contribution as it relates -- do I need to read the question basically?

DR. LANGSTON: No.

DR. WAGES: The information that I can gather from this meeting, as it relates to public health is, at best, the contribution is minimal. And if you look at specifically the information presented at this meeting, by the experts it is actually zero.

I mean, you know, there was just not nothing

there to support its contribution. But, at best, if you look at overall pathogen shedding, and its minimal to no effect.

As far as contamination of carcass, there was no evidence that I gathered that addressed the specific use of antimicrobials in any therapeutic or sub-therapeutic affected the contamination of the carcass. And I am presuming that is at the processing level.

By all means, we did get a lot of information of everything else that contributed to that carcass contamination. So, my answer to question 1 is minimal to no evidence that supports any relationship.

Number 2, which antimicrobial drug use conditions in food producing animals is more or less likely to affect pathogen carriage or shedding.

Based on the information that we were presented, there were no specific uses that could draw a conclusion, both therapeutic and sub-therapeutic, depending on the individual -- you know, there was an individual that it was a plus, and then it was no effect.

The Canadian epidemiology studies had the same thing. So I think if we look at, based on history, you know, sub-therapeutic has been the focus because that is why we have our 558.15 studies. But, based on what we

have heard here, neither one significantly affects -- I hate to say significantly, because confers a statistical evaluation.

And, from my standpoint, number 3, do I think the potential for antimicrobial drug use in effecting pathogen load is sufficient toward evaluation as part of the drug approval process, absolutely not. I just have not gotten any information that I could support a reasoning on why.

DR. LANGSTON: And that is for both therapeutic and sub-therapeutic use?

DR. WAGES: Correct, both therapeutic and sub-therapeutic. Thank you.

DR. CARSON: As a newcomer to this committee, and as a toxicologist that does not deal with pathogens on a regular basis, kind of like Alex, hopefully, I came into this committee meeting and this experience with no preconceived notions, an open mind, and was looking for science-based data upon which to make a decision.

And so, I have learned a lot in the last 24 hours or so. However, based on that, and concurring with others on the committee and their previous stated opinions, and taking into account the -- again, the science-based information.

I think the great preponderance of information

presented here that I was able to absorb and interpret including observational studies, including controlled studies, including literature review, the great preponderance of information is that this does not support a "significant," again, role of antibacterial antibiotic use in pathogen load.

And, along with that, the -- again, the information about the factors that does affect pathogen load certainly I think almost everything I heard through the HACCP information to the on farm experiences, again, observational studies, would put the use of antimicrobials at a very, very small, or even insignificant role in this particular area.

And also, I would agree, the question number 3, my answer is no.

DR. LANGSTON: And just for clarification, that would imply that in answer to number 2, there are no agricultural practices or drug use practices to influence pathogen load particularly?

DR. CARSON: The question is no. And I should also clarify this is both therapeutic and sub-therapeutic. Thank you.

DR. LANGSTON: And, please, each member, please so state, if you would.

DR. GLENN: Thank you. I continue to want to

know whether pathogen load is a critical control point in our seeking, you know, improved human health, as regards to food borne illness. So I really appreciated hearing all of the data that are apparently available.

Regarding number 1 and the contributions to pathogen shedding and contamination of carcasses, I agree totally, 100 percent, with what Dennis said in his reading.

With regard to the conditions of use of antimicrobial drugs, there was no clear cut definition of what those might be. We looked at types and classes of antimicrobials, types of bugs, a little on feeding, care and handling, stress, transportation, but nothing comes out in a uniform way to say, you know, that is the condition.

So, I do not think there is any conclusion there that can be made on one condition over another. And then, I do not think that pathogen load studies are warranted, based on the review of the scientific literature that we have seen.

DR. LANGSTON: Richard.

DR. WOOD: Well, as I stated earlier, as with all of us, pathogen load is a concern for all of us. And I come to this table as the consumer representative very much aware of, and out of my own organization's

concern, as well, relating to pathogen load and shedding as being a very important food safety and human health question.

