VMAC Meeting
October 13, 2004

PARTICIPANTS

MEMBERS PRESENT:

John T. Waddell, D.V.M., Chairperson
Susanne Aref, Ph.D.
Arthur L. Craigmill, Ph.D.
Sherman (Skip) W. Jack, D.V.M., Ph.D.
Gregory Jaffe, Esq.
Katrina L. Mealey, D.V.M., Ph.D.
John J. McGlone, Ph.D.
Lisa Nolan, D.V.M., Ph.D.
Mark G. Papich, D.V.M.
Marguerite Pappaioanou, D.V.M., Ph.D.
Richard A. Sams, Ph.D.
Dennis P. Wages, D.V.M.

CDER AIDAC MEMBERS PRESENT:

James E. Leggett, Jr., M.D.
Christopher Ohl, M.D.
L. Barth Reller, M.D., D.T.M.&H.
Nathan Thielman, M.D.

FDA, CVM STAFF PRESENT:

Jeff Gilbert, D.V.M., Ph.D.
Karen Lampe, Ph.D.
Aleta Sindelar, R.N.
Stephen Sundlof, D.V.M., Ph.D., Director
Linda Tollefson, D.V.M., M.P.H.

I N D E X

VMAC MEETING
October 13, 2004

KEYNOTE: "---" Indicates inaudible in transcript.
A*@ Indicates phonetically spelled word.

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

8:30 A.M.

MS. SINDELAR: Hello. Before we start with the program I am Aleta Sindelar. I am the Exec Sec for the Veterinary Medicine Advisory Committee. And we have two statements that need to be read into the record. And I would like to invite the Chair, Dr. Waddell, to please first come and read the first statement to the meeting.

DR. WADDELL: Okay.

ABoth the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting FDA believes that it is important to understand the context of an individual=s presentation.

For this reason the FDA encourages you, the open public hearing speakers at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include the company=s or a group=s payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

Likewise the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement it will not

preclude you from speaking.@

MS. SINDELAR: Thank you, Dr. Waddell. And I will read the conflict of interest statement for the Veterinary Medicine Advisory Committee, October 13, 2004.

AThe following announcement addresses the issue of interest with regard to this meeting and is made part of the public record to preclude even the appearance of a conflict of interest at this meeting on October 13, 2004.

Federal conflict of interest laws preclude the participation of committee members and consultants in advisory committee meetings if they have a conflict of interest unless a waiver of exclusion is granted by the agency.

The associate commissioner for external relations FDA has appointed Dr. Susanne Aref,

Dr. Gregory Jaffe, Dr. James Leggett, Dr. Katrina Mealey, Dr. Christopher Ohl, Dr. L. Barth Reller, Dr. Richard Sams, and Dr. Nathan Thielman as temporary voting members for this meeting.

Based on the submitted agenda for this meeting and a review of all financial interests reported by the committee participants it has been determined that all interests in the firms regulated by the Center for Veterinary Medicine which have been reported by the participants prevent no potential for conflict of interest at this meeting with the following exceptions.

Dr. John J. McGlone discloses consulting with competing firm under negotiation. Magnitude is less than $10,000 to $50,000. Dr.

McGlone discloses a grant with a competing firm. Magnitude less than $100,000.

Dr. Katrina L. Mealey discloses consulting with a competing firm. Magnitude is less than $10,000, excuse me, $10,001. Dr. Mealey discloses a grant with a sponsor. Magnitude is greater than $300,000. She also discloses two speaking interests with two competing firms. Magnitude is less than $5,001 each.

Dr. Christopher A. Ohl discloses a speaking interest with a sponsor. Magnitude is less than $5,001.

Dr. Mark G. Papich discloses four consulting interests. One with a sponsor and three with competing firms. All four interests are less than $10,001 each. Dr. Papich discloses two grants. One is with a sponsor and the second is with a competing firm. Both are less than $100,000 each. He also discloses two speaking interests. One with a sponsor. Magnitude is less than $5,001. And one with a competing firm. Magnitude is from $5,001 to $10,000.

Dr. Marguerite Pappaioanou discloses stock interest with a competing firm. Magnitude is less than $5,001.

Dr. John T. Waddell discloses stock interest with a sponsor. Magnitude is less than $5,001. Dr. Waddell also discloses consulting with a competing firm. Magnitude is from $10,001 to $50,000. He also discloses one speaking interest with a competing firm. Magnitude is less than $5,001.

In accordance with 18 U.S.C. 208(B)(3) a waiver has been granted to Dr. John J. McGlone,

Dr. Katrina L. Mealey, Dr. Christopher A. Ohl,

Dr. Mark G. Papich, and Dr. John T. Waddell.

Under these terms of the waiver Drs. McGlone, Mealey, Ohl, Papich, and Waddell will be permitted to participate fully in discussions and deliberations to address microbial food safety concerns related to the agency=s assessment of the information and strategies for addressing and managing any potential human health microbial food safety risks.

In the event that discussions involve specific products or firms not on the agenda for which FDA participants have a financial interest the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the public record.

With respect to all other meeting participants we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment upon. Waivers are available by written request under the Freedom of Information Act.@

Thank you. And Dr. Sundlof, we can proceed.

Welcome to VMAC

by Dr. Stephen Sundlof, Director CVM

DR. SUNDLOF: Thank you Aleta. And welcome and good morning everybody. My name is Steve Sundlof and I am the Director of the FDA Center for Veterinary Medicine. And it=s my honor and privilege to welcome you all to this meeting. This is somewhat of a first, a historic first, for the Veterinary Medicine

Advisory Committee meeting because we are here to consider the microbial safety of a new antimicrobial presented to FDA for approval.

(Slide)

And what is historic about is that this is the first product, the first category one drug or critically important drug that is being evaluated under compliance policy, I am sorry, Guidance for Industry Number 152.

Pfizer Animal Health has submitted an application with CVM for the use of tulathromycin in cattle and swine. Tulathromycin is an injectable macrolide antimicrobial agent intended for therapeutic use in the treatment of swine respiratory disease and bovine respiratory disease.

Today CVM will seek input from the VMAC on the agency=s assessment of the information and strategies for managing any potential microbial food safety risks.

The VMAC will discuss the microbial food safety of an antimicrobial drug application currently under review for use in food producing animals in accordance with the FDA Center for Veterinary Medicine=s Guidance for Industry Document 152.

Microbial safety is that part of the human food safety evaluation that looks at the impact of the use of antimicrobial drugs on the development of resistance among pathogenic zoonotic bacteria of human health concerns such as Salmonella, E. Coli and Campylobacter. We are not seeking recommendations today on whether or not the product should or should not be approved.

Now before we go any further, I would like to introduce the members of the VMAC who will be joining us today. Dr. Arthur Craigmill from the Department of Environmental Toxicology, University of California, representing toxicology.

Skip Jack from the College of Veterinary Medicine in Mississippi, Mississippi State University. John McGlone from Texas Tech University. Lisa Nolan from the Iowa State University. Mark Papich from North Carolina State University.

The Chair is Dr. John Waddell from Sutton Veterinary Clinic in Sutton, Nebraska. Representing epidemiology is Marguerite Pappaioanou from the Centers for Disease Control and Prevention. And Dennis Wages is representing avian medicine.

In addition we are fortunate to have today with us some individuals who will take the place of retiring committee members. We are in this kind of transition period between members who have rotated off as of the first of this month and new appointees to the committee.

And we are very happy to have with us Susanne Aref, who is with Virginia Polytechnic Institute and Greg Jaffe who is Director of Biotechnology Project for the Center for Science and the Public Interest.

Also VMAC members or VMAC consultants who will become VMAC members on November 1st are Katrina Mealey from Washington State University. Rick Sams who is from Ohio State University.

And in addition to those folks we have some supplemental experts from the Center for Drug Evaluation and Research, the human drug approval center in the FDA. And these are members of the Anti-Infective Drugs Committee. We have Dr. James Leggett, who is Chair of that committee. Nathan Thielman from Duke University Medical Center. Christopher Ohl from Wake Forest University. And Dr. Barth Reller from Duke University Medical Center.

In addition we have some consultants. John Powers who is an expert

in human medicine and explains the importance of macrolide antimicrobials in human medicine. And John has been very instrumental in helping us develop Guidance for Industry Document 152.

(Slide)

In addition we have with us Mike Apley who is a former VMAC member and an expert in antimicrobial resistance as it relates to animal medicine and specially production animal medicine. And he will explain the importance of macrolides in veterinary medicine.

(Slide)

So again this is a, it is a historic meeting. The drug under review is a macrolide, a category one drug, a critically important drug in human medicine and thus it is eligible for VMAC review under our Guidance for Industry Document 152.

It is a qualitative risk assessment. That is what GFI 152 is intended to be. And in keeping with the open transparent process that we develop in accordance with Document 152, we want to make sure that this is an open and transparent process.

So with that I will turn the podium over to Dr. Linda Tollefson.

Brief Background for Today=s Discussion

by Dr. Linda Tollefson,

Deputy Director Center for Veterinary Medicine

DR. TOLLEFSON: Thank you Dr. Sundlof. Good morning and welcome to everyone. I want to particularly thank the committee for taking time out of your busy schedules. It=s very helpful to the FDA to have your insights, your expertise. So we are very grateful to you.

We have a relatively well defined issue before the committee today. Simply the microbial safety of a new animal drug with respect to antimicrobial resistance.

(Slide)

This is a food safety issue. I think everyone is aware of that. Because food producing animals are reservoirs of food-borne pathogens in humans such as Salmonella, Campylobacter, E. Coli, 0157 and so on.

Antibiotic resistant pathogens can be present in the animals due to the use of antimicrobials in these food producing animals. And we know from our monitoring that the resistant pathogens contaminate carcasses and also retail meat so that humans may be exposed in the organisms transmitted through food to them.

(Slide)

Now the agency is reviewing the microbial safety of all uses of all antimicrobials for food producing animals. We published a Guidance for Industry in October of 2003, outlining a recommended approach for assessing this issue prior to approval.

And the guidance uses a qualitative risk assessment process to arrive at an overall risk estimation. An overall estimate of the risk to humans. Initially we start with the hazard characterization to determine if a risk assessment, if a qualitative risk assessment is even needed.

(Slide)

In this process, once the hazard identification is gone through, has essentially three components all of which are treated equally in terms of the risk.

The first is the release assessment that tries to get at the probability

that use of the drug will result in the emergence, selection, and dissemination of resistant bacteria.

Next is the exposure assessment which is a likelihood of human exposure to the pathogen, to the resistant pathogen. And it=s actually independent of the drug which you will see later.

And the consequence that should be, consequence assessment which is integral to this process is essentially the importance of the antimicrobial to human medical therapy. Now the criteria for developing this ranking of drugs that we use was developed by our Center for Drug Evaluation and Research with a great deal of help from the Anti-Infective Drugs Advisory Committee, which the Chair and another member are present here today.

And it served us very well actually I must say. We have been pretty successful using those criteria.

(Slide)

When you end up with these three arms so to speak, these three steps of the process, you integrate it into an overall risk estimation which comes out qualitatively as low, medium, and high.

We don=t discount the value of quantitative risk assessment. However, our experience has shown that that we generally don=t have the data to do such an in-depth quantitative risk assessment.

We advise sponsors to go through this qualitative process if something comes up in the process that needs to be further defined, then it may be in their interest to expend the resources for a quantitative risk assessment. But so far we have been pretty successful using this.

Once we have an overall risk estimation then we have specific risk

management steps, strategies that are, you know, just aligned with the risks that we have estimated the drug to cause to human health. And included in that is a VMAC, is a Veterinary Medical Advisory Committee review.

(Slide)

We end up in the risk estimation, we end up categorizing the drugs as a category one, two, or three. And for all category one drugs and some of the category two drugs we may choose to convene an advisory committee to discuss the application. And we do intend to do this for all new products. Particularly for critically important drugs.

And we also intend to include the Anti-Infective Drugs Advisory Committee. I think it=s important for members of that committee to keep involved with power interpreting the criteria that they did such a great job in developing. And also these meetings will be public so that we can have open comment from all stakeholders, and also transparency.

(Slide)

Now specifically today what we are going to do is we have asked Dr. John Powers from the Center of Drug Evaluation and Research to present information on the importance of macrolides in human medical therapy, and Dr. Mike Apley to do the same for animal medicine.

Then Dr. Scott Brown will be putting forth what the company has done with information on use of tulathromycin in cattle and swine. Specifically for the microbial food safety.

We do have a public comment period where we want to have comments on the proposed use. And of course we want to gain the Veterinary Medical Advisory Committee=s insight also, which is why you are here.

(Slide)

In trying to get to this, as Aleta mentioned and as Dr. Sundlof mentioned also, this is not really a question of should we or should we not approve the drug. What we want to do is a little bit narrower then that. We want to ask a series of questions to determine if the Veterinary Medical Advisory Committee agrees with the Center for Veterinary Medicine=s assessment. So it actually in many ways is broader than that. It=s going to help us in the future.

(Slide)

The first one is do the findings presented in the drug sponsor=s assessment as a qualitative risk assessment using Guidance for Industry 152, demonstrate that the drug is safe with respect to the potential for transfer of antimicrobial resistant organisms to humans. It=s pretty straight forward.

(Slide)

Are there other issues to consider relative to this class of macrolides/triamilides of antimicrobial agents? For example other species for which it should or should not be approved, food/animal species. Routes of administration that are or are not acceptable. Indications that are or are not appropriate on the label. Any other relevant issues.

We will have Drs. Jeff Gilbert and Karen Lampe from our human food safety division go through what some of the risk management strategies are and what the label of the drug will be looking like.

(Slide)

Then finally are the risk management recommendations appropriate or should they be modified?

(Slide)

Our first presentation is by Dr. John Powers on importance of the macrolides in human medicine. Next, as I mentioned, Mike Apley from Iowa State will be giving the importance of macrolides in animal health. And then Scott Brown of Pfizer Animal Health will be doing the product presentation.

Dr. Powers is a lead medical officer for the antimicrobial drug development and resistant initiatives in the Office of Drug Evaluation in the Center for Drug Evaluation and Research.

Prior to joining FDA he was an assistant professor in the division of infectious diseases at the University of Maryland School of Medicine. And he is currently an assistant clinical professor of medicine at the University of Maryland and assistant clinical professor of medicine at George Washington University School of Medicine.

In addition he is an infectious disease -- as an attending physician at the National Institute of Allergy and Infectious Diseases at NIH and sees patients and attends on the infectious diseases services.

Importance of Macrolides to Human Medicine

by John H. Powers, M.D.

Antimicrobial Drug Development and Resistance Initiatives

Office of Drug Evaluation IV, Center for Drug Evaluation

and Research, U.S. Food and Drug Administration

DR. POWERS: Thanks Dr. Tollefson. Thanks Dr. Sundlof for inviting me to talk to you today. Let=s get plugged in and get all the technical difficulties out of the way here.

As Dr. Tollefson mentioned the folks at the Center of Veterinary Medicine asked us at the Center for Drug Evaluation Research, I guess about two

years ago now to try to help out with one part of the overall risk assessment. And that was to develop a ranking of drugs based on their importance in human medicine which as you can tell is a pretty daunting task given all the antibiotics that are actually out there.

So what I would like to do today is to go over with you some information about macrolide drugs in general. How we came up with that ranking of drugs. And then how we applied that to macrolides. And then talk about some of the important uses of macrolides in humans. There we go. We got all the technical difficulties out of the way.

(Slide)

So the fastest way to put somebody to sleep is to show one of these structure slides of what an antimicrobial actually looks like. But I just wanted to get it out of the way just to show you why macrolides are called what they are called.

Erythromycin was first derived in 1952. And it gets its name because it was actually isolated from a mold called Streptomyces erythreus was actually found in soil in the Philippines, which is the auspicious start of many antimicrobials that are actually found in dirt.

So macrolide are called what they are called because they are made up of these macrocylic lactone rings. And they are actually fairly large molecules. And as you can see on this slide that big central ring structure is that macro-lactone ring.

Macrolides for the most part are made of 14 membered rings but arithromycin is a related class called azalides which is a 15 membered ring. There are five macrolides, or in the general class of macrolides, drugs that are approved by the FDA.

The oldest of those was erythromycin which I said was in the 1950's. Clarithromycin and azithromycin were actually approved in 1993. Dirithromycin came a little bit later. And then telithromycin was just approved in April of 2004. Telithromycin is considered a ketolide but that actually is still within the same 14 membered ring class. It just has one little difference in that it has a ketone added to that ring structure.

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So when we were asked by the Center of Veterinary Medicine folks to actually help out with this guidance the overall purpose of this guidance was really this desire to preserve the usefulness of antimicrobials of greatest importance in the treatment of human disease.

And Guidance 152, as Dr. Tollefson said, includes this categorization of drugs based on the relative importance in human medicine. The drugs are ranked as critically important, highly important, or important in human medicine. A reason why there is no unimportant category is we don=t consider any drugs that we have out there as unimportant in the treatment of human medicine.

It=s also important to realize though that this piece of the categorization of drugs in humans is really part of the hazard identification and the consequence assessments of the Guidance.

So even though a drug may be considered critically important for its use in humans, that drug may still not rank very high in the overall risk assessment because even though it is important in humans resistance may not develop in animals. Or that resistance may not be transmitted to people.

So that doesn=t change the fact that that drug is still critically important in humans. It=s very important to make that distinction. Because one of

the things that came up at our advisory committee was well why should we be ranking these drugs as critically important if it=s not going to result in transmission from animals to people. That is not the question. The question we were asked by CVM was how important are these drugs in treating human beings.

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So a Joint CVM-CDER team helped develop this categorization. And what we thought was very important in this process was the first thing would be to develop the criteria by which one would determine that a drug is important or not. And then apply the criteria.

And we thought this was very important to ensure a fair approach and a lack of bias in actually doing these rankings. It seems to be is that if a drug is newer or if a drug has a broader spectrum of activity people seem to just assume well it must be more important.

Actually when you look back at the clinical trials and the actual indications for some of these drugs, penicillin is indicated for more diseases then any drug out there. And probably because it=s been out there the longest we have the most experience. But also you cannot minimize the importance of older drugs.

It=s also important to realize that a lot of newer drugs that are studied actually end up showing similar activity, not improved activity, over older drugs. So we thought it was very important to develop this criteria first.

So then we actually took this criteria and presented it at an open public meeting, I think in this room if I actually remember, in October 2002. And then again to a second meeting of the Anti-Infective Drugs Advisory Committee in January of 2003. And Drs. Leggett and Reller were at that meeting.

And we refined this criteria. It was initially ten pieces of the criteria and we refined it down to five based on the advice that was given at that advisory committee. And several folks that are involved in the animal health industry actually presented at that meeting.

And one of the important points that came out was that we needed in some way to link this to gastrointestinal illness. So we actually did that. And we included that as part of the rankings.

And again these rankings are based solely on the importance of drugs in human medicine not the degree of transmissibility of resistance from animals to humans. And not even the degree of resistance that might develop in humans either. The real question was what would happen if we lost these drugs in human medicine. How important would that be?

(Slide)

So these criteria were actually five that we came up with finally in the final assessment. One is the antimicrobial is used to treat enteric pathogens that cause food-borne disease. And that is something that the folks in the animal health industry thought was very important as well is that we somehow needed to make the treatment of enteric pathogens important because that is where we see the most direct link between animals and humans.

The second one though that our advisory committee thought was very important was, regardless of gastrointestinal disease, if that drug is used as the sole therapy or one of few alternatives to treat serious human disease or the drug is an essential component among many antimicrobials in the treatment of human disease.

And I will go over that because macrolides actually are a part of multi-

drug regimens that are very important. And if you lose the macrolide piece the rest of the drugs won=t work either.

Then the other criteria were that the antimicrobials are used to treat enteric pathogens in

non-food-borne disease. For instance E. Coli, although we know that it can cause gastrointestinal illness also can cause a range of infections in humans. Anything from pneumonia to urinary tract infections to meningitis.

The fourth and fifth criteria were related to resistance. One a drug would be more important if there is no cross-resistance within the drug class and absence of linked resistance with other classes. So if there isn=t resistance yet to that drug that is more important to try to preserve that. And then the last was there is no

cross-resistance -- oops, I guess I just repeated that one.

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So finally the drugs that meet criteria one and two are considered critically important. In other words it treats gastrointestinal illness and it=s a sole therapy for important disease in human beings.

If it just meets criteria one or two those would be considered highly important in this risk assessment. And drugs that meet any of the criteria three, four, or five are considered important.

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So we then applied this ranking to macrolides. And again it seems almost incongruous and other countries have tried this ranking as well and came out with different assessments that we did. When we looked at some of those rankings from other countries we couldn=t figure out what criteria they were using

when they actually made those assessments.

And sometimes that is why their assessments look different than ours. But in an effort to be very transparent about this we applied the criteria to the drugs, not deciding whether the drugs were important and then try to figure out a reason afterwards.

So we applied these criteria. And we looked at treatment of diarrheal disease due to Campylobacter species as a gastrointestinal illness where macrolides are recommended to treat. And Dr. Thielman is actually one of the co-authors on the infectious disease society guidelines on the treatment of gastrointestinal illness.

Also macrolides are one of few alternatives in treating potentially lethal diseases in humans such as the treatment of community acquired pneumonia and rarely nosocomically acquired pneumonia due to Legionella pneumophila also called Legionnaire=s Disease.

It=s also used in the treatment of pertussis due to Bordetella pertussis also called whooping cough in children and adults. And it=s also used in the treatment and prevention of disseminated infection due to Mycobacterium avium intracellulare complex in patients with AIDS.

So I am going to go through each of those and talk about how important those drugs are as part of a treatment regimens in those diseases. But you can see then that macrolides fulfill criteria one and two in terms of treating gastrointestinal illness and being important sole therapies or one of few alternatives in treating human disease.

(Slide)

So let=s go through some of those uses of macrolides in human

medicine. Macrolides are recommended for treatment of disease caused by Campylobacter species. Campylobacter are very, very common. And in fact they are one of the most common causes of all bacterial infections in the world.

One can actually ask the question well aren=t we more just concerned about what happens in the United States rather than what happens in the world as a whole. And I think you only need to look at diseases like SARS, and Avian Flu and those kinds of illnesses to realize that bacteria just don=t respect borders. So if it=s a worldwide problem it may become a problem in this country as well. And we need to take a more global look at this approach.

Campylobacter can cause diarrheal disease and it can also cause systemic illness as well. And some of the complications of that diarrheal disease can include things like Guillain-Barre syndrome, which is a paralytic disease where people can actually stop breathing, and reactive arthritis as well. And Campylobacter even in the U.S. is one of the most common causes of bloody diarrhea.

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The majority of people with Campylobacter have self-resolving disease. And in fact it=s not even recommended to treat those people with antimicrobials. However, in patients at the extremes of age and immunocompromised patients like those with AIDS this actually can cause a disseminated disease, spread to the blood stream and can actually result in death. So it has the potential to be a lethal illness.

Treatment is recommended in patients with more severe forms of the disease like dysentery which is severe bloody diarrhea with abdominal cramping and systemic signs like fever. And the treatment appears to be more effective

when given early in the course of illness.

And as I said, according to the infectious disease society guidelines macrolides are considered the drugs of choice for documented disease with Campylobacter species. Quinolones are often used as empirical treatment for this disease but quinolones often cannot be used in certain populations such as children where quinolones may be associated with joint complaints. Also other alternatives such as tetracyclines cannot be used in children as well given their potential for teeth staining or bone abnormalities in children.

Macrolides actually have shown to be effective if given early in the course of disease and placebo controlled trials for Campylobacter.

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Legionnaire=s Disease is actually a disease that was described in our lifetimes. It=s an intracellular pathogen. Legionellapneumophila is what actually causes it. And it was actually described in Philadelphia at an American Legion convention which is where the disease and the organism gets its name.

It certainly can be potentially lethal as in the original description in 1976, 34 out of the 182 legionnaires who became infected died. That just shows you the potential lethality of this.

And subsequent studies show that pneumonia due to Legionella pneumophila at least in one study that was done in an ICU in Spain by Torres showed it=s the second most common cause of pneumonia at least in their ICU. And also was the second most common lethal infection after streptococcus pneumonia. So if you get this infection it=s actually very likely to be a severe infection.

Macrolides and quinolones are the only drugs that are actually FDA

approved that are proven effective in the treatment of this disease. There is more experience in the use of macrolides. Macrolides were actually used empirically in 1976 when these people became ill and it was noted that was one of the drugs that actually helped to make people better.

Some of the newer quinolones have been studied but the number of patients in clinical trials that have been infected with Legionella has actually been quite small. So there is more experience with the use of macrolides in this particular setting.

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Since 1981 we have obviously seen the impact of AIDS across the globe. And one of the diseases that people can get especially when they are in the advanced stages of AIDS is an infection due to an organism called Mycobacterium avium and a very closely related organism called Mycobacterium intracellulare. These are caused by mycobacteria organisms that are related to the same organism that causes tuberculosis.

Disseminated disease widespread throughout the body usually occurs in patients with advanced AIDS. And the people that don=t have AIDS this same organism can cause symptomatic disease in the lungs usually in people with chronic obstructive pulmonary disease.

In patients with AIDS you can find this organism in almost any organ in the body. At autopsy people have had this in the liver, the spleen, and even organs like the eye and the brain this organism has been found in.

The disease consists of fever, drenching night sweats, weight loss and anemia. For all the world these people look like they have cancer. They feel terrible. They lose a lot of weight. And they have such severe anemia that they

often require blood transfusions.

We used to treat this with quadruple combinations of drugs including ciprofloxacin, amikacin, chlophazamine, rifampin, and ethambutol. And in truth those drugs didn=t even do a whole lot.

When that four drug combination was originally studied, it showed some diminution in symptoms but didn=t decrease the mortality of the disease at all. And those drugs were not easy to give. In fact chlophazamine can make patients actually turn a very interesting shade of purple. So those drugs were not without their side effects as well.

When clarithromycin was introduced in the early 1990's it had a dramatic impact on the course of this disease. And as part of a multi-drug regimen with ethambutol it actually, studies have shown it actually decreases the mortality in disseminated microbacterial disease.

So these drugs are the mainstays of therapy. And in fact both clarithromycin and azithromycin have been shown to prevent the disease as well, which has had a huge impact on patients with AIDS.

So if the organisms become resistant to either clarithromycin or azithromycin that has correlated with a poor outcome in those patients. So this is one of the settings where resistance to macrolides actually has been shown to be important.

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Pertussis is a very, very common disease. We don=t think about it this much in the United States because most children are immunized. This disease is caused by Bordetella pertussis and the illness is more commonly known as whooping cough.

Across the globe this disease causes 40 million cases a year, so it=s not uncommon, and results in 360,000 deaths. The disease is very striking when you see it. The kids cough and cough and cough to the point where they can=t breathe anymore. They will actually turn blue and become apenic and kids have been known to actually seize because they become so hypoxic while they are coughing so violently.

It=s most common in children and especially in under developed countries. But actually studies even done in the United States show that 20 to 30 percent of adults with prolonged cough for more than a week actually can have this disease.

The reason is it=s thought that immunity wanes from the vaccine that you get as a child by the time you become an adolescent so that you can become reinfected with this as well.

Again macrolides are considered the drugs of choice for the treatment of pertussis. And contrary to prior placebo controlled trials it appears that given early on that erythromycin can actually decrease the cough and have some impact on the disease. The alternative is trimethoprim sulfamethoxazole which is associated with its own risks of skin rash, et cetera.

So those are really the lethal infections for which macrolides are commonly used. And that is why we categorize them as critical in human medicine. But we didn=t even touch upon the things for which macrolides are even more commonly used out there in the community.

(Slide)

Macrolides are used in the prevention of recurrence of peptic ulcer disease due to Helicobacter pylori. And again this is another organism that was

discovered in our lifetimes. And actually while Nathan and I were at the University of Maryland we were there when Dr. Marshall decided to swallow a whole vat of Helicobacter pylori just to prove that this organism actually caused peptic ulcer disease.

I thought that meant he had another disease swallowing a whole bunch of bacteria. Not something that I would have wanted to do. But it=s actually important because macrolide resistance in Helicobacter is actually associated with recurrence of the disease. So this is another place where resistance may be important.

But where macrolides are really commonly used is as one of many alternatives in upper respiratory tract disease and pneumonia. One of these macrolides is the best selling antibiotic in the entire world. So that tells you how commonly macrolides are actually used in human disease.

(Slide)

Just to touch on, these are two slides that I added this morning because I thought this would be important to go through. And that is touch upon some issues related to macrolide resistance. Resistance to any antibiotic occurs by one of three mechanisms.

One is that an enzyme or some other mechanism may actually alter the drug itself. Two is that the drug cannot attach to its target for some reason. Or three is that the target is altered. So two of those three mechanisms are important when we talk about macrolide resistance. The first is that the macrolide may not be able to attach to its ribosomal target.

(Slide)

Macrolides work by inhibiting, by binding to the ribosome inside the

cell and preventing protein manufacture within the cell.

A mutation in the mefA gene actually causes an efflux pump to pump macrolides out of the bacterial cell so that they can attach to the ribosome and do their job. This efflux pump confers low level resistance to macrolides. But still that resistance is cross resistant to other macrolides. But these organisms may still remain susceptible to clindamycin and streptogramin and at least for some organisms they may remain susceptible to telithromycin as well.

I think it is important to point out something I didn=t say on the first slide. Telithromycin is not the drug we are talking about today, obviously tulathromycin. They sound very, very similar. I need I guess to be very articulate when I am saying this. They are very different drugs and I think we need to keep that in mind today. It is even in a different class in that telithromycin is a ketolide. Not a different class but at least a different chemical structure.

So the second way that mutation may occur is actually mutation at the target site of macrolides which is the ribosome. And this can occur by mutation in the ermB gene which confers high level resistance to all the macrolides again with this potential exception of telithromycin for some organisms. But also confers cross resistance to clindamycin and the streptogramins as well.

The clinical significance of macrolide resistance really varies with what organism you are talking about and what disease you are talking about. There are numerous articles out there in the literature that say we are not really sure what the significance of macrolide resistance is in upper respiratory tract diseases or even in community acquired pneumonia.

It=s not that macrolide resistance isn=t important. It may be that the break point that we use to define macrolide resistance may not be actually

accurate in describing who is going to fail and who is not going to fail treatment.

1. However, it does appear to be clinically meaningful in some diseases like disseminated Mycobacteriu avium complex disease and in peptic, reoccurrences of peptic ulcer disease due to Helicobacter pylori.

(Slide)

So in conclusion then macrolides --. Let me say one more thing about safety related to macrolides. A couple of weeks ago there was an article published in the New England Journal of Medicine which got a lot of press which said that erythromycin when given with some other drugs can be associated with an increased risk of cardiovascular disease. And I meant to put that on here as well.

The reason I wanted to mention that is that is really nothing new to the FDA. Those potential side effects have been in the label for erythromycin for years. We know that drug, drug interactions with macrolides are an issue. And we know that macrolides can also prolong the QT interval and can be associated with cardiovascular risk as well.

What that study was helpful in was sort of quantifying the risk of when you give macrolides and was probably good in reinforcing to clinicians that you need to be careful about what other drugs you give in addition to macrolides.

So you really, as with all drugs, you need to weigh the risks and benefits of giving that drug in a particular setting.

(Slide)

So in conclusion macrolides are important drugs in the treatment and prevention of human disease. According to the criteria that we discussed and have been presented at the anti-infective drugs advisory committee in the past macrolides are ranked as critically important given that they treat gastrointestinal illness and they are one of the sole or few alternative therapies for serious and life threatening disease in humans.

Macrolides are either the sole or one of few alternatives to treat a variety of infections in human beings including some that are not as life threatening as well. Thanks very much.

DR. TOLLEFSON: Thanks John.

(Applause.)

DR. TOLLEFSON: Are there any questions from the committee for Dr. Powers?

(No audible response.)

DR. TOLLEFSON: Okay. If not then I would like to introduce Dr. Mike Apley who will discuss the importance of macrolides in animal health.

Dr. Apley is a Doctor of Veterinary Medicine and he

also has a Doctor of Philosophy Degree. He is an associate professor in the Department of Veterinary Diagnostic and Production Animal Medicine at Iowa State. He is a diplomat of the American College of Veterinary Clinical Pharmacology. And he works with veterinarians throughout the United States concerning use of drugs in food animals as well as beef cattle health with a focus on feedlot cattle.

He teaches beef production medicine and participates in medicine and other production animal courses. His research interests include infectious diseases in cattle, application of drugs in food animals and antimicrobial research.

He is currently President of the Academy of Veterinary Consultants and Director of the Veterinary Antimicrobial Decision Support System Project. Thank you, Mike.

Importance of Macrolides to Animal Medicine

by Dr. Mike Apley

Diplomat, American College of Veterinary Clinical Pharmacology Veterinary Diagnostic and Production Animal Medicine

Iowa State University

DR. APLEY: Thank you and good morning. I realized that I may have a problem when I found I thoroughly enjoyed reading all the documents relating to this meeting and could

read them without going to sleep. They are very interesting subjects.

I was asked to speak today on the importance of macrolides in veterinary medicine. Currently we have one 14 member ring compound, erythromycin. And then two 16 member ring compounds, tylosin and tilmicosin, two macrolides which you will not find used in human medicine. Erythromycin is the one that directly overlaps for us.

I will make some --. These are the ones that are labeled for use in veterinary medicine. I will make a few comments towards the latter part of my talk on some of the newer classes of macrolides that are finding some use in companion animals in veterinary medicine on an extralabel basis.

(Slide)

I just wanted to make a quick point on macrolide susceptibility testing as we talk about our attempts to target our applications in veterinary medicine. I have taken the liberty of adapting macrolide break points from the NCCLS M31-A2 document.

And I have also included some extended range information that we are using for testing at Iowa State University with the caveat, I am not actually going to go through and present data but some of these actually get outside some of the standardized methods as we look at some

of the organisms we might be testing for. Only tilmicosin as NCCLS validated breakpoints for veterinary applications.

(Slide)

And these are for bovine respiratory disease, Pasturella hemolytica and these, excuse me, and swine respiratory disease for these pathogens. It=s now called Mannheimia haemolytica, that would be and this is incredibly small. I realize. I apologize. This will be on the website. The Mannheimia haemolytica breakpoints are also applicable to Pasturella multocida.

We use an erythromycin breakpoint that is adapted from human medicine. Tylosin is directly tested with a set of breakpoints that I have been unsuccessful in determining exactly where those came from. I=ve had numerous conversations with people. But it will be tested. So we have one with validated breakpoints for applications. One of the things -- in veterinary medicine.

One of the things that is going on within the NCCLS group which we have members of here today is actually looking at trying to develop pharmacokinetic, pharmacodynamic based breakpoints with clinical data possible for ones where we don=t have sponsor supported validated breakpoint.

(Slide)

I thought the best way perhaps to do it was to go through label indications. We have a widespread of label

indications of macrolides in veterinary medicine. Almost solely in production animals.