It is a question that I think the expectation is from the public part, public's aspect, that that question will be addressed on all fronts, and in every way possible.

As we stated in our discussion earlier, I did not find a satisfactory answer to the question -- of question 1, or many of the questions before us, in what was provided to us. There is no preponderance of evidence.

For me though that does not mean that we do nothing and do not move forward. As I stated earlier, it means that we must continue to move forward and gather what is needed. More research needs to be accomplished. And, as I stated earlier, I am a bit perplexed why that research has not been there since the '70s, when this concern was first identified, or even before that.

Perhaps, instead of the review of literature, the Center for Veterinary Medicine should conduct its own carefully constructed study, although I do not want to see them delay the implementation of the framework because of having to do another risk assessment, and

that has to all then be held with intention.

I am equally concerned, and I know this is shared by others with who I work and around this table, about the need to move forward in a timely fashion in implementing the framework document.

Because, contrary to other drugs that are other, antimicrobials are not static but very dynamic, and concerns related to antimicrobials need to be addressed in as timely and as quickly as possible.

But with this lack of clarity, a bottom line concern is that we not abandon a tool of pathogen load studies without putting a better tool in its place, either by completing the data gathering, or creating another model.

But a tool, of course, is the resistance in threshold studies and the approval process that we have been developing. But, again, that also is still on paper, and without moving the framework together to its conclusion is not yet an alternative for us.

I am concerned about the potential for new drugs raising issues and showing a pathogen load that we have yet to consider. And if we do not move forward on this, no framework by which to address what pathogen loads those new drugs might create other than a post-approval surveillance system.

Relating to question 2, because we are concerned about the impact on food. Drugs that are fed near the time of slaughter are probably of most concern, that is why I was raising questions about withdrawal times.

I think that really becomes a focus, and we were greatly helped this morning by one of the presentations at that point. Because that appears where the antibiotic could have the most impact on pathogen load and in reverting back to normal after several weeks after withdrawal, if those weeks exist.

Also, in this area, be concerned about again, even though it was defined with us, I am not sure that we are clear about the definition of what is a therapeutic use, or a non-therapeutic use, or a sub-therapeutic use, or a preventative use. And I think that does need to be clarified and agreed to.

Also, another aspect of this question has to do with how the therapeutic or sub-therapeutic uses, in relationship to treating an individual member of a herd, or the entire herd or flock, even with therapeutic antibiotics, some are fed through water and feed.

So, number 3, my answer I guess is yes, to both sub-therapeutic and non-therapeutic, and even though the evidence is scant and inconclusive.

It is, yes, because given the rapid rise in the prevalence of food borne disease during the last 20 years, along with changes in the food processing industry, that create the potential to multiply pathogens, along with the demographic changes that can lead to a greater number of people at risk in the population, the concerns expressed in the early '70s, when 558.15 was being put together, are even more relevant today.

While the evidence does not suggest that all antibiotics lead to an increased pathogen load, some do, and some in the future may well do. And I believe it is the responsibility of CVM to discover these before approving drugs.

Given the difficulty of withdrawing already approved drugs, as I mentioned before, under the existing regulatory scheme, and even when that process is put in place, taking months if not years, the level of preapproval scrutiny for new animal drugs must be held high to protect human health.

So I get to move to question 4, the only one at this table that can maybe. I think that studies should be conducted in vivo, perhaps, as part of on farm trials, if possible.

These studies should look at the animal

populations for which the drug approved, at a minimum, enterococci, salmonella, campylobacter, and E.coli should be considered. The drugs should be administered as would be in actual use.

Ideally, these tests could be a part of the efficacy and animal safety tests. At a minimum, a model needs to be developed that is predictive. The study should focus on the impact of the drug and pathogen loads at the time of slaughter. The bottom line for me is that pathogen load should be considered. Thank you.

DR. MACDONALD: I was very impressed with the tremendous number of variables that affect the pathogen load, salmonella shedding issue, that are massive and do dictate that particular effect.