So I have pulled these out of the Compendium of Veterinary Products. It=s very handy to go in and search the actual labels. You could also have a very authoritative source in the Green Book. I used this one.

And I want to make it very clear that a listing of the label application does not necessarily indicate the frequency or extent of the use in animals. So we are going to go through applications.

And we will also go through some of the national animal health monitoring system data that was from the 1999 B-feed lot study and the 2000 swine study to give us an idea of some of the applications of these products.

(Slide)

So let=s start out with tylosin label applications in food animals. In beef cattle and non-lactating dairy cattle we have label applications for the bovine respiratory disease complex. I left disease out of the complex there. And in this case its Pasturella multocida and what would now be called Actinomyces pyogenes. I have left these as they actually are on the label.

Foot rot which is necrotic pododermatitis. It=s an infection by the antirobic agent Fusobacterium necrophorum which can be a serious problem in cattle at certain times of

the year. It=s primarily associated with wet conditions but will be surprised by them in some dry conditions also. And this is a very important application of the macrolides and in metritis.

The bovine respiratory disease complex is one of our primary challenges. We will come back to that and talk a little bit about it as we look at the NAHMS data. In the feedlot practice that I am most familiar with we attribute about 75 percent of our morbidity and about half of our mortality to respiratory disease in these animals.

(Slide)

Here are some applications in swine. Arthritis, swine pneumonia, erysipelas, and acute swine dysentery. The swine dysentery would be a very important application. Erysipelas is one where we have very good effect using penicillin G and that would be one of the primary drugs there.

(Slide)

A widespread application of tylosin phosphate in the feed for beef cattle. And we will talk a little bit about some of the NAHMS estimates of the breadth of that application is for reduction of incidence of liver abscesses, Fusobacterium necrophorum again, and Actinomyces pyogenes in feedlot cattle.

(Slide)

And again we are in the feed additive for tylosin. We have moved over to feed additives as opposed to injectable. Swine there is a label for increased rate of weight gain and improved feed efficiency, swine ileitis caused by Lawsonia intracellularis and for prevention of swine dysentery caused by serpulina hyodysenteriae. It=s two very important applications of that product in swine.

Also maintaining weight gains and feed efficiency in the presence of atrophic rhinitis and treatment and control of swine dysentery following initial medication with tylosin soluble in drinking water. And we will talk about the water applications.

So in this case with this compound we are able to apply it injectably through the feed as a feed additive or in the water. And it=s very important to make sure that everyone is aware that in veterinarian medicine extralabel use in the feed is illegal. So any use other then specified specifically on the label for feed additive products is outside of the law. And it=s not permitted.

(Slide)

There are some poultry applications on the label. Increased rate of weight gain and approved feed efficiency in chickens. Improved feed efficiency in laying chickens. And for the treatment of Mycoplasma gallisepticum in broiler and replacement chickens.

(Slide)

Now on to tylosin tartrate water medication, let me jump back up again. And that was the last of the feed additives. In water medication in swine we also have the label for swine dysentery. So we have injectable feed and water medication.

One of the very important things in swine medicine is that there are times when it=s necessary to treat the entire group and individual animal injection is prohibitive both in time that it can be applied in, labor, and disrupting the pigs, the stress of going through the entire population of the pigs. So the ability to apply medications through the water or through the feed is very important.

(Slide)

Water medication in chickens, again, Mycoplasma gallisepticum, the chronic respiratory disease, and control of chronic respiratory disease also by Mycoplasma synoviae are on the label.

(Slide)

And for turkeys there is a label for maintaining weight gains and feed efficiency in the presence of infectious sinusitis.

(Slide)

This is one that has come on in the last few years. Tylosin tartrate has been cleared and is included in one

line of cattle growth promoting implants by inclusion of an additional tylosin tartrate pellet containing 29 milligrams of tylosin with the hormonal implant which can help to reduce injection site reactions and infections at the site of that implant placement. Those implant lines are available either with or without this tylosin additional pellet.

(Slide)

That wraps up the label applications for tylosin. We will come back a little bit more to some of the national animal health monitoring system data that is included later in the talk.

This is timicosin, one of our 16 member ring compounds, and again this one is not used in human medicine. It is labeled in cattle and sheep for the treatment of bovine and ovine respiratory disease associated with Mannheimia haemolytica. And also in cattle it is indicated for the control of respiratory disease in cattle at high risk of developing BRD also associated with Mannheimia haemolytica.

So this compound has both a treatment and a control claim. But the control claim is only for cattle. Treatment for both cattle and sheep.

(Slide)

In swine it is approved only as a feed additive. It is not injectable. In cattle and sheep it is approved

only as an injectable. This drug if injected in swine would be fatal. If given through the feed to control the amounts it is not fatal and is a safe and effective therapy for swine respiratory disease, actinobacillus pleuropneumoniae and Pasturella multocida.

Now this drug is also unique in that it is our only drug currently that is dispensed and used under a veterinary feed directive that must be issued by a licensed veterinarian in order for this drug to be included in the feed as a therapeutic agent for the pigs. So a unique role of that macrolide.

(Slide)

Lastly, the last one we will cover with label applications in food animals is erythromycin. And in beef cattle we have approvals for shipping fever, pneumonia and pneumonia-enteritis complex. And as you go back to some of the older approvals it=s one of our challenges for example as we work on the bad system of, you know, how the language and applications used in older approvals kind of come in as we have evolved. So you may see some differences in how things are referred to here.

But also for foot rot. And it has the stress and metritis. The thing about erythromycin and tylosin that we always keep in mind especially in cattle is that we can have significant injection site reactions with these products.

Tilmicosin is given sub-q, subcutaneously.

Erythromycin and tylosin are labeled for inter muscular injection. They may be used sometimes on an extralabel manner intravenously. You have to really watch what you are doing. But they are used carefully and placed only in the neck for beef quality assurance purposes. But again going back on foot rot, tylosin is probably one of our most effective compounds for that.

(Slide)

In dairy cattle we have pneumonia, foot rot, metritis, shipping fever, and stress also. And this is one of our few compounds that is a parenteral injectable compound. It=s actually labeled for pneumonia in dairy cattle. We have some others that may be used. It=s not as wide as the breadth of the compounds that are approved for respiratory disease in beef cattle, cattle not intended for dairy production.

(Slide)

In swine for erythromycin we have pneumonia, rhinitis, and bronchitis. Specifically for sows metritis and leptospirosis at the time of farrowing. And in baby pigs one week of age or older it is labeled for scours. In my experience we would not look to the veterinary labeled macrolides in swine and beef cattle anyway as a drug of choice for inner-bacteria ATA infections, E. Coli or

Salmonella would not be one we would reach for in those compounds.

(Slide)

In sheep we do have a label of prevention of dysentery in newborn lambs and upper respiratory infections. Whenever you see a sheep label you are seeing a rarity in veterinary medicine. We have very few products that are actually labeled and approved for use in sheep at the current time.

(Slide)

Also available is an erythromycin mastitis syringe. And you will see it=s split into what we call wet cows and dry cows. That means lactating cows and cows that are in the dry period between lactations, and labeled for various staff and strep organisms involved in mastitis in cattle.

(Slide)

Now erythromycin is also available as a feed additive in chickens and turkeys. It is labeled as an aid in the prevention and reduction of lesions and in lowering severity of chronic respiratory disease.

In chickens an aid in the prevention of infectious coryza. And in chickens and turkeys as an aid in the prevention of chronic respiratory disease during periods of stress.

(Slide)

There is also a water medication solution. And this is for the aid and control of chronic respiratory disease associated with Mycoplasma gallisepticum. And then in replacement chickens and chicken breeders an aid in the control of infectious coryza due haemophilus gallinarium.

(Slide)

And in growing turkeys as an aid in the control of bluecomb caused by organisms susceptible to erythromycin.

(Slide)

So I have selected some information, beef and swine. You also find a summary of this I noticed in the submission document from the sponsor, and I noticed that the data was very similar that we had selected. This is from the National Animal Health Monitoring Service and there is a website that you can click to and find the index to go to the swine and the beef.

And you will notice this is in the handouts for those of you who have handouts because I am completely incapable of leaving a presentation alone up to the last minute. But this will be included on the website. I apologize for that.

(Slide)

So the beef feedlot data is from a survey conducted in 12 states. And this would represent approximately 84 percent of the U.S. feedlot inventory. And as a rough

number varying from year to year we would have somewhere around 28 million head of cattle sent to harvest that are fed cattle.

This survey estimated that about 14.4 percent of all cattle placed in feedlots develop respiratory disease such as shipping fever after arrival. We talk a lot about treating calves in feedlots but in reality probably 60 or 70 percent of the cattle placed on feed are yearlings up around a year of age or so and then roughly about 30 percent would be what we would classify as a calf.

(Slide)

So approximately two-thirds of the metaphylaptically treated cattle or cattle administered in antimicrobial because they are at risk of developing BRD during early stages about two-thirds of those receive tilmicosin. And these cattle represent about six point seven percent of the cattle placed on feed and about ten percent would then receive those treatments.

(Slide)

This survey reports that tilmicosin, florfenicol and tetracyclines were the primary antimicrobial drugs for the initial treatment of BRD. All feedlots included tilmicosin was reported as the primary drug for that in about 31 percent or one-third of the groups. Florfenicol about 21.9 percent and the tetracyclines roughly right in there

around 20 percent also.

(Slide)

So what percent of feedlots used to follow antimicrobials in feed or water as the health or production management tool by antimicrobial used and by feedlot capacity. So that was a general heading that included other drugs that may go through the water or feed. So that heading doesn=t necessarily mean both of these for that way.

But of the smaller yards, 1,000 to 8,000 head capacity. About 12.1 percent reported using tylosin. About 41 and a half percent of the ones of 8,000 or more capacity reported using tylosin in that manner.

(Slide)

For all cattle placed in --. Now this is all cattle instead of all feedlots. So this is about what percent of the cattle by asking each yard how many of their cattle would be subjected to that.

In yards of 1,000 to 7,999 head capacity about 16.1 percent of the cattle were estimated to have received tylosin in the feed or water. It would be feed primarily. 8,000 or more capacity about 47 percent. Putting all of the feedlots together about 42.3 percent of the cattle were estimated to have received tylosin in other than an injectable format.

(Slide)

About how long was it used? Feedlots that used the

specified antimicrobials in the feeder water, so in this case we are talking about tylosin estimated about how long those animals would be exposed to that antimicrobial by weight class. And for cattle less than 700 pounds at the time of arrival, and this would get down more into our calves, they estimated around 145 days. 700 pounds or greater at the time of arrival, getting into the yearlings, about 138 days.

(Slide)

That concludes the beef cattle data that I selected. The NAHMS swine data, this was as survey conducted latter part of 2000, first part of 2001. And it was conducted in 17 states representing about 94 percent of the U.S. pig inventory.

(Slide)

I am going to start out with the grower finishing pigs. There seems to be more extensive information there on that. This is the percent of sites that give the following antimicrobials in water. So we are talking about in water to grower finishing pigs.

If we combine all uses we have about four percent. Four percent would be administering tylosin through the water. And respiratory disease treatment was 1.2 percent of the sites. Tylosin 2.7 percent for enteric disease split out separately from 4.1 percent for any reason. And again these are percent of sites not necessarily percent of pigs.

Percent of sites.

(Slide)

Now we are going to talk about injection in grower finisher pigs. So these would be pigs that have come out of the nursery into the final production phase for growing out to being finished hogs. For disease prevention about three and a half percent received tylosin by injection. This is sites utilized for injections. The highest one was respiratory disease treatment at 13.8 percent. And for any reason about 30.7 percent, roughly 31 percent of the sites administered tylosin by injection for any reason.

(Slide)

Now we are switching to the last one which is in feed. So this is tylosin in feed. They listed them by category. For any reason it now is 56.3 percent. Average number of days and feed for all reasons was 62, 62.3 days. Ranged everything from growth motion, disease prevention, respiratory disease treatment was actually the lowest, and enteric disease treatment. 31.3 percent of the sites reported in the last six months using tylosin in the feed for the purpose of growth promotion whereas 56 percent overall percent of the sites reported that.

(Slide)

The nursery age pigs data on there was quite a bit more limited. Sites with nursery age pigs, and this reported

the percent of sites that used the following antimicrobials or feed animals. And the feed of nursery age pigs, and in the actual table title it says Afor growth promotion.@ But some of these such as tilmicosin would not have that on the label. They are for therapeutic use. So the table has to include both growth promotion and therapeutic use.

At this time when this one was taken tilmicosin was 3.6 percent of the sites. I am not sure if that would be at that low of a level today. I don=t have data to say different. But this was earlier back on in the release of that product. Tylosin, 23.2 percent. And the average days on those were in the upper 20's. And then a combination product tylosin incelphamesazine* about 6.6 percent of the sites.

(Slide)

So that concludes the food animal related comments. I wanted to talk a little bit about some extralabel uses of macrolides in veterinary medicine. And I have very limited use on here. It may just be limited use. Very may be too extreme. And I tell you right away on these I don=t have a way to quantitate these. So now we are just basically letting you know that they are used.

(Slide)

Oral use to dogs and cats, very limited. Significant gastrointestinal upset is possible. There are

places where the spectrum may be appropriate but we are always aware of that. Of course when we get into non-ruminant herbivores such as horses and rabbits with the macrolides we currently use in veterinary medicine we stay away from them because of potential gastrointestinal upset.

(Slide)

Now azithromycin is one that has had pharmacokinetic well characterized in companion animals. And there is some use, especially in dogs. Clarithromycin has also been evaluated. And we do tests for some of these in more refractive isolates sent to our microbiology labs in these companion animals.

(Slide)

I think every veterinary student when they come out of school when told that a foal has respiratory disease due to Rhodoccus equi can recite rifampin and erythromycin as the drug combination of choice. One of the things that is being found now is they are having less and less clinical success with that combination especially on some brood mare installations.

So there is just in the 2004 Journal of Veterinary Internal Medicine been a study published comparing clarithromycin/rifampin, azithromycin/rifampin and erythromycin/rifampin for this application and reporting that the clarithromycin/rifampin is the superior combination of

that when we run into foals who were reactive to erythromycin/rifampin combinations. Some example of one use there. With that that would conclude my comments.

DR. TOLLEFSON: Thank you, Mike.

(Applause.)

DR. TOLLEFSON: Are there any questions for Dr. Apley from the committee?

DR. LEGGETT: Two questions. What is the average length of time for therapy of bovine respiratory in swine diseases? Is it like seven days, ten days? And then the second question is pharmacokinetically what are serum levels when it=s given as a food additive or water additive in terms of the controlled prophylaxis aspect as opposed to treatment?

DR. APLEY: Okay. The first one on duration of therapy in the two species, injectable therapy in both species would be down in that three to five day range. Cattle, the routine if you have your ideal situation you would get 70 to 80 percent of them after the first three to five day course of therapy depending on the drug. We now have drugs that go out to seven.

You would then get about a 50 percent treatment response rate with second and third treatments. We usually discontinue treatment after that third treatment which depending on your drugs and the regimen may be anywhere from nine to 12 to 13 days maximum. The vast majority would be

three to five days.

Swine, the water medication duration reported I think was in the six to seven day range for most of them if they go through the water. Injectable would be a shorter period also.

In pharmacokinetics of macrolides serum concentrations is a real interesting subject. When you try to model off of serum concentrations for macrolides, for many of our macrolides, you are somewhat frustrated in making predictions off that. You start looking at tissue concentrations which brings its whole other realm of uncertainties.

For example with tilmicosin given to swine extremely, extremely low serum concentrations but still effective for the disease based on tissue activity of the drug. Bioavailability of erythromycin is fairly decent when that goes through there.

DR. OHL: Question related to off-label use. While there are quite a few labeled indications so as maybe there isn=t much off-label use, but I was just wondering if you could say by a proportion or by percentages how much in either cow or swine would be considered off-label?

DR. APLEY: Well, the feed would be zero. It should be zero. Better be zero. People are watching me here.

(Laughter)

DR. APLEY: I think it really is. People are very aware of that and will follow that. In water I would have a hard time estimating on that. I would rate the macrolides as probably one of the higher on labeled use compounds we have. Tilmicosin when you look at the label use of that would be extremely high where we use it within label. One of the things there is we get up into the higher cost drugs. But respiratory disease would be a very primary target of that.

So yes, I would put that class as one that is fairly highly used on-label. Maybe some other input.

DR. WADDELL: Mike, I just say that there would be very little off-label use. There may be some extralabel use when it comes to other pathogens that were not on the label. For instance tylosin water soluble for use as a treatment as Lawsonia for the proliterative enteritis in pigs.

But the other thing that you didn=t mention, Mike, was for pigs especially with the advent of the Lawsonia vaccine the use has dropped precipitously.

Another thing, Mike, I would like to ask you is in our course of practice in beef cattle and swine we have been unable to attain the injectable form of erythromycin for maybe six to eight months now. And I guess I haven=t figured out why that is. But we are not using it because of that. And I think the other practitioners are in the same boat.

DR. APLEY: Thanks.

DR. TOLLEFSON: Any other questions for Dr. Apley? Go ahead Dr. Ohl.

DR. OHL: Could you just clarify for me again which drugs and which labels would be prescription only versus which would not require a veterinary prescription?

DR. APLEY: Tilmicosin is prescription only, an injectable. The Pulmotil again is the veterinary feed directive only through a licensed veterinarian. Erythromycin and tylosin would both be OTC. Correct?

DR. WAGES: Except extralabel use.

DR. APLEY: Right. And the feed, there is no extralabel use in the feed. But the injectable components would both be available OTC. Now when they are available over the counter they are legally used by a producer only strictly according to label. And any extralabel use is only allowed within a valid veterinary client patient relationship through a prescription.

DR. TOLLEFSON: Thank you.

(Applause.)

DR. TOLLEFSON: Dr. Scott Brown will present the product that is the subject of today=s meeting. Dr. Brown is a Diplomat of the American College of Veterinary Clinical Pharmacology. And his current position is Senior Director in Metabolism and Safety at Pfizer Animal Health. He is

responsible for pharmacokinetic drug metabolism, human food safety, environmental safety, and microbial safety studies in support of new drug discovery and new product registration.

Tulathromycin Solution for Parenteral Injection

for Treatment of Swine and Bovine Respiratory Disease

Microbiologial Effects on Bacteria of

Human Health Concern: A Qualitative Risk Estimation

by Dr. Scott Brown

Senior Director, Metabolism and Safety

Pfizer Animal Health

DR. BROWN: Thank you very much. It=s a pleasure to be here. We have been waiting for this day for quite a number of weeks now. And we are looking forward to the discussion.

The role that I have here is to provide to you an overview of the product, the usage, and the microbial safety assessment through the qualitative risk assessment Guidance 152 that the sponsors provided and submitted to CVM.

Much of the proprietary data that is being presented here and will be discussed here has been submitted to the agency for their review and understanding. In addition we provided to you the briefing document which includes not only our own internal documentation of the risk assessment but in addition the external references that relate to that.

(Slide)

I would like to thank Dr. Apley and Dr. Powers for their really great background for this discussion. So we are going to get into the nitty gritty a bit. I would like to provide for you first of all once again a bit of a risk analysis terminology from Guidance 152. We will provide a hazard characterization for tulathromycin.

I will provide to you an overview or a summary of the tulathromycin risk estimation before we then go into a more detailed discussion of the qualitative risk estimation. That will include the release assessment, the exposure assessment, and the consequence assessment, followed by the overall risk estimation. And then finally our conclusions.

(Slide)

It is important to provide a back drop for what this product is intended to have as indications. The indications upon approval will be for the treatment of bovine respiratory disease associated with the label pathogens and for the control of bovine respiratory disease in cattle at high risk of BRD. It will also be approved for the treatment of swine respiratory disease associated with the label pathogens.

It will be indicated as a single parenteral injection by prescription only to both cattle and swine. And it will not be used in lactating dairy cows or pre-ruminant

calves.

(Slide)

Now first of all a bit of an overview of the risk analysis terminology under FDA/CVM Guidance 152. That has already been described to a certain degree. Here you see the title. We affectionately call it our microbial safety file guidance. That was released a year ago. And it=s the reason why we are here today.

(Slide)

This is a schematic diagram of the qualitative risk analysis under Guidance 152. It=s important to make sure that we have a good understanding of the terminology. So I will first of all talk about the release assessment. And this is verbatim from Guidance 152.

> AThe release assessment should describe those factors related to the antimicrobial new animal drug and its use in animals that contribute to the emergence of resistant bacteria or resistant determinants in the animal.
>
> The release assessment should also estimate qualitatively the probability that release of the hazardous agent would occur.
>
> For the purpose of this assessment process the boundaries of the release assessment span from the point the antimicrobial new animal drug is administered to the

food producing animal to the point the animal is presented for slaughter or the animal derived food is collected.@

AThe exposure assessment describes the likelihood of human exposure to the hazardous agent through food-borne exposure pathways. The exposure assessment should estimate qualitatively the probability of this exposure to bacteria of human health concern through food related pathways.@

AThe consequence assessment describes the relationship between specified exposures to a biological agent, that is the hazardous agent, and the consequences of those exposures to human beings.

For the purposes of this risk assessment FDA has decided that the potential human health consequences of exposure to the defined hazardous agent may be estimated qualitatively by considering the human medical importance of the antimicrobial drug in question.@

Finally the three of those are brought together for the overall risk estimation.

AThe overall risk assessment of the risk associated with the proposed use of the drug and the target food producing animal following the integration of the release assessment, exposure

assessment, and consequence assessment.

The risk rankings represent the relative potential for human health to be adversely impacted by the emergence of antimicrobial resistance associated in a food-borne pathogen with the use of the drug in food producing animals.@

Now there are a few additional terminologies that need to be described.

(Slide)

And so that is here in this next slide where we talk first of all --. Sorry. We will first of all focus on Campylobacter. The reason this risk estimation the risk analysis is focusing on Campylobacter is because Campylobacter is treated in human beings with macrolides. It=s important to recognize that we are not addressing Salmonella and E. Coli because macrolides are not used to treat Salmonella and E. Coli.

Macrolides are also not used to treat enterococcal infections. And macrolide resistant determinants are possibly transferred in Enterococcus but tulathromycin activities is attenuated in the milieu where enterococcal organisms are found. And we will describe that in a few minutes.

(Slide)

Now the hazard under consideration today is the

human illness that is caused by antimicrobial resistant bacteria attributed to an animal derived food commodity and treated with a human antimicrobial drug of interest.

Specific to this discussion today we are talking about Campylobacteriosis caused by a macrolide resistant Campylobacter attributable to consumption of beef or pork and with that disease Campylobacteriosis being treated with the macrolide.

(Slide)

The hazardous agent is the antimicrobial resistant food-borne bacteria of human health concern. In this case macrolide-resistant Campylobacter. Again, that are in or on a food producing animal, beef, cattle, or swine and are a consequence of the proposed use of the new animal drug, in this case tulathromycin.

(Slide)

The specific risk is in the probability that human food-borne illnesses is caused by that antimicrobial drug resistant bacterium, in this case campylomacroide resistant Campylobacter attributable to an animal drive food commodity, beef or pork, and treated with the human antimicrobial drug of interest, a macrolide.

Now it is important to recognize that this terminology may be slightly different then usual casual use terminology. We will be confining ourselves to the specific

terminology of Guidance 152.

(Slide)

So I would like to turn our discussion now to an overview of the summary of the risk estimation for tulathromycin.

(Slide)

The sponsor believes that there is a low probability that macrolide resistant Campylobacter will be selected as a result of the proposed tulathromycin use. As I will show later there is attenuated microbiological activity of tulathromycin in colonic contents due to low pH in the colon and due to binding to fecal substrates.

Macrolide resistance occurs by mutation in Campylobacter. That frequency of spontaneous mutation is low and is not apparently impacted by tulathromycin. And there is no evidence of transferable macrolide resistance, that is genetic transfer material. Finally there is no unique resistance mechanism that has been detected.

(Slide)

Furthermore the proposed use of tulathromycin supports a low release. It=s parenteral use under veterinary prescription only. It will be administered to individual animals, not pre-ruminants. It will be a single injection that will assure a full course of therapy. There is no requirement for repeated administration. And recognize that

the treatment of BRD and SRD usually occurs at a time substantially before slaughter.

If you look through these criteria of usages you can see that these are highly aligned with the judicious use principles that have been supported by FDA, CVM, as well as the American Veterinary Medical Association.

(Slide)

We believe that the selection pressure that would be exerted by tulathromycin will be no greater than that for macrolides currently used in livestock. Because of that attenuated activity in the colonic contents and feces, because of the mechanism of action and cross resistant profiles in food-borne pathogens are the same as current use macrolides.

Because macrolides are already used for swine respiratory disease and bovine respiratory disease. Because macrolides resistence in Campylobacter is acquired by mutation and not genetic acquisition. And that despite that greater than 30 years of macrolide use in livestock, and as Dr. Apley showed by a variety of routes administration and a variety of indications, macrolide resistant Campylobacter jejuni from humans is still low, in the range of one to three percent with no trends being observed over time.

(Slide)

With respect to the exposure assessment, we will

come back to this particular table in the latter part of the discussion. But this is a table that comes out of Guidance 152. And it talks about the probability of human exposure to Campylobacter. And it takes two factors to come up with that probability.

A consumption rate of per capita consumption of the commodity being low, medium, or high. And the amount of contamination of that commodity with the food-borne organism of concern, again categorizes high, medium, or low.

(Slide)

In the case of beef, consumption is considered high in the United States. The amount of beef contamination is described as low in the Guidance document and that combination of high consumption and low contamination yields an overall exposure recommendation for beef of medium.

(Slide)

Guidance 152 also provides a default position for swine which indicates a high consumption of pork and indicates a high amount of pork contamination although that is at the carcass level and not at the retail level. If you were to use that same default categorization that would yield an overall exposure assessment of high.

(Slide)

The sponsor proposes that that should be modified because recent data at the retail level indicates a

Campylobacter contamination in retail pork is low, less than five percent. And that would provide that overall categorization of low according to Guidance 152.

Therefore a high pork consumption and a low pork contamination with Campylobacter again yields a medium exposure recommendation.

(Slide)

Regarding consequence assessments, as Dr. Powers described, macrolides are defined in Guidance 152 as critically important for human medicine. And he very eloquently described the reasons for that.

(Slide)

If you then take those three assessments, release, exposure, and consequence and define the release assessment as low, exposure assessment as medium, and consequence assessment as critically important that yields a high overall risk estimation according to the algorithm in the Guidance. That is the case for beef. That is the case for swine.

It is also important to recognize that the algorithm creates a high risk estimation regardless to what the release assessment is or the exposure assessment is if the consequence assessment is defined as critically important. And I will come back to that in the more detailed discussion.

(Slide)

So the sponsor conclusions with respect to microbial safety of tulathromycin are that the proposed label use of tulathromycin, includes the management considerations of prescription status. An inherent low extent of use due to parenteral single dose administration, and this advisory committee review. And macrolide resistance in Campylobacteriosis in human beings is currently being monitored by the National Antimicrobial Resistance Monitoring System.

With these management considerations approval of the proposed indications for injectable tulathromycin in cattle and swine poses no appreciable risk to public health with respect to microbial food safety.

That concludes the summary or the overview of the risk estimation. I would like to go into more detail then with respect to the qualitative risk estimation beginning with the release assessment and specifically within that discussing the chemistry and disposition of tulathromycin.

(Slide)

Tulathromycin is defined in the subclass of triamilides in the major class of macrolides. As you heard earlier macrolides is a very broad class of antimicrobial. Ketolides are one subclass. Triamilides are also another subclass.

Tulathromycin is defined as a triamilide because of

the three basic amino groups that I have shown here in circles. And that creates a highly charged form and solution. The pks are shown there.

The important part is that the chemical structure of tulathromycin aids in the penetration of the outer membrane of gram-negative bacteria. Like other macrolides as a whole they are lipophilic when unionized. And tulathromycin specifically is metabolically stable.

(Slide)

It=s mechanism of action is similar to other macrolides. That is it inhibits protein synthesis. It binds to the 23s ribosomal RNA of bacterial ribosomes. It competes for erythromycin binding. Specifically it binds to erythromycin sensitive ribosomes but if there are erythromycin resistant ribosomes, those ribosomes do not bind tulathromycin.

There is broad spectrum activity against bacterial respiratory disease pathogens in swine which is not an aitme of discussion for this particular microbial safety assessment.

(Slide)

In a variety of food-borne microorganisms that were evaluated for the MICs, you can note that the MIC-90's for these food-borne organisms is remarkably high and in fact even for those that do not have an MIC-90 because of the

number of strains you can see that the range is quite high as well.

(Slide)

Not only are the MICs of these food-borne microorganisms relatively high but in addition it=s an important phenomenon of tulathromycin to look at the effective pH on microbiological activity.

The normal NCCLS Quality Standard Guidelines indicate that the pH for testing of Campylobacter, or sorry, testing of these organisms should be in the range of 7.2 to 7.4. And you can note the MICs of these organisms at pH of 7.4 and 7.2.

It is important to recognize the colonic pH is lower than that pH noted here. And in fact it can be substantially less than 7.0. You can note for these organisms that the MIC values for tulathromycin are substantially elevated such that even in a pH of 6.5 the MICs are greater than 128.

It=s an important consideration when we consider the fecal excretion of tulathromycin.

(Slide)

Now just a quick overview about the pharmacokinetics of tulathromycin in cattle and swine. First of all the absorption is very rapid with the peak concentration in plasma occurring in about an hour. The half

life is approximately 90 hours in plasma. And you can see the very large volume of distribution of tulathromycin which is again consistent with that of other macrolides.

The availability after parenteral injection approaches 90 percent. At studies looking at lung homogenic concentrations the lung homogenites are about 60 to 70 fold higher in concentration in tulathromycin than plasma concentrations. And data strongly support a phagocytic cell accumulation of tulathromycin.

(Slide)

For swine the picture is remarkably similar. Again a peak concentration occurring at approximately one hour after dosing. Approximately a 90 hour half life. Again a very large volume of distribution which indicates large tissue disposition and the bioability approaching 90 percent.

And again in swine lung homogenic concentrations of tulathromycin are approximately 60 fold higher than concurrent plasma concentrations. And once again phagocytic cell accumulation is strongly expected and noted in some studies.

(Slide)

Now with respect to microbial safety excretion in the gastrointestinal tract is an important consideration. Thirty to 60 percent of the total dose is excreted in the feces depending upon the species. Peak concentrations range

from 30 to 100 micrograms per gram of material with the average being in the 20 to 40 microgram per gram range. Ninety percent of that is unchanged drug chemically.

However tulathromycin activity in colon contents in feces is substantially attenuated. As I mentioned earlier the pH has a substantial affect on the microbial activity of tulathromycin. Furthermore there is a significant percentage greater than 70 percent that binds the fecal solids.

A study done looking at the in vitro activity of tulathromycin when sterilized feces were added to growth media show that there was a substantial reduction in activity when that situation occurred for E. Coli, Enterococcus, bifidobacterium, and Fusobacterium.

(Slide)

So with respect to chemistry and disposition it is important to recognize that there is low in vitro activity against enteric food-borne pathogens, particularly with respect to the activity found at pHs in colonic contents.

Couple that with high fecal binding of the drug and the fact that the concentrations in colonic contents are transient would indicate that the exposure in those food-borne organisms is relatively low.

(Slide)

I will turn our attention now to resistance mechanisms, genetics, and location. And again Dr. Powers

provided a very good overview of the mechanisms of resistance for macrolides with target site modification, drug inactivation and efflux pumps being the major mechanisms of resistance.

It=s important to recognize that the erm gene discussion that he had is the target site modification that is inducible or constitutive. And it turns out that although erythromycin induces the inducible form of the erm gene tilmicosin and tulathromycin do not induce the inducible form of the erm gene.

Now while these are overall mechanisms of macrolide resistance it=s important then to zero in on the resistance mechanisms in the organism of interest.

(Slide)

Before we get there I just want to note that macrolide resistant genes can be transferable. However there has been a study done internally which showed that there was no difference in the transfer frequency when tulathromycin was added indicating that that transfer frequency in certain bacteria is not enhanced in the presence of tulathromycin.

(Slide)

Now with respect to transferable resistance determinants it=s important to recognize that those transferable genes for macrolide resistance have not been reported in Campylobacter. Unlike other bacteria the erm

gene resistance has not been reported in Campylobacter. Macrolide resistance is due to mutation only in extensive studies that have been done looking at Campylobacter resistance.

(Slide)

Constitutively expressed erm genes confer cross resistance to macrolides, lincosamides, streptogramin B, as Dr. Powers described. And it would be anticipated that tulathromycin and tilmicosin have similar cross resistance profiles for human pathogens. But recognize that both of those are weak inducers of the erm gene.

It=s important to recognize that efflux pumps are a mechanism for export of macrolides out of bacteria. Efflux pumps tend to be relatively non-selective and so it would be expected that tulathromycin would be able to utilize those, or be a sub-straight for those export pumps when they would be present in the bacteria.

Campylobacter have high erythromycin MICs. When they do that they would also have high tulathromycin MICs. That is to say there is extensive cross resistance between erythromycin and tulathromycin in Campylobacter.

(Slide)

A study was done looking at a number of strains of E. Coli, Salmonella, Enterococcus, and Campylobacter looking at the frequency of point mutations. And it was found that no

tulathromycin or macrolide resistant mutants were found at the frequencies expected for spontaneous mutation in all those species that were exposed to tulathromycin.

And the spontaneous frequency for resistance is anticipated to be less than ten to the negative ninth, these studies confirm that frequency.

(Slide)

So in summary macrolide resistance in Campylobacter, there is target site modification that has been shown to occur. It has been shown by mutation only in Campylobacter and not by genetic transfer of material. There has not been drug inactivation that has been shown to occur with Campylobacter either by mutation or genetic transfer. There is some evidence of drug efflux pumps that have occurred by mutation in Campylobacter not by genetic transfer. And in fact those efflux pumps that transport macrolides in Campylobacter are remarkably rare.

(Slide)

So conclusions. The three types of macrolide resistance mechanisms, once again, there are many of the genes that are transferrable, erm genes being the most notable one. However, that is not been the case with Campylobacter in that the Campylobacter macrolide resistant Campylobacter occurs via the chromosomal mutation and the frequency of that is very low in the order of less than ten

to the negative ninth.

(Slide)

Turning our attention now to resistance selection pressures in the field and you will see some significant overlap between what I am saying here and what Dr. Apley has presented. So I might fly through them a little bit faster.

(Slide)

As an example though I would like to show you bovine respiratory disease. Bovine respiratory disease is a clinical diagnosis. The people who are the most familiar with the animals and the feedlots will be able to notice by visual inspection a normal healthy animal.

They can also then recognize by the physical appearance and the posture an animal that is depressed, an animal that has labored breathing. And when those clinical signs are observed in the feedlot pins those animals are then brought in and they are inspected more carefully physically. And a physical diagnosis and a clinical diagnosis of BRD is determined at that point. Similar kinds of clinical diagnosis are done for swine respiratory disease as well.