An antibiotic use could play a role. But I was very impressed that in all of the data presented, this was a very minor, if at all, existing phenomena. So, as an experimentalist, I would find it very hard to think of -- looking at the evidence that we have heard over the last day or so, and saying this is something that we can study.

So my conclusion is that this, as a preapproval evaluation, as evidenced by the 558.15 studies, have not been predictive of what will happen in natural practice.

So, I have to agree with Dennis and Barbara that I cannot support this type of evaluation on a preapproval basis. I do not think the effect is there to the point that it can be measured without super human heroic type efforts. And that applies for both therapeutic and sub-therapeutic.

DR. LANGSTON: I would presume then that question 2, there were no drug use practices likely to effect pathogen?

DR. MACDONALD: That is right.

DR. WADDELL: On question 1, I just think that the preponderance of the data that was presented indicates that the answer is clearly negligible to zero. On question 2 -- and this applies to both sub-therapeutic and therapeutic, and everything else in between.

Question 2, there appears to be no evidence that use conditions have any bearing on carriage or shedding. And the answer to number 3 is no, and the reason is the science just is not there yet.

DR. HOLLAND: I can save a few minutes. He copied my notes. He stated it basically the same way I would have stated it.

DR. KOCHEVAR: I would just reiterate earlier remarks to say that I think that because we have been

charged with looking at this question as it relates to public health, despite all of the information we have received, we really have not had any evidence that addressed that, the hypothesis that pathogen load, as it increases, increases the incidents of risk of food borne disease in humans.

And so, that does not mean that we do not need that data. And I would strongly encourage the FSIS efforts that are ongoing, you know, to be pursued and completed because that is a question that really needs to be answered.

However, independent of that, the information, as others have said, that we have been presented with does not lend itself to a science-based decision to continue to include pathogen load as part of a preapproval process either for therapeutic really or for sub-therapeutic.

I think there is just too many problems associated with the studies that have not been able to be fixed to make this data useful in that regard.

And so, I would like to say that I do think there needs to be a preapproval piece that tries to address this effectively as we can, the notion of antimicrobial resistance.

I appreciate that is in the framework

document. I guess I would just go on record as saying I think it is very important that we do have models and studies that will address these issues. I just do not think that pathogen load is the one to put the resources into.

I would have to agree that on number 2, the conditions that seem to have the most effect on pathogen load had nothing to do with the way you gave the drug. It had to do with environmental issues, and things unrelated to administration of the drug.

And so, I think I have already answered number 3.

DR. LANGSTON: Just for clarification, relative to number 1, you, of course, mentioned that there was no evidence presented relative to the correlation to human health. Is that how you want it listed as evidence lacking?

DR. KOCHEVAR: I would say the evidence is lacking that provided the correlation to human health; that the evidence is abundant that pathogen load studies as they are conducted now do not suggest that the contribution of antimicrobial drugs is limited.

DR. LANGSTON: Thank you. Anne.

DR. PARKHURST: I am feeling that the information is limited. But my take on that is that the

studies were not designed to look at the relationship with public health at this point, and that that is an area that still needs to be looked at, and that a model we should find.

Is there a way to develop a model that would be predictive?

And that could be working with HACCP to see as they indicate, as they try to move there to tighten their regulation, it may be that they bump up to the point where that is a critical control point, what happens on farm.

I mean, we just do not know that at this particular point. So, I would say that we do not have enough evidence to answer number 1. I do agree that number 2, there does seem to be a lot of environmental conditions. And so, when you design the model, and you design your studies, you would identify what environmental conditions you want to be working under.

And, number 3, I think I have answered that. I do think that we should be looking at ways to build that model and not ignore the potential for the information that pathogen shedding might have when we do the evaluation of drugs.

The approach for conducting these studies I think that, you know, we really have to weigh out the

situations in which the micro organisms will be used, and agree on ways to measure that.