(Slide)

Now again I will take some data from the 1999 USDA NAHMS survey presented a little bit differently. You might ask yourself the question why is this 1999 and why is this

2000 and why aren=t there more recent data.

Well it turns out USDA NAHMS conducts their surveys on every five year basis for that particular commodity group. So in fact this year they are once again looking at feedlot cattle and those data will be available a year from now or so.

(Slide)

As Dr. Apley showed approximately 15 percent of cattle that arrive in the feedlots will develop respiratory disease. And then the other diseases that are identified are significantly farther back in the incidence rate. I want you to also recognize that that means that there is almost 80 percent of the animals that come into feedlots that do not get sick.

As Dr. Apley said, I think he said, it=s roughly three quarters of the animals of morbidity in feedlots is attributable to BRD and about half of the deaths in feedlots are attributable to BRD. There are some documents and data that provide these percentages here.

If you think about the cost to the industry considering that there are currently approximately 23 million cattle in feedlots and the residence time in feedlots is about six months, if you estimate 15 percent BRD on 23 million cattle that would say that somewhere in the neighborhood of three and a half million cattle in feedlots

are affected by BRD. You can imagine what the costs are to the producers for that degree of morbidity and mortality.

(Slide)

Now the swine data from 2000 from the USDA NAHMS program, producer identified causes of death were queried in that large survey. And it was found that respiratory disease accounted for 40 percent of the grower finisher deaths in swine according to producers. The nursery data indicated that number was approximately 28 percent.

Again in both instances respiratory disease was far and away the leading cause of death according to the producers.

(Slide)

So you can see that BRD and SRD are significant diseases that affect the industry causing it a great deal of morbidity and mortality.

(Slide)

Again I am going to summarize in about two slides what Dr. Apley took ten minutes to provide which is the summary of the approvals and indications for macrolides in livestock. Erythromycin, tylosin, and Tilmicosin injectable in oral formulations and again tilmicosin as an oral formulation in feed being the only one that is approved under a veterinary feed directive.

(Slide)

Again summarizing the currently approved macrolide uses and there were a few that Dr. Apley brought, quite a few that Dr. Apley mentioned that I did not capture here. But the major ones are the treatment of respiratory disease, treatment of cattle at high risk of respiratory disease, control of a variety diseases many of them being enteric diseases such as swine dysentery, metritis, mastitis, so forth. And then a variety of specific growth promotion plains.

(Slide)

If you look at the USDA NAHMS survey of 1999 in cattle looking at the percent of all cattle that received antimicrobials in feed or water these are again the data presented a little differently then Dr. Apley showed.

The tylosin is far and away the number one antimicrobial administered in cattle in feedlots in the feed or the water. And the primary reason for that at least my understanding is that that is because of the liver abscess indication for tylosin, the prevention of liver abscesses at slaughter.

(Slide)

If you consider the percent of swine production sites that gave antibiotics to weaned pigs as a preventive practice you can see that a large percentage provides feed as a preventive practice. Injectable antimicrobials are used as

a distant second in swine production sites. Water medications, this is a whole group or whole pen water medication. And then finally individual animal oral administration. So a variety of ways to administer antibiotics in swine.

(Slide)

A USDA APHIS info sheet in March 2002 summarized the five most common antibiotics by route of administration given to grower and finisher pigs. And if you look at the bars here, tylosin, chlortetracycline and bacitracin are the top three antimicrobials administered in the feed in grower and finisher pigs.

By injection tylosin, penicillin and then perhaps a close third between oxytetracycline and ceftiofur. If you look at water medication again tylosin, oxytetracycline and chlortetracycline with a little bit of sulfadimethoxine plunked in there as well.

What is important to note in this particular graph is that tylosin is the only of the antibiotics that is in the top five by all three routes of administration.

(Slide)

Dr. Apley provided these data as well which shows the percent of swine sites that use antimicrobials in feed in grower and finisher for any reason. And the top three as he mentioned earlier, tylosin, chlortetracycline and bacitracin.

(Slide)

In the feedlot survey the question was asked what is the percent of all cattle that receive an injectable antimicrobial for any reason whatsoever. And it was lumped into the new long acting, conventional long acting and so forth. But the take home message here is that approximately 20 percent of the cattle in the feedlots receive an injectable antimicrobial for one reason or another.

That is not inconsistent with 15 percent of those animals having respiratory disease when they come on arrival. But it=s a misconception to believe that the majority of animals in feedlots receive an injectable antimicrobial. In fact only one out of five animals apparently does according to this survey.

(Slide)

When asked the question about what are the major antimicrobials used as the primary initial BRD treatment recognizing that feedlots have the choice of choosing or having a choice of which antimicrobial to administer, they have chosen, the percent of all feedlots, 30 percent of them have as their initial choice tilmicosin with florfenicol and tetracycline tied essentially for second place.

(Slide)

And the other piece to recognize and this is an important consideration with respect to the on arrival

indication for treatment of bovine respiratory disease. If you look at all the arriving cattle into feedlots about 10.4 percent of those cattle that are arriving according to this survey received an antibiotic in a metaphylactic or on arrival at risk situation.

Part of the reason is that antimicrobials are considered an investment on the part of the producer and the veterinarian and they don=t want to administer a costly antimicrobial for an unnecessary reason.

(Slide)

In that same survey the criteria that are currently used as standards of practice for choosing which cattle are coming in should be treated on arrival for bovine respiratory disease. These are the particular criteria that are considered the major ones.

First of all the appearance of the cattle on arrival. Do they look bad? Do they look like they are going to be getting bovine respiratory disease? What is the source of those arriving cattle? Is that source typically shipped to that feedlot animals with respiratory disease?

Is there BRD that is being diagnosed in some of those arriving cattle? Or are there other prior BRD problems from those source cattle? Is there a known history that there was no vaccination for bovine respiratory disease in that source of cattle?

The less important criteria included shipping distance and season of the year.

(Slide)

Turning our attention to swine injectable antimicrobials, according to a Doane Animal Health Marketing Survey that was available to the sponsor injectable antimicrobials are a distant second to in-feed use of antimicrobials in swine and injectable penicillin commands nearly two-thirds of the market in terms of the number of doses. And you can see that oxtetracycline, tylosin, lincomycin, and ceftiofur are also used as injectable antimicrobials in swine.

(Slide)

So a summary of the injectable antimicrobial use in cattle and swine is number one the use of therapeutic antibiotics is an investment for the producer. Less than 20 percent of all of the feedlot cattle receive an injectable antibiotic. And only slightly more than ten percent of those cattle arriving receive an antibiotic when one or more of those at risk factors is present.

There are a variety of antibiotics that are used for treatment of those disorders in cattle with macrolides being a major player. And macrolides are one of several that are used as injectables in swine as well.

(Slide)

Again reminding you that the indications and the dosage regime for tulathromycin are for the treatment of bovine respiratory disease associated with the label pathogens. And for the control of BRD in cattle at high risk for BRD.

For the treatment of swine respiratory disease associated with the label pathogens. Administered as a single parenteral injection in cattle and swine by prescription only. And not for use in lactating dairy cows or pre-ruminant calves.

(Slide)

This assures, particularly this one single dose of therapy assures compliance. One of the things that is of major concern in judicious use is compliance with the full course of therapy and the appropriate dosage regimen. This single dose, pharmacokinetic profile assures a full course of therapy and assures compliance when an animal is treated. And it reduces the stress of restraining the animals for additional dosages.

(Slide)

So concluding the resistance selection pressures in the field BRD and SRD are important bacterial infections with animal welfare, animal production costs.

Antibiotics are administered to cattle and swine by various routes and for a variety of indications. Injectable

antimicrobials are a small subset of the antibiotics used in livestock and for therapeutic purposes only. And tulathromycin is only one of several injectable antibiotic choices that the veterinarian will have for the treatment of BRD and SRD.

(Slide)

It is believed therefore that selection pressure exerted by tulathromycin will be no greater than that for macrolide products currently used in livestock. Considering that these approvals have been out there for more than 30 years that selection pressure has also been there. Multiple indications, multiple routes of administration. And the use of tulathromycin by prescription parenteral injection only to individual animals is believed to provide no appreciable additional selection pressure.

(Slide)

So what is the baseline prevalence of resistance? Well with respect to Campylobacter programs have been out there for a number of years. However they have used a number of different sampling strategies and a number of different isolation procedures. NCCLS performance standards those for in vitro sensitive testing have only recently issued standardizing the methodologies for susceptibility testing. However, NCCLS has not yet established macrolide breakpoints that are predictive of efficacy against Campylobacter.

It is important though to recognize that the CDC NARMS program has looked at isolates from human beings and have consistently used the E-test. And so at least in that particular survey system there is a consistent methodology for testing Campylobacter resistance.

USDA NARMS Veterinary Isolate Program currently monitors resistant Campylobacter isolates from poultry but not from cattle or swine. And it=s important to note that the USDA NARMS has recently conducted monitoring in retail beef and pork commodities.

(Slide)

A summary U.S. Campylobacter macrolide resistance surveys from 1998 to 2003 is provided here in this table. Campylobacter jejuni, Campylobacter coli. According to the NARMS data from 1998 to 2003 the macrolide resistance in Campylobacter jejuni is in the order of point two to five point one percent. With Campylobacter coli it=s 11 to 23 percent.

If you look at the Campylobacter isolates from human beings and to the NARMS survey the resistance to macrolides is in the order of one to three percent with no numerical trends over time. Looking at Campylobacter coli it=s just simply because Campylobacter coli is not nearly as common a cause of Campylobacteriosis in human beings. The number of isolates identified through the NARMS program is

too few to estimate a resistance rate.

And in the recent USDA NAHMS survey looking at Campylobacter in cattle looked at the macrolide resistance and found that only two of 92 isolates of Campylobacter jejuni isolated from cattle were resistant to macrolides. And two of 26 Campylobacter coli isolates were found to be resistant to macrolides.

(Slide)

So the prevalence of macrolide resistance in human isolates of Campylobacter jejuni is in the order of one to three percent with no trends over time. And the prevalence of macrolide resistance in Campylobacter jejuni in pigs cannot be assessed due to the limited isolates in that particular species.

(Slide)

So the release assessment summary now concluding this whole area of release assessment. The probability is low that macrolide resistant Campylobacter will emerge or be selected as a consequence of the proposed use of tulathromycin. Because it=s mechanism of action and cross resistance profile in food-borne pathogens is the same as that of macrolides used in livestock currently. Because it=s activity is attenuated in colonic contents and feces. Because resistance to macrolides in Campylobacter is acquired by mutation, not by gene acquisition. And because the

mutation frequency, sorry, the mutation rate is at the frequency of spontaneous mutation.

Recognizing that macrolides are currently used and have been used for swine respiratory disease and bovine respiratory disease, and despite over 30 years of macrolide use in livestock through a variety of indications and a variety of routes of administration, baseline prevalence shows that macrolide resistant Campylobacter jejuni from humans is low with the range of one to three percent with no trends over time.

(Slide)

I would like to turn our attention now to the second component of the assessment. That is the exposure assessment. And again I familiarized you with this particular table earlier. But I would like to go through it again and make sure that everybody is familiar with it.

(Slide)

This is a template from Guidance 152 for the probability of human exposure to the pathogen. The exposure assessment. And it takes into account the amount of the commodity being consumed by human beings and the amount of the commodity that is contaminated with the pathogen of concern or interest.

So you can see that the columns here are the high, medium, and low categorization. And the rows are identifying

the amount of commodity contamination being high, medium, or low by categorization.

And so Campylobacter in beef the exposure recommendation is taken specifically through the default assessment from Guidance 152 which determines that beef consumption is high by human beings in the United States. And carcass contamination with Campylobacter in beef is low, that is less than five percent.

Those two default assessments then yield the medium probability of human exposure to Campylobacter or the medium exposure assessment.

(Slide)

If we turn our attention to the default assessment from Guidance 152 pork consumption is considered to be high in the United States by human beings. And carcass contamination with Campylobacter is also considered to be high according to surveys looking at carcass contamination.

That would yield a high probability of human exposure to Campylobacter. But recognize that people don=t eat carcasses. People eat retail meat. So it=s important to recognize and understand the retail exposure or retail contamination Campylobacter.

(Slide)

Now the primary isolate in swine is Campylobacter coli and Campylobacter jejuni is really found in less than

five percent of isolates from swine and swine carcasses. It=s important to know that through a variety of surveys and a variety of studies swine contamination rates with Campylobacter decreased substantially as swine move through the food chain, that is from slaughter to retail.

It=s important also to recognize in epidemiologic studies of Campylobacter the primary risk factors include consumption and handling of raw or undercooked poultry. Consumption of raw and unpasteurized milk. Untreated surface water. And most notably pork and beef consumption are considered low risk factors by all assessors of Campylobacteriosis in human beings.

Camplyobacteria jejuni is the causative agent with 90 percent of the CDC isolates from human beings through the NARMS survey being camplyobocateria jejuni.

(Slide)

So what I am providing to you in this schematic is what happens to the prevalence rate of Campylobacter contamination from the farm site to the retail site. And what I have provided to you is the prevalence rates according to these particular references at the time, first of all ins swine feces, you can see that the prevalence rate of Campylobacter in swine feces is very high.

The prevalence is zero to 32 percent in carcasses and in processing. And in fact through the processing

sequence of events the contamination rates consistently get lower and lower such that if you look at a variety of studies at the retail level the prevalence rate of Campylobacter in pork is in the less than five percent range regardless of whether it is ground pork for sausage or whether it is pork chops or other types of retail meat.

(Slide)

So with that in mind the sponsor proposes that the exposure recommendation for Campylobacter in pork should be as follows. Again high pork consumption. But because the retail amount of pork contamination is low, less than five percent, we propose that the categorization here should be low and the overall exposure recommendation should be medium.

(Slide)

I will turn our attention very quickly to the consequence assessment. Guidance 152 defined the macrolides as critically important in human medicine. And Dr. Powers provided a very detailed and thorough understanding of that. Sponsor does not wish to contest the consequence assessment.

(Slide)

So when you put those all together what you find is again going back to the diagram release assessment, exposure assessment, consequence assessment, what is the overall risk estimation?

(Slide)

For beef, as a reminder the release assessment is considered to be low based upon the characteristics of the compound tulathromycin and its particular use patterns associated with this approval.

The exposure assessment in beef is considered to be medium because of the data provided. And it=s a critically important category of antibiotics and that yields a high risk estimation.

(Slide)

I am going to switch the slide here and you will see that the only thing that changes that it is now the assessment for swine. Again, low release assessment. Medium exposure assessment. Critically important consequence assessment yielding high risk estimation.

(Slide)

Now, it=s also important to recognize that under the Guidance 152 algorithm anything that has a consequence assessment of critically important is by default according to the algorithm considered high. To have an overall risk estimation that is high.

However, as you can see because of the release assessment and the exposure assessment there can be mitigations on that high overall risk estimation based upon the release and exposure assessments themselves. So high

perhaps is not always as high as others.

(Slide)

If you remind yourself that the extent of use has to be considered when an antimicrobial is considered for mitigation strategies, Guidance 152 declares that the extent of use is considered low if individual animals are injected and if the duration of use is either short or medium. And that then spans the time frame of less than 21 days.

Tulathromycin clearly qualifies as having a low extent of use.

(Slide)

Now Guidance 152 provides a table of potential risk management steps. With the overall risk categorization as high, medium, or low, or categorizations of one, two, or three, within a variety of factors that can be used to potentially, or potentially be used to mitigate the risk associated with those antimicrobials.

Marketing status. Whether there would be extralabel drug use restrictions. What is the extent of use of the product itself. Is there post-approval monitoring. And is there a VMAC review.

So taking that and making that very specific for tulathromycin the sponsor recommended risk management steps are as follows. The categorization we accept as a category one or high based upon the critically important

categorization. And that is a default from Guidance 152.

Marketing status is proposed to be by prescription only. We propose that there be no restrictions on extralabel drug use. And the reason for that is that there is already broad macrolide use ongoing in livestock. And extralabel use restrictions on this product would provide no change to that selection pressure.

The extent of use is considered low. It is an individual animal injection and not for mass medication. It=s not for use in lactating sows or pre-ruminant calves. There is currently a post-approval monitoring system, that is the NARMS system, looking at Campylobacter resistance from human beings. And the VMAC review as you can see is currently occurring.

(Slide)

So with that in mind the sponsor conclusions regarding the microbial safety of tulathromycin is that the proposed label use of tulathromycin includes inherently management considerations of prescription status, an inherently low extent of use due to its parenteral single dose administration and this advisory committee review, recognizing that macrolide resistance in Campylobacter is currently being monitored by the NARMS system.

It is the belief of this sponsor that with these management considerations approval of the proposed

indications for injectable tulathromycin in cattle and swine poses no appreciable risk to public health with respect to microbial food safety.

(Slide)

I would like to make sure and acknowledge a large list of contributors to this effort. The primary contributors you can see on the left hand side. We had an extended review team that included not only those from Animal Health Veterinary Medicine RND but also from Pfizer Animal Health and Pfizer Global Pharmaceuticals as well as Pfizer Global Research and Development. I thank you and would entertain any questions.

(Applause.)

DR. TOLLEFSON: I would like to propose that we take a break and then come back for questions. Is that all right? Okay. So let=s come back at 11:00 and we will start with asking Dr. Brown questions. And then we will go to the Center for Veterinary Medicine Response. Thank you very much.

(Whereupon, a recess was taken.)

DR. TOLLEFSON: Thank you very much. I would like to get started by having the committee ask any questions for clarification that they may have of Dr. Scott Brown. And actually if you also have questions for Dr. John Powers or Dr. Mike Apley you could ask them at this time.

DR. MEALEY: I think I need a little bit of clarification on this pH issue. Maybe it=s the difference between the macrolides that are used in people versus this newer tulathromycin.

But if some of the macrolides used in people are effective in the various acidic pH of the gastrointestinal tract of humans for Helicobacter pylori in the stomach and possible duodenum I assume the pH is quite a bit lower than in the colon, why would tulathromycin have such affect or decreased affect in the lower pH whereas some of these other macrolides don=t appear to? Or can someone clarify that for me?

DR. BROWN: Let me paraphrase and make sure I have got it correct. And that is the question of the pH issue that we brought up with tulathromycin why is that not the same issue with other macrolides. Or conversely is that overstated with tulathromycin because the efficacy of other macrolides when administered orally in human beings?

DR. MEALEY: (Nodding of head.)

DR. BROWN: Okay. One of the things to remember is that tulathromycin is a triamilide. It has three ionizible amino groups. It=s pH dependency is greater than that for other macrolides. So when you have got the three ionizible amino groups with the pk=s that they have, its pH response and activity is a different profile than that for other

macrolides. So I think that is the specific answer to the question you are, I think, asking.

We do see if you think back about the MIC ranges for those organisms that lessens at 6.5 pH the MIC values were greater than 128 micrograms per mil. Those are the data we have and that is a different profile then what you would see for other macrolides.

DR. WADDELL: Marguerite, you had a question?

DR. PAPPAIOANOU: Yes. Actually I had two questions. One is on the exposure assessment and the issue of either looking at carcass consumption or retail meat. In terms of reading the proposal it seemed the retail meat for swine included pork chops only. Is that right? Are there other types of meat that were included in the retail meat survey?

DR. BROWN: So to paraphrase, again paraphrasing the question and making sure I have it right. You are asking whether the data we have on retail pork contamination is only from pork chops. Or are there other retail pork commodities that are included in that?

DR. PAPPAIOANOU: (Nodding of head.)

DR. BROWN: The primary survey that was used as the basis for our discussion comes from the FDA review of the retail cuts. In that particular study pork chops were the only pork commodity that was looked at at the retail level.

There are other surveys that have been done looking at pork contamination at the retail level which includes ground pork. And the same conclusions can be made that the contamination with Campylobacter is less than five percent.

DR. PAPPAIOANOU: And is there any information available on what consumption occurs in the United States for other products, such as skin, knuckles, feet, other parts of pigs that are consumed by customers?

DR. BROWN: So what is the consumption of unique pork commodities, pork feet and those sort of things. I don=t have those information at this point.

DR. PAPPAIOANOU: Okay. Thank you.

DR. TOLLEFSON: I might be able to help in that a little bit. The USDA does do national food consumption surveys and it would include all pork containing products. I think a large amount of pork is used in the consumption of like luncheon meats and so on.

However, in just speaking in reference to Campylobacter keep in mind that those are fairly or highly processed. And the camplyo contamination is probably quite low. You know, it might be a problem with Listeria post processing or something. But for Campylobacter it=s low for all those types of meat.

In the retail meat surveys that we do in NARMS we do use pork chops. And one of the reasons for that is that

they are the least likely to be frozen. So we have a better chance of isolating the Campylobacter should it be there.

DR. PAPPAIOANOU: But just maybe having lived in the South for 21 years I am now very aware that a lot of people eat skin products from pigs. And are those highly processed or is there just, is there any information on that?

DR. TOLLEFSON: They are cooked. You mean like chitlings?

DR. PAPPAIOANOU: Pork rinds.

DR. TOLLEFSON: Pork rinds.

DR. : Deep fried.

DR. TOLLEFSON: Yes. They are cooked when you get them. The ones you buy in grocery stores are highly processed. There could be home cooking which I don=t know anything about.

DR. PAPPAIOANOU: Okay.

DR. TOLLEFSON: Okay.

DR. PAPPAIOANOU: Thank you very much. And then I had a second question on NARMS. And the data that is has been presented indicates a fairly low percentage of Campylobacter isolates that have been shown to be resistant to macrolides. But I wondered if someone could comment about the methods of NARMS in the sensitivity of that system.

For example, is it fairly sensitive so that it would be very, it would pick an infection if it occurred.

Or, you know, would you have to increase the amount of infection substantially before you would be able to pick it up with the system?

DR. TOLLEFSON: No. That is a good question. Marguerite is referring to the human arm of NARMS. And there is an issue with detection limit where we have seen what other resistance to other drugs where it may blossom after it reaches a certain point. But, if the committee wants, I know Dr. Fred Angulo is here who runs the human arm of NARMS, if he could answer that question. John, should we do that now or do you want to do it later?

DR. WADDELL: He can do it in open comments.

DR. TOLLEFSON: Keep it brief, Fred.

DR. ANGULO: Yes.

(Laughter.)

DR. ANGULO: Thanks for the floor. The mike isn=t working.

MS. : It=s on.

DR. ANGULO: Thanks. Thanks for the floor. Well as people know we test about 350 Campylobacter isolates a year from sick humans. There are approximately 30,000 to 45,000 culture confirmed Campylobacter infections a year in the United States which represents about 1.4 million Campylobacter infections in humans a year of which as I said 30,000 to 40,000 are culture confirmed.

We just test 350 of those isolates in NARMS. Of the isolates we receive in NARMS about 90 percent of them are jejuni and the others are coli. The erythromycin resistance in the jejuni as has been described has been low at one to three percent.

I disagree with the statement from Dr. Brown that there insufficient data to conclude about erythromycin resistance in coli. We have tested almost 100 Campylobacter coli isolates and about eight percent of the coli isolates are erythromycin resistance with no discernible trend.

What is clear, or what the question I think was asked about what is the robustness of the human surveillance data and could we detect an increase of erythromycin resistance in Campylobacter. And we could probably with C. jejuni. But we could not do it very quickly with coli since we only receive about ten to 20 C. coli isolates a year.

It would take a while to see a doubling of the resistant rates. If the rates would increase from eight percent to 16 percent amongst coli it would take us several years to have sufficient data to detect that increase. And then it would take several years to do the epi studies to determine the sources of those infections.

Of course we are just receiving the isolates and we don=t discern exactly where the sources were. So the question for the sensitivity of surveillance it would take us

a number of years to detect that an increase, that if this drug were to result in erythromycin resistant C. coli that we transmitted through the food supply infecting humans it would take us a number of years to detect it with our current surveillance platform.

DR. TOLLEFSON: Thank you.

DR. WADDELL: Dr. Wages.

DR. WAGES: I just, Marguerite brought up a good point regarding carcass contamination versus retail. And I think it=s important to keep in mind that when Guidance 152 came out the purpose we felt on human exposure was the actual public at risk population.

And were actually going to be exposed the majority, I won=t say majority, but up to 30 percent in poultry and probably over half of the swine products are what we consider value added. They have been cured, processed, fully processed cooked, et cetera. And the exposure at that point to Campylobacter is next to nothing.

I mean I would challenge somebody to come up with cooked products with outbreaks of Campylobacter in humans. And so that is a big thing when you look at the actual exposure to public to these Campylobacter. Or are you actually assessing the exposure to the processing plant workers who are going to be exposed to those carcasses there. So that is an extremely important point as we go through 152

in food animals to get the correct exposure. Because a lot of that is for the process. And there is virtually no risk.

DR. WADDELL: Dr. Papich.

DR. PAPICH: Scott, I just had a question about the kinetics. You mentioned a little bit about it and the fact that it has a long plasma half life of 90 hours or so. Are you able to show what this data that shows how long that is above the MIC of susceptible organisms? Either for the plasma or alternatively maybe for the tissue? So for example lung concentrations and how those concentrations over time relate to the MIC?

DR. BROWN: If I understand your question, your question relates to the efficacy of tulathromycin. Is that true?

DR. PAPICH: Well not necessarily efficacy but pharmacokinetic data plasma or tissue concentrations in relation to MIC of susceptible organisms. PKPD essentially.

DR. BROWN: Okay. I am going to look for some guidance. I believe, you know we prefer not to share and divulge proprietary data with respect to efficacy and that relates to the target organisms in the MICs and the PKPs= relationship for the therapeutic effect.

I am happy to address that if you can help me understand how your question is headed toward microbial safety.

DR. PAPICH: Well, let me put it another way. Given the MICs of Campylobacter how long do the concentrations that you achieve with this drug, how long are they maintained above MIC for Campylobacter?

DR. BROWN: Okay. So now you are asking about questions in the gastrointestinal tract, the concentrations in the gastrointestinal tract. Concentrations in the gastrointestinal tract of total active drug, or total drug by chemical assay peak at about three to four days after dosing. They are in the range on average of 20 to 35 micrograms per gram of material. And the decline to concentration of total drug of less than one microgram per gram of material by either six days in one species or ten days in another.

I remind you that that is a total drug there by chemical assay and doesn=t reflect the microbiological activity because greater than 70 percent of the drug is bound to fecal solids and is not micro biologically active.

And couple that within the pH effects it would be anticipated at what total drug is present would have a significantly attenuated activity. And Campylobacter in MICs are in the range of four micrograms per gram at optimal pH.

DR. WADDELL: Dr. Craigmill.

DR. CRAIGMILL: Yes. A question for either Dr. Apley or Dr. Brown relating to the extralabel uses perhaps in minor species. And a loaded question, are there

any species in which you would not wish to see this drug used extralabelly?

DR. BROWN: So are there species that I would prefer it not to be used in an extralabel fashion. Our concerns are for the approval of this product according to label indications and that the veterinarian has the opportunity to use this product judiciously in an extralabel manner as he so chooses. I am not going to speculate on what species I think would not be appropriate for extralabel drug use.

DR. CRAIGMILL: If I could clarify. Not necessarily just species but other extralabel uses as well.

DR. BROWN: Well it=s an injectable antibiotic. And so I think that you are looking at extralabel uses --. I would be cautious about trying to extrapolate to anything else at this point. I think there is plenty of evidence that there are many indications and routes of administration for other macrolides. And perhaps the safety of those supports that macrolides are safe for use in livestock.

DR. APLEY: I think there is --. I am going to join Scott in not speculating on that. I look forward in the years to whatever happens, I guess. But I look forward to seeing continued susceptibility data and when we have a chance to look at pharmacokinetics and things like that in the future. It would be a chance to discuss that then.

DR. WADDELL: Dr. Jaffe.

MR. JAFFE: Thank you. I had a question in the assessment and your talk, Dr. Brown. You talked about there is a distinction made between cattle and swine and how the drug will be used by a veterinarian.

Talking about both for animals that have the disease but also for cattle it specifically says for animals that are at known high risk. And I wanted to understand why that distinction is made by the sponsor.

And then also what affect that has on the market or the extent of use if you didn=t have that. Or how does that affect how many cattle will be potentially injected with the drug?

DR. BROWN: So again trying to paraphrase. You are trying to compare and contrast the indications that we have are proposing for cattle as opposed to those for swine. And particularly highlighting the control of BRD in at risk animals.

MR. JAFFE: (Nodding of head.)

DR. BROWN: Okay. One of the key differences, and I will defer to Dr. Apley for more of the production differences. But one of the key differences in cattle is that there is a large, a very large proportion of beef cattle that are transported to feedlots and are susceptible to bovine respiratory disease at a key time in their life. It=s

associated with the stress of shipping.

A phrase that is used oftentimes is shipping fever. What that means is that those animals have a higher possibility or probability of acquiring bovine respiratory disease because of the close confinement that they have at shipping and because of the shipping stress.

That phenomenon isn=t nearly as widespread in swine and so the production pattern in swine doesn=t lend itself nearly as appropriately to treatment in an at risk situation because there is not nearly as well defined an at risk population in swine.

Having said that then you asked the question about what is the relative use. And the only data I can go back to is to remind you of the data from the USDA survey of NAHMS in 1999 which said that about ten percent of the animals on arrival receive an injectable antibiotic in an on arrival, at risk program.

And about 20 percent receive an antibiotic by injection for any reason at all while they are in the feed yard. That would give you some possible comparison of the different use pattern for at risk versus the rest of the uses for injectable antibiotics in cattle.

DR. APLEY: From a production standpoint I think one of the questions is always what puts the breaks on just using it in everybody. Just using it in everyone that comes

in.

A quick little economics deal. Right now for a 500 pound calf coming into a feedlot we are laying out $600 to $650. We hope if you look at those cattle over a ten year average I would by average making $10 to $20 clear profit per head. To put a drug into those animals at arrival, the ones we currently have cleared for control, it=s going to be $10 to $12 per head.

So I am coming really close to my hope long-term profit to put that drug into them. So there is a huge economic break on applying these. So we really critically make the decision on if those animals are at risk where we feel that the benefit of that drug would benefit the health and well being of those animals enough that it would work for us.

MR. JAFFE: If I could ask a follow up or a second question. I guess currently now there are a lot of different both macrolides and other drugs that are used for respiratory disease in both bovines and in swines and in cattle.

And I guess the question I had is by putting this new drug on the market will it be therefore be a replacement of existing drugs? And if so, which ones? Or whether it will be an additional therapy used on top of the therapies that are used in feed and water and injected now?

DR. BROWN: So again trying to speculate on use

patterns in something that is not yet approved.

DR. TOLLEFSON: Scott is hoping that it is going to be used and the only one that will be used. Right?

(Laughter.)

DR. BROWN: I think it=s important to recognize that veterinarians need a choice in which antimicrobial to use. And from the data from the NARMS survey different feedlots make different therapeutic choices.

If you look at the label indications and the proposed uses for tulathromycin you would anticipate that it would be going head to head against a variety of others that are labeled for the same thing. Macrolides, phenicols, other kinds of antibiotics as well.

I think it is also important to recognize that it=s unlikely that based upon the economics it=s going to be used in addition to other things that are already utilized because that would be an additional expense on top of what they are already using. And so the economic driver would be to not add additional cost to the production but rather to reduce cost.

DR. WADDELL: Dr. Aref.

DR. AREF: I just wanted a clarification. This is pretty minor. It looks like human resistance to macrolides is like one to three percent or something like that. Macrolides have been around for 30 years. But there is a

statement in the documents that says that long term use has not increased the product. But the long term use that looks like was studied was only from 1997 or 1999 through 2004. So I think that period doesn=t really reflect the long term use.

DR. BROWN: So are you asking a question or are you making a statement?

DR. AREF: I am making a statement that I oppose the long term use sentence, I guess.

DR. BROWN: Thank you for your statement.

DR. WADDELL: Dr. McGlone.

DR. McGLONE: Thank you. I just have one quick question and then a follow up. What might be, I know you probably don=t know specifically, what might be the withdrawal period of this product? Would it be days, weeks?

DR. BROWN: There will be a withdrawal period that will be determined by the FDA.

DR. McGLONE: Okay. So my question relates to the recurring theme of the relationship between stress and use of these products and/or microbial resistance. If the products are intended to be used early in the production phase, let=s say long before processing, and that the drug is cleared long before processing of the animal and so on, during the evaluation and I am really talking about the quantitative evaluation in food safety, were those determinations made in stressed animals? Or not?

And if it=s not, if stress brings out the organism at processing let=s say because of the stress for transportation to slaughter if that is a time when the drugs would not be used anyway then maybe there is not an issue towards the end of harvest.

DR. BROWN: I apologize. I am going to have to paraphrase because that was a difficult question to try to synthesize. You are asking about the use pattern of this product near the time of slaughter and whether coupled with the transport stress to the slaughterhouse would have any consequence on shedding of organisms.

DR. McGLONE: At that point and then earlier. Two points.

DR. BROWN: Okay. From an economic consideration I think it would be, it would not be expected that a producer would use a macrolide or other long acting antimicrobial very near slaughter. This is an investment in something that is going to have therapeutic action for several days and they would want that to take place.

So I would anticipate that use pattern wise it would be several days prior to slaughter at the earliest time when somebody would use an antibiotic of this nature. Couple that with the fact that BRD is something that happens typically early in the feedlot cycle I think it=s safe to assume that for the most part this product will be used some

period of time before transport for slaughter.

DR. McGLONE: So if I understand it correctly, it seems unlikely that the drug would contribute to changes in microbiological resistance much later. You know months or weeks later. That is unlikely? Is that true?

DR. BROWN: I think that is a fair statement. We have some data that have been generated looking at Salmonella after administration of tulathromycin and we found no change in the shedding of Salmonella as a result of tulathromycin usage. That was something that was done for a completely separate purpose.

But that would indicate that at least in that instance that there is no change in the shedding of that particular food-borne organism.

DR. WADDELL: Dr. Leggett.

DR. LEGGETT: As a follow up to that, sort of the area that we are looking at, I have a question that I don=t know the answer to. What is the rate of mutation reversion? In other words, could we be developing resistant Campylobacters that then we don=t see because the mutation is never averted. And could this theoretically be some risk there that we are not measuring?

DR. BROWN: To my knowledge we have not looked at mutation reversion. But the expert is in the audience and I will ask Dr. Tom Gootz from Pfizer Global Research and

Development to address that question.

DR. GOOTZ: Tom Gootz from human health side. I am not aware of --. I agree, I am not aware of anyone who has looked at reversion rates to the point mutations in Campylobacter or even gram positive organisms at the ribosome.

And those things point mutations not acquisition of new genetic material, if they in fact reverted they would be no longer be resistant and it would be in essence a nascent organism.

Looking at the same four mutation frequency as well, which is pointed out in Dr. Brown=s presentation. Because there are point mutations of ribosomal RNA are quite infrequent, about one times to ten to the minus the ninth, either in Campylobacter from animal sources, human sources, wherever.

DR. WADDELL: Dr. Ohl.