We were presented with several different methods. There needs to be agreement on which method would be the most productive, and you would want to use that. Those are all issues that I think people designing the studies would keep in mind.

DR. LANGSTON: So your answer to 3 is yes, and your answer to 4 is yes, but develop a new model?

DR. PARKHURST: Yes. And I would like to know how -- I do think it is important that we do move on, that we do say, well, okay, you need to be using these drugs as we develop this model. And so, how would post-approval monitoring help us keep the pathogen load component in there, as well as the resistance load?

DR. LANGSTON: Any drug use conditions in Section 2 you want to comment on?

DR. PARKHURST: Not at this time.

DR. HASCHEK-HOCK: Okay. Based on the available scientific data, neither therapeutic nor sub-therapeutic antimicrobial use appears to contribute significantly to pathogen shedding that leads to carcass contamination and adversely affects human health.

Many other factors confound this issue. The use of HACCP plays a major role in decreasing any

potential effect of this.

I would just like to point out, though it is not part of the charge that irradiation of meat should be further pursued because it would certainly be able to kill the surface bacteria. And that is the major concern from the slaughter house.

On the second question, no conditions have been shown to affect pathogen shedding.

Third question, answer to the first part is no. And why not? I do not believe that the current tests as used are predictive. This does not mean that pathogen load should be ignored.

More studies are needed, and predictive models need to be developed. I would suggest that some research funding be allocated to identify areas that need to be addressed in these models.

DR. LANGSTON: Alicia.

DR. ANDERSON: My comments refer to therapeutic and sub-therapeutic use. I think that what has been presented today is inconclusive. But, basically, I think that the pathogen shedding studies have very limited, if any, usefulness in preapproval studies, based on what I have heard so far today.

As far as question number 2, I do not have any comment. I do not think there has been showed one way

or the other.

I think that as far as what is necessary for a preapproval study certainly toxicity to the animal residues, the class of the drug, which is already being done by FDA, is necessary; also, if it is possible to know what determinants of resistants, and if resistants, if it is possible to cause resistance due to selective pressure. I think those are the important things that FDA should be looking at in preapproval studies.

But the primary way to protect the public health is to be able to -- I think to be able to stop use of a drug if it has been shown to be a danger to public health.

So I think FDA's full power of regulatory authority really should be focused more on the post-approval of a drug. I would recommend also that the FDA framework document be put into place as quickly as possible, in order for them to do that.

Once the FDA is in place and is ready to do mitigation efforts if necessary, I think that the pathogen shedding testing can be discontinued. I do not think it would be necessary anymore.

But, again, once FDA has the power to do mitigation efforts, and that once a drug is approved, they are following and doing surveillance very closely

on that drug, both in humans and in animals.

And, if necessary, they can pull the drug very quickly and very easily and not go through the incredibly complicated and difficulties that they have to go through now if they decide to pull a drug.

But once that is in place, and FDA is able to do that, I think that the pathogen shedding studies can be discontinued.

DR. LANGSTON: So, again, for my clarity, your answer to number 3 is at present no?

DR. ANDERSON: Right, but it is conditional.

DR. LANGSTON: Okay. My view is that though I share the concerns for pathogen load as a public health issue, that the evidence as presented to us indicates that there is little to no public health significance associated with pathogen shedding associated with drug use.

Accordingly, I see no real drug use conditions that affect pathogen shedding with the one notation that if the organism is resistant, and that drug has a susceptibility profile associated with it, that pathogen may replicate.

But I viewed that really as a monitoring, post-surveillance -- post-marketing surveillance issue for monitoring for resistance rather than preapproval.

And I would adamantly say that as things presently exist, there is no reason to require preapproval pathogen load studies.

**Summarize and Adjourn Meeting**

DR. LANGSTON: Okay. So, in attempting to summarize what the committee has said, we had two members that indicated that they did not feel that indicated that they did not feel there was enough evidence to make a decision on question 1, as to the contribution of drug on pathogen shedding; all other members, however, felt that there was very little effect to no effect.