DR. OHL: Yes. I actually have four questions which I will ask in sequence. Do you have any data, Dr. Brown, on the environmental persistence of the stability of this compound in terms of maybe in surface water or soil?

DR. BROWN: Actually that really probably isn=t relevant to the questions that are before us in this, you know at this particular juncture, I wouldn=t think.

DR. OHL: Well, how about specifically if I ask

would it be in hog lagoons or in manure situations?

DR. BROWN: All right still it is not addressing the questions before us today as far as bacterial safety or microbiological safety.

DR. OHL: All right. I will move on to my second question. Related to the comparison in fecal binding between this compound and that of the other macrolides that are currently used, you had mentioned the fecal binding of this compound and I was wondering how that compares in relation to the other macrolides in fecal binding.

DR. BROWN: The studies we did were not looking specifically at the comparison of fecal binding with existing macrolides. The data we have indicates that over 70 percent is bound to fecal solids for tulathromycin. I would be speculating if I began to talk about what kind of binding there was for other macrolides.

DR. OHL: In the brief that was presented to us there was mention of challenge experiments with Salmonella type typhimurium after injection with tulathromycin at two different dosages. I was curious were any similar challenge experiments ever done with Campylobacter either susceptible to resistant? And if so how did it change the populations?

DR. BROWN: We did not conduct challenge studies with Campylobacter.

DR. OHL: And this could be for anyone on the

panel. But I was curious as to the Campylobacter susceptibility profiles to ketolides and whether or not there would be speculated cost resistance to ketolides for the mutational point resistance in Campylobacter.

DR. APLEY: I am not aware of any data that looks at that in gastrointestinal organisms. Since the development for those drugs is really concentrated on respiratory tract pathogens.

DR. BROWN: To my knowledge we don=t have any data looking at tulathromycin to ketolide in Campylobacter. I look at Dr. Gootz. I believe that is the case.

DR. GOOTZ: That is correct. I am not sure that the human health side has any resistance frequency data for ketolides such as ketech in Campylobacter. As was stated by Dr. Powers most of that business and need is directed toward gram positive respiratory tract infections in humans where we do have data and literature with respect to frequency of resistance and cross resistance. But it=s really a very different group of organisms.

DR. WADDELL: If there are no other questions specific to Dr. Brown, Marguerite has a question for Dr. Powers.

DR. PAPPAIOANOU: I am interested in the animal human interface and I am curious as we have been hearing about what is happening with the drug and implications with

the enteric situation in the animal and possible contamination then of food product that would go into people in terms of implications then for antibiotic, that transfer of antibiotic resistance to people what your thoughts are or have been as you have heard this discussion.

DR. POWERS: Yes. I think one of the issues that always comes up with this is that what we are doing is trying to form hypotheses without the data to actually confirm those or not.

What we are trying to say is well perhaps because of decreased binding in the stool and organisms that we don=t see on the carcass of an animal how is that going to translate into people.

One of the issues that is always difficult in public health is you want to prevent this before it becomes a problem and the analogy I always use is you tell your kids not to play with matches and if your kid says well show me the ashes, it=s a little too late at that point in time.

So we are trying to prevent --. To actually get the data to prove it would be actually having the problem we are trying to prevent in the first place. When you think about macrolide use in general, not specifically to this product, the issue here is that even though we may not use macrolide -- it=s due to a collateral damage issue. Even though we may not use macrolides specifically directed at an

organism we may get resistance to another organism or another class of drugs.

An example I can think of here would be although macrolides are not specifically used to treat entercoccal infections cross resistance does occur with some drug classes that are used to treat entercoccal infections, specifically streptogramins.

So if use of macrolides in an animal resulted in cross resistance in entercocci which then obviated the use of streptogramins in humans that might be an issue. How likely is that to occur? Well that is the problem. We don=t really know how likely that is to occur. But I guess what we are saying is there is a potential there and that is why there is cause for concern.

DR. WADDELL: One more question. And then we will move on to the CVM response.

DR. RELLER: I would like to follow up on Dr. Ohl=s query. I understand that the assessment, the release assessment, the exposure assessment, and the consequence assessment, that takes into account as best as one can assess the direct effect. But he was addressing the indirect effect.

And I realize that it is not on the table by the grid that we are constrained by. But shouldn=t it be considered at some point by someone because the arguments

that have been put forth to put the boundaries on the assessments could in fact be applied to other antimicrobials and other organisms as there is not a problem when the published literature and in some ways common sense raises the question well, maybe. And that has to do with the indirect consequences. Ground water, lagoons, runoff. I mean there are arguments put forth about how Campylobacter is acquired.

Well, what the pork chop one buys in the supermarket is not a problem in terms of exposure assessment. But does that mean that the use in swine necessarily means that there is no human exposure through other mechanisms? You know, I just raise the question and the more I hear I wonder whether we are capturing all of the relevant issues in the constraints of the grid for assessment. Or only considering the direct as opposed to the indirect consequences.

DR. WADDELL: Hopefully the CVM might address that issue, and how. You know, a lot of those issues were addressed in the deliberations on 152. And so maybe the CVM response might want to cover that.

DR. TOLLEFSON: Yes. I will ask Dr. Gilbert to address it more specifically. But Dr. Reller you are absolutely correct. We are only looking at the direct effects in Guidance for Industry 152. There are other studies that the sponsor goes through where we can get some

information on the indirect effects. But we elected not to do that in a systematic way because we really don=t know all the answers. Or even some of them.

Also in our research on this issue we have determined that the food-borne route, the direct route, is by far the driver. Also the Environmental Protection Agency is looking at specifically the risks from lagoons, animal waste, and so on. But let me call Dr. Jeff Gilbert. He is going to just briefly give the CVM response. And I will ask him if there is anything he can share about environmental impact assessments. Dr. Gilbert is chief of our microbial food safety team in our division of human food safety.

CVM Response/Comments

by Jeff Gilbert, Esquire

DR. GILBERT: Thank you. Good morning everyone. I will be very brief. In fact, I have only one slide. So maybe that will make everybody happy and we can get on with the public comments.

Basically we, the agency, agree with the conclusion reached by the sponsor on the proposed use of tulathromycin in swine and cattle. And it really gets back to the slide which you have seen before. It=s in Guidance 152. Dr. Brown presented it a couple of different ways and kept referring to it.

The nature of the drug being critical. It=s a

human medicine of macrolides. It puts this in category one. With that comes possible risk management considerations. And I know the VMAC may touch on these later during deliberation. We see it of course the marketing status is Rx. Extralabel use we may get into at some point as far as prohibition as a class rather then an individual drug.

Extent of use again Dr. Brown pointed out how it is to be used in the number of cattle and that sort of thing. It really puts it into a low extent of use. Post approval monitoring. Macrolides are already covered in NARMS and will continue to be so that is already in place.

And as he pointed out as an advisory committee that is what we are here for today is the VMAC. So we have those categories for risk management in place already pretty much for the category one drug. And that is how we see it. So we do agree with their conclusion on that.

Some of the questions that the VMAC will be presented with I think get to other considerations and you may touch on those.

Back to the comment a moment ago about specifically if you are asking about environmental routes or other routes, because of the qualitative nature of this risk assessment sponsors are welcome to bring to the table what they have. So if someone had some definitive information on that we may be able to take a look at it. You know, in exposure routes,

other things like that.

But so far nobody has come with that because they would have to probably, I don=t know how much it would cost to run an environmental study to look at all these things. So we have sort of steered away from that also.

It=s my understanding it=s not really our bailiwick and a lot of the jurisdictional issues with EPA or with some of the other areas get into that, the states, and we really don=t address that sort of thing. So those are just some short thoughts on that.

But we would be interested in seeing that sort of data if it ever does come to the table in one of these situations.

So with that, that is basically where we are at on the conclusions that we came to with the company.

DR. WADDELL: Question?

DR. PAPPAIOANOU: Yes. Thank you. Point of clarification. This turns on extralabel use it seems that the sponsor had said that extralabel use restrictions are not required for this approval because macrolides have them approved and used extensively for a variety of indications in poultry, swine, cattle, and other animal species. So that seems not to be in agreement with what you have there. Can you clarify that?

DR. GILBERT: Dr. Brown was speaking specifically

to tulathromycin not to macrolides in general. And --.

DR. PAPPAIOANOU: So what is your response to it? That is what I am curious about.

MR. GILBERT: Well, Dr. Tollefson, Dr. Sundlof you can step in. I think basically with extralabel use, notice how I dished that off. With extralabel use I think that is something that it is on the table as a consideration for risk management. However, that gets into some issues about is this something to be applied pre-approval or is this something that you have to do post-approval. There are some legal issues there. Those sorts of considerations.

So, at this point internally we are not recommending that extralabel use be prohibited, you know, for this case, for tulathromycin for these two applications. Later on we may hear from VMAC, we may hear from public something else that may come on where this changes. Does that sort of cover it?

DR. PAPPAIOANOU: I am just saying that FDA would agree or has no issue with there being extralabel use.

DR. GILBERT: At this point we don=t have that at this stage.

DR. BROWN: So, just for clarification the slide says that extralabel use, Ano@. You mean no? Or no restrictions?

DR. GILBERT: No extralabel use.

DR. PAPPAIOANOU: And that doesn=t seem to agree with the proposal made by the sponsor.

DR. TOLLEFSON: Right. I can clarify a little bit. The extralabel use under AMDUCA, the Animal Medicinal Drug Clarification Use Act, whatever, something like that.

(Laughter.)

DR. TOLLEFSON: We would have to be on the extralabel use for all macrolides. So it=s not a product specific issue. We can do that. I mean it=s a relatively low burden on the agency=s part to propose to ban it. But it wouldn=t, you know, we would have to take into account all the other macrolides that are approved. I am not so certain there are any extralabel uses when you consider all the uses that are approved. We would have to look at that. But it would be the class basis not just tulathromycin.

DR. CRAIGMILL: I am a little confused because I thought some of the sulfonamides were specifically prohibited from use in dairy cattle. And so that class was not necessarily --. Are we to in our deliberations consider specifically extralabel use of tulathromycin recommendations?

DR. TOLLEFSON: You can consider any number of things. I guess, and you are right, actually Dr. Craigmill, that it=s not just specifically a class. But in this case tulathromycin is an injectable product that --. Well, yes you can. I guess I shouldn=t say anything more.

DR. WADDELL: Dr. Sundlof.

DR. SUNDLOF: Yes. Let me just try and provide some clarification because it=s actually a fairly complicated issue. As Dr. Tollefson stated with the passage of the Animal Medicinal Drug Use Clarification Act, AMDUCA, it defined the criteria by which we can prohibit extralabel use.

And the standard is that extralabel use presents a risk to public health. As opposed to may present a risk to public health which is also in AMDUCA.

So, we have defined various levels of risk and the burden, the regulatory burden to prohibit extralabel use rests on the standard that it presents a risk to public health. At this point in time I don=t think we have met that burden to establish that it does present a risk to public health.

Back to Dr. Craigmill=s question about sulfonamides and why those are prohibited but not as a class. Sulfonamides went on that list prior to the passage of AMDUCA. And with the passage of AMDUCA came the standard of presents a risk which is again the burden of proof is on the FDA to establish that there truly is a risk and that has to be substantiated with scientific evidence.

If that drug were to be evaluated again today under those standards it may come out differently. Or we may in

fact have band on a class basis. But the fact that that looks to be an odd one is a historical artifact rather than based on the current regulatory standards.

DR. GILBERT: Okay. Thank you.

DR. SUNDLOF: Thank you.

Open Public Hearing

by Ms. Aleta Sindelar

MS. SINDELAR: Great. This is the open public hearing portion of the meeting. Sorry for the delay. Very important questions. Many that are a part of the deliberations. So based on the information exchanged already to the speakers I would like to first invite the speakers of this morning back to the table when we return from lunch such that questions can be additionally posed to the speakers this morning.

So let=s move on with our six registered speakers. Please limit your comments to five minutes or less. We will take the six registered speakers. Break for lunch. Come back at 1:00 o=clock and reconvene for those who wish to make additional comments.

The first of our registered speakers is Susan Prolman from the Union of Concerned Scientists.

MS. PROLMAN: Hello. Thank you very much. Again I am Susan Prolman. I am speaking on behalf of the Union of Concerned Scientists. And I would like to thank the

committee very much for this opportunity to provide comments today.

The Union of Concerned Scientists applauds the Food and Drug Administration=s Center for Veterinary Medicine for convening VMAC to consider the impacts of the possible approval of the injectable tulathromycin on the efficacy of human drugs.

The Union of Concerned Scientists also commends the agency for developing the scientific framework outlined in its Guidance for Industry Number 152. Although we continue o have concerns with some of the assumptions imbedded in the Guidance.

It is important that reviews under Guidance 152 be conducted in a transparent manner with meaningful public participation. We appreciate this opportunity to comment today and we hope that today=s public comments as well as the views expressed by the committee will be reflected in the FDA=s final determination.

Before turning to the application for approval before the committee we would like to make a general point about the regulation of antibiotics used in animal agriculture. While the Union of Concerned Scientists understands and agrees that applications for new approvals of antibiotics in animal agriculture raise important issues such applications represent small quantities of use when compared

to already approved uses.

The current uses include millions of pounds of antibiotic drugs in classes used in human medicine. The substantial resources devoted to this new application for approval can=t help but raise the more pressing issue of the public health risk associated with the massive ongoing uses.

Macrolides, the class to which tulathromycin belongs is one of those used non-therapeutically in animal agriculture. The Union of Concerned Scientists agrees with the FDA=s assessment that macrolides in human medicine is critically, macrolide use in human medicine is critically important and that there is an overall high risk estimation for this drug.

UCS believes that if evaluated under Guidance 152 other macrolides like tulathromycin would be considered critically important and represent a high risk. As such it seems likely that these macrolides would not be approved for therapeutic, excuse me, for non-therapeutic uses were they to be presented as new applications.

The Union of Concerned Scientists urges the FDA to use this application as a take off point to set a time table for reviewing the ongoing non-therapeutic uses of macrolides as well as other antibiotics important in human medicine in animal agriculture.

One problem that arises in the context of this risk estimate and others that may follow is the reliance on estimates of antibiotic use in animal agriculture. Clearly risk estimates could be more reliable and certain if based upon accurate antibiotic use in animal agriculture.

Clearly risk estimates could be more reliable and certain if based upon accurate antibiotic use data. At this juncture the Union of Concerned Scientists renews its call for the federal government to establish a meaningful ongoing data collection requirement and system so that in the future exact figures will be available for similar risk estimates.

With respect to the application for approval of tulathromycin solution for parenteral injection for treatment of bovine and swine respiratory diseases, while the U.S. agrees that the application has characteristics of low release and low exposure the Union of Concerned Scientists believes that important questions should be answered before a decision is reached regarding the application for approval.

First, why is a new antibiotic drug needed for this use? Has the evolution of resistance diminished the efficacy of other drugs? What are the alternatives to this approval? In considering alternatives the federal government should look not only at alternative drugs but also options for disease prevention including improving the conditions in which animals are raised and transported in order to lower

the rates of respiratory diseases.

The risk estimate stated that respiratory disease was ranked as the number one producer identified cause of mortality in both nursery pigs and grower/finisher swines. Responsible for 28 percent of nursery deaths and 40 percent of grower/finisher mortality. It also cited estimates that a majority of mortality at cattle feedlots is attributable to bovine respiratory disease.

It is incumbent upon the federal government to thoughtfully examine why rates of respiratory disease are so high and what preventative measures can be taken to reduce the rates of disease and the huge reliance on pharmaceuticals to prevent deaths at concentrating feeding facilities.

Second, what would the actual usage of tulathromycin be if this application is approved? On the one hand it appears that human exposure to resistant bacteria as a result of use of this drug will be low because of several factors. The drug is formulated for parenteral injection as a single dose to provide a full course of therapy.

It will be available only by veterinary prescription to individual animals. It is not intended for whole herd use. Pfizer reports that the microbiological activity of tulathromycin is substantially diminished due to the neutral, to acidic pH in the colonic contents and feces and that macrolide resistance in Campylobacter occurs by a

mutational event in Campylobacter and not by acquisition of macrolide resistance genes.

On the other hand --.

MS. SINDELAR: Please present your closing --.

MS. PROLMAN: What?

MS. SINDELAR: Could you please submit a closing statement?

MS. PROLMAN: I have just one more paragraph here. On the other hand the drug will not be used only for therapy but will also be prevented, excuse me, will also be for prevention of respiratory diseases in cattle and swine. The respiratory diseases at issue are endemic due to the conditions in which the cattle and swine are kept and transported.

The drug could be used for compensatory purposes in millions of animals. The Union of Concerned Scientists recommends that if the FDA chooses to approve, the approval should be limited to the treatment of animals diagnosed with the disease and others at imminent risk of contracting the disease. In no case should approval extend to compensatory treatment that would be given to animals on a routine basis.

Finally, if the FDA approves this formulation of tulathromycin the Union of Concerned Scientists urges the FDA to prohibit extralabel uses. Thank you.

MS. SINDELAR: Thank you. Our second speaker is

Richard Wood, Executive Director of Food Animal Concerns Trust.

MR. WOOD: Thank you. And I am joined also by Steven Roach, our Food Safety Program Manager at Food Animal Concerns Trust as well. That doesn=t mean we are both speaking in five minutes. We are going to do ten minutes total, okay. Even though it=s 12:00 noon.

I am Richard Wood. I am the Executive Director of Food Animal Concerns Trust or FACT. I am a former member of VMAC and just can=t stay away. I appreciated my time serving on this committee and appreciate the opportunity to speak before you now.

FACT is a non-profit organization that advocates for better farming practices to improve the safety of meat, milk and eggs. FACT has a long history of working with the FDA and other federal regulatory agencies to help develop an appropriate response to antimicrobial resistance.

For example in 1994 FACT came before a joint meeting of this committee and another advisory group to ask the FDA not to approve fluoroquinolones for use in poultry because of concerns with resistance. The FDA did not take our advise at that time but in 2000 after seeing the resistance rise in Campylobacter the agency moved to take the drug off the market.

We appreciate the opportunity to comment today. To

reaffirm Dr. Sundlof=s comments this VMAC meeting is very important because it is the very first public discussion of an actual application of FDA=s new approach to managing the risks from antimicrobial resistance set out in Guidance 152.

We commend the FDA for the work it has done in creating a method for evaluating the risk of new animal drugs. We also feel that this meeting is a good start in making the risk evaluation as open a process as possible.

FACT believes that the credibility of the FDA and all regulatory systems is dependent upon its level of transparency. By making the risk assessment publicly available and by providing adequate time before this meeting for public review the FDA has greatly increased consumer and stakeholder confidence in the process.

We strongly support public meetings such as this one for drugs important to human medicine. We hope that the openness shown in this meeting will be the norm as the FDA goes forward with other risk assessments.

FACT accepts the results of the Pfizer risk assessment that tulathromycin is high risk as defined under Guidance 152. Given the importance of the macrolide class of drugs in human medicine including its use for the treatment of Campylobacter, the second most common bacterial cause of food-borne illness in the U.S., not mentioning worldwide, a

finding of high risk was expected.

While we have reservations about some assumptions made in the release assessment we feel that the outcome of the risk estimate for this macrolide is appropriate. As with the previously speaker though our greatest concern with this risk assessment is that it does not apply its findings to all uses of macrolides in animal agriculture.

As was repeatedly stated in this risk assessment the mechanisms of resistance of this drug are equivalent to those for the other macrolides used in animal agriculture. Because tulathromycin is considered high risk Guidance 152 clearly states that its use should be limited to individual animal treatment.

So then the next question for the FDA that it needs to address is if it would not be appropriate to use this drug in feed and water because of concerns about resistance why allow tylosin to be used in animal feed for growth promotion?

As was illustrated in the macrolide use slides this morning today=s application of Guidance 152 should be followed by steps to respond in a similar fashion to the vast bulk of macrolide drugs already approved without an appropriate risk assessment.

This is a central concern in responding to the compound before you today. Now Steve Roach, our food safety program manager will address some of our concerns about how

the risk assessment was applied.

MR. ROACH: Hello. I appreciate having the opportunity to comment before this committee. Again FACT agrees with the sponsor that prescription status and limiting the use to individual animal injection are appropriate to managing the risks from this high risk drug.

FACT differs with Pfizer on whether monitoring under the existing NARMS program can be considered a risk management step. FACT also disagrees with Pfizer that extralabel use is appropriate for this drug.

FACT agrees that NARMS monitoring is important. But in this case it cannot be considered a risk management step because there is no ongoing monitoring of Campylobacter isolates in swine and cattle. Unless these are added NARMS monitoring cannot be considered a risk management tool for this drug.

In addition without having data available on the use of this and other macrolide drugs it will be difficult to connect changes in resistance to drug use.

Finally the surveillance alone cannot be considered a risk management step unless it is tied to some plan of action when resistance rises. As we have seen with the fluoroquinolones even when the FDA believes it has clear evidence that an approved drug is causing a human health risk it is very difficult for the agency to correct the problem.

Unless these shortcomings are addressed we cannot agree that monitoring by NARMS should be considered a risk management step.

Given the importance of macrolides to treat Campylobacter infections FACT believes the extralabel use restriction that is suggested by Guidance 152 be required. The sponsor argues that extralabel restrictions are unnecessary because of the many other macrolides that are already approved.

FACT strongly disagrees that these other approvals somehow mitigate the risks from this drug. Indeed as Richard Wood pointed out this risk assessment clearly shows that many of these other approvals would not be allowed if Guidance 152 were applied to them.

And Dr. Sundlof suggested that a finding of high risk is not sufficient to require extralabel use limitations. But we don=t know of any other mechanism that the FDA has that would add the extra hurdle. So this is a risk assessment method that we are aware of.

And so if there is some other way to get a higher risk from high risk then we are not aware of it. So we would hope that we would stick to what we have right now unless we want to go through the whole process of developing another method for finding a higher risk.

FACT believes that high risk drugs such as this one

should only be used when absolutely necessary. And when the efficacy of the use has been shown. We feel that the proposed indication for disease control in cattle is poorly defined and either should be omitted all together or qualified.

In its approval in Europe tulathromycin is only to be used for disease control when the presence of the disease in the herd has been established before preventive treatment. Allowing this drug to be used to treat a whole pin of cattle in anticipation of the stress of transportation would be contrary to the recommendation of Guidance 152 for individual animal treatment.

FACT feels that limiting control claims to infected herds would be an appropriate compromise between unlimited preventive use and not allowing preventive use all together.

Finally, FACT believes that the risk assessment downplayed several potential risks in the release assessment. We are particularly concerned that the potential for --- resistant elements be transferred to grand positive bacteria such as entercocci were not adequately addressed.

FACT agrees with the sponsor that the selection pressure resulting from the intended use of this drug will be small compared to the use of macrolides for mass medication in feed and water. But we feel that the risks from this drug should not be downplayed because it is better than other

approved drugs that have not gone through the risk assessment process.

In the end because of the importance of this drug to human medicine these shortcomings of the release assessment did not change the overall determination of high risk. FACT=s overriding concern in this case is that this will set a precedent for how FDA considers other drugs that do not have such a direct connection to an enteric pathogen.

We hope that in the future the FDA will require drug sponsors to better address the potential of compensable bacteria to transfer resistance and to take into greater consideration the potential for co-existence and cross-resistance stats that is a multiplier of risk.

In terms of setting precedence FACT does not believe it is appropriate for Pfizer in its application of Guidance 152 to use retail meat data in the exposure assessment instead of the approach set out by the FDA. It is inappropriate to compare levels of contamination on carcasses with the levels at retail.

Tolerances at retail level should be much lower then at the carcass level. And we need to remember that we have 98 million swine slaughtered in the U.S. each day and however many, you know, maybe 257 out of that, so five percent of 98 million is quite high.

I would like to conclude by joining Rich Wood in commending the FDA for its work in creating and now implementing Guidance 152. At the same time it should be noted that FDA has still not made a public timetable for addressing the already approved drugs.

As this risk assessment from Pfizer shows macrolides as a class are a high risk to public health and should not be used for mass medication of animals. We also hope that the shortcomings of --- is used to manage risk can be addressed and also that the FDA will restrict the use of this drug to its labeled claims. Thank you.

MS. SINDELAR: Thank you. Our next speaker is Larissa McKenna with Keep Antibiotics Working.

MS. McKENNA: Good morning. My name is Larissa McKenna and I am speaking on behalf of the Keep Antibiotics Working Coalition. KAW is a coalition of thirteen health, environmental, consumer, humane, and other advocacy groups. We seek to protect the effectiveness of life saving antibiotics by curtailing overuse of these drugs in agriculture where they are now used primarily to compensate for poor animal husbandry practices

The KAW coalition commends the FDA for their work done to create a new regulatory framework for addressing the risk from antimicrobial resistance through Guidance 152. The risk assessment at hand clearly shows that Guidance 152 can

be successfully applied.

However, KAW has repeatedly stated in its comments to the agency that there has still not been a timetable published for addressing drugs that have already been approved.

Given that this risk assessment has found that macrolides are a high risk to human health we are keenly interested in the agency=s plan for addressing the numerous other macrolides that are currently approved for use in feed and water.

In addition, the agency needs to move forward on evaluating the vast bulk of other drugs. It has been almost a year since the final guidance has been published. And this is the first time its implementation has been applied to a drug.

There are over 50 drugs currently approved for use in feed and water for food animal production. At the rate of one drug per year it will take the agency over a half a century to complete the risk assessments on the drugs currently approved. We encourage the FDA with human health impacts in mind to please speed up the process.

Again we would like to thank you again for the opportunity to comment here today. And for your continued work on this issue. Thank you.

MS. SINDELAR: Thank you. Our next speaker is

Tamiko Thomas from the Humane Society of the United States.

MS. THOMAS: Hi. My name is Tamiko Thomas. I am an animal scientist with the Humane Society of the United States. The agency rests as the nation=s largest animal protection organization with over eight million supporters nationwide.

I would like to commend the FDA for opening this risk assessment under Guidance 152 up for public comment. The FDA should continue to ensure the assessment under Guidance 152 is open for public discussion. I hope the FDA will speak to whether this kind of public forum will be the norm for future antibiotic risk assessments.

In terms of the risk assessment the determination that tulathromycin is high risk as determined by Guidance 152 is acceptable. For this reason it would seem prudent not to allow extralabel use.

I hope the FDA will speak to whether or not previously approved antibiotics that are in the class similar to this drug and their allowable uses will be reassessed in light of the fact that this drug is being determined to be high risk.

I would also like to know while doing risk assessments of antibiotics is important work what should be occurring in conjunction with this effort is an examination of on farm procedures and conditions that are resulting in

high levels of antibiotic use. There are a number of intensive farm practices that can cause animal suffering and these issues need to be addressed.

The shipment of veal cows that are too young and have inadequate immunity, feeding cattle, high levels of concentrates resulting in a variety of illnesses, barren and crowded conditions in boiler houses and swine facilities, inadequate ventilation, inadequate biosecurity measures are all examples.

While therapeutic uses of antibiotics will always be a necessary tool an increased focus on prevention is required to ensure good animal welfare and to reduce the use of antibiotics by agriculture.

As an example the HSUS actually supports the certified humane label for animal products which has guidelines developed with the welfare of the animals specifically in mind. One of the requirements is that the sub-therapeutic use of antibiotics is strictly prohibited. The success of this program illustrates that a reduction in antibiotic use is achievable.

So in conclusion I would just like to thank the FDA for this opportunity to comment and for all its work on Guidance 152.

MS. SINDELAR: Thank you. Our last speaker is Gary Weber. He is from the National Cattlemen=s Beef Association.

MR. WEBER: Thank you and good afternoon. I have copies of my remarks at the back of the room and I believe the committee has copies in their book.

The National Cattlemen=s Beef Association appreciates this opportunity to share our views regarding both the process of evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human concern in general and specifically issues associated with the use of antimicrobials to treat bovine respiratory diseases.

The NCBA is the largest organization representing America=s cattle industry. Initiated in 1898, the NCBA is the industry leader in providing education and in influencing the development and implementation of science and risk analysis based public policy to protect the health of the U.S. cattle herd, provide safe and wholesome food and improve producer profitability. In this regard we also strive to preserve the industry=s heritable and our future.

The prompt and effective treatment of bovine respiratory disease in cattle is one of the most important steps necessary to protect the health and well being and assuring the availability of products for this purpose is very important.

The qualitative risk estimate for tulathromycin documents the significance of bovine respiratory disease to

cattle health and as well as our profitability. We are committed to continuously improving the health of the U.S. cattle heard and having access to safe and efficacious products to treat bovine respiratory disease is critical.

In addition, the NCBA is a strong advocate for ensuring a science and risk analysis based approach to evaluating antimicrobials. This opportunity to evaluate the risk associated with the approval of tulathromycin through application of the Guidance for Industry Document 152 is of great importance.

Not only have we been supporters of this process but we have also supported post approval monitoring and other monitoring procedures to ensure we have the data necessary to ensure all antimicrobial products retain their safety, efficacy, and are not associated with producing significant antimicrobial resistance problems that would jeopardize human and animal health.

In this regard, we are completely supportive of the NARMS program. And as evidenced by the number of times data from NARMS was employed in the qualitative risk assessment it is easy to see how important the collection of unbiased microbiological samples and evaluation by NARMS is to sound science and risk based decision making.

As the review process for tulathromycin proceeds forward I want to share with you some additional facts and

perspectives which I believe add to the data that illustrate the very low risk posed by the use of this for treatment of bovine respiratory disease.

First of all it=s clear from the review of the qualitative risk estimate that the use profile of this product as it has been discussed leads to reduced problems. And notably the fact that it=s a single injection with great potential for easy use means that you have less animal stress and less use on other antibiotics and other treatment regimes. So that is a very positive factor.

It also seems as if the therapeutic concentrations of the drug will get to the site of activity within hours, last for an appropriate amount of time, and quickly reduce the disease spread and of course provide quick relief to the animals. And last but not least being that it would be veterinary prescribed is an additional factor.

An additional important factor adding to the assurance is a prudent use of products such as tulathromycin is a fact that all animal health products approved by the Food and Drug Administration for use by the cattle industry are evaluated by the National Cattlemen=s Beef Association Quality Assurance program. This program initiated by the National Cattlemen=s Association in 1988 is an industry wide program that contributes to the safe and efficacious use of antimicrobials. In fact I am going to summarize here. There

are a number of factors that come into play and most important is that we emphasize through this program the importance of proper and safe use of drugs, following label withdrawal periods, record keeping, inventory management, and other measures. BQAP is operational in 42 states which represents over 98 percent of fed cattle and 95 percent of cow/calf producers.

One last point I want to raise relates to the fact that we continue to support the reduction of food-borne illness related to beef consumption in the United States and abroad. These efforts are very significant as the risk of acquiring an antimicrobial resistant pathogen as a consequence of the use tulathromycin is a central issue in the qualitative risk estimation process.

In my document I provided you there are two graphs which show the prevalence of E. Coli on 57:H7 which is monitored routinely by USDA and the concurrent reduction in these levels as associated with interventions we have put in place.

In fact the Centers for Disease Control and Prevention recently reported that occurrence of several illnesses related to food-borne, that caused food-borne illness since 1996 have declined. Salmonella down by 17 percent, E. Coli down by 42. Listeria down by 70. All of these risk reduction measures that have taken place and

result in reduced food-borne illness will concurrently reduce the risk in Campylobacters. We proceed forward in proving the microbiological profile of our products.

We are confident that additional technological and procedural advances will continue to reduce the risk of food-borne illness and consequently the risk asserted with potential antimicrobial resistant Campylobacter which is already low. It will continue to decline.

In conclusion, my evaluation of the qualitative risk estimate associated with tulathromycin for parenteral injection, for treatment of BRD, bovine respiratory disease, illustrates how useful the Guidance for Industry Part 152 review process can be. The resulting data indicates very clearly to me that the risk of tulathromycin relative to antimicrobial resistant Campylobacter is low. The potential benefits to the health and well being of cattle are extremely high.

And consequently we support the approval of this important new antimicrobial and we pledge our continued efforts to ensure judicious use of this and all animal health products approved by the FDA for use in cattle production. Thank you again for this opportunity to share these thoughts with the Veterinary Medical Advisory Committee and the Food and Drug Administration. Thank you.

MS. SINDELAR: Thank you very much. As noted

before we will take our break for lunch at this time and reconvene at 1:00 o=clock in the interest of meeting a timely schedule. Thank you.

(Luncheon recess was taken.)

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

1:10 P.M.

MS. SINDELAR: So what I would like to do at this time is get back to our open public comments. And I would like to remind each person who would like to make a public comment to state their name clearly and their affiliation for the benefit of the transcriber. And please try to limit your comments to five minutes or less to give others a chance to also make comments as well before we get into VMAC clarifications and deliberations.

I know there are at least two of you out there and I said I wouldn=t name you to come to make your public comments. I know that there is one. Rich Carnevale, please come forward.

DR. CARNEVALE: Thank you. I am Dr. Richard Carnevale of the Animal Health Institute. For those of you who don=t know who the Animal Health Institute is we are the primary trade association --- and biological focus --- products for both pets and food producing animals. Vaccines and pharmaceuticals. So we have a great --- issue with

antimicrobial resistance of the particular topic of this meeting.

We are pleased to comment on this advisory committee proceeding on behalf of our member companies. Pfizer of course is a long standing and well respected member of the Animal Health Institute.

Antimicrobials have been used safely for many years to prevent and treat livestock and poultry diseases and to enhance production. Antimicrobial products have been stringently regulated by the FDA for safety and effectiveness over the last --- years.

The industry for many years has been meeting high standards for assuring the human safety of animal drugs used in food producing animals as mandated by the Food Drug and Cosmetic Act and regulations.

These standards have covered safety testing for both residues in food and for the transfer to humans of antimicrobial resistant bacteria through the food supply. Numerous guidance documents have been made available to the industry by CVM which has guided this testing over the years. Guidance for Industry 152 which was discussed this morning is the latest such document to specifically address the resistance issue for the approval of antimicrobials in food animals.

The topic of this committee is focused on the

valuation under 152 of a specific antimicrobial product in the macrolide class. Now you can hear me better. The issue of resistance and its impact on human heath is not one of possibility but rather of probability.

That is why AHI endorses the principle that each antimicrobial product must be evaluated on an individual basis to address these concerns taking into account the specific antimicrobial compound, the intended species, the use conditions, and the specific food-borne bacteria that could be of concern to human health. And I think that was demonstrated this morning in Scott Brown=s presentation.

AHI endorses the established principles of risk assessment to accomplish this. While we have made our concerns clear to CVM for some of the overly proscriptive criteria in Guidance Document 152, we are pleased that after several years of uncertainty the agency has provided a step forward in implementing a risk based approach to this problem.

Regarding the specific topic of this meeting the committee should take into account, as was mentioned, that macrolides antibiotics have been used safely for many years in food producing animals.

There is no evidence that their use has contributed to adverse consequences in the treatment of infections in humans. The majority and continued successful use of this

class of compounds in human medicine is mainly against certain