Anyone disagree or want to comment on that first conclusion or summary?

DR. KOCHEVAR: Richard and Anne were the two?

DR. LANGSTON: Yes, relative to the contribution of drug use conditions on pathogen shedding, there was one note that concern occurred relative to drugs fed near slaughter, and another note relative to resistant pathogens to that particular drug needing to be addressed.

But, again, all other members felt that there were no drug use conditions. In fact, the second one I mentioned also agreed there were really no drug use conditions affecting pathogen shedding.

As far as whether or not the potential for antimicrobial drug use to affect pathogen load is sufficient to warrant evaluation. We had two members expressing that, yes, there was sufficient evidence to include it.

Both seemed to indicate that, in relation to that question number 4, their answer was that a model needed to be developed to address these, to take into account the correct population, the actual use conditions, the time of slaughter relative to the drug use and the pathogen load at those points.

All other members felt that at present the pathogen load study should not be required for either therapeutic or sub-therapeutic use -- approval -- preapproval.

Any comments or corrections in those interpretations?

(No response)

DR. LANGSTON: With that then, we are concluding the business of this committee. I am sure there will be some post-meeting comments by Dr. Sundlof and/or Ms. Sindelar.

On behalf of the committee, I want to thank Ms. Sindelar for arranging this, and the hospitality of the FDA in providing the information we needed.

Certainly, the speakers for the good quality of their presentations.

And, as chair, I want to thank the members of this committee for the excellent work that they have done.

DR. MACDONALD: And, as a member of the committee, we thank you for your leadership.

(Applause)

DR. SUNDLOF: And I add my congratulations, Mr. Chairman, for an excellent job.

Before we adjourn, we do have one additional item that I wanted to address. And that is that some of the members are going to be rotating off this committee. And we thought that we would like to show those members a little token of our appreciation for all of the hard work they have done for this committee.

So, as I call your name, could you come up please and receive your plaque. The first person is Dr. Wanda Haschek-Hock.

(Applause)

DR. SUNDLOF: The next person is Dr. Bob Holland.

(Applause)

DR. SUNDLOF: The next person who is going to be leaving us -- I just want to say that although these

folks are leaving this committee, we continue to have numerous, numerous occasions to collaborate on various issues whether it is toxicity issues, or minor use issues, or USP issues, or consumer or CODEX issues.

The next person is Richard Wood.

(Applause)

DR. SUNDLOF: I just want to say about Richard that, as a consumer representative, I could not pick anybody that I think is more balanced, and harder working, and more committed, and takes up the mantel of the consumer movement better than Richard does. He has been just a tremendous member of this committee.

He also has participated in other committees such as the CODEX Committee, where he is an active participant. He did receive the Commissioners special citation for his role on this committee and other activities. We will certainly be missing him. But he is going to continue, right, with CODEX, on a number of other issues. So, again, Richard, thank you for everything.

(Applause)

DR. WOOD: Okay. Thank you, yes. And I just wanted to say how much I value the respect that has come from the director in the agency and from other members of the committee. As we all may vary in our opinions,

we all seem to relate as one. And thank you.

DR. SUNDLOF: And, finally, our chairman.

(Applause)

DR. SUNDLOF: So, congratulations. Cory continues to work with us on committees such as the USP, and we have other issues such as VADS, and a number of other activities.

So, the great thing is we still have everybody working with us. It is sad that we lose these people, but there will be another group coming and they will be as strong as this group, I am sure. Thank you once again.

And, with that, Aleta, are there any closing?

MS. SINDELAR: Just thank you everyone.

DR. SUNDLOF: Yes, I would like to thank Aleta, and I would like to thank the committee that worked so hard to come up with all of the speakers, and all of the questions and issues regarding this, and for all of the members of the panel, the VMAC Committee, and for all of the contributors, again, thank you very much. This has been very beneficial to the CVM.

(Whereupon, the meeting was adjourned at 12:45 p.m.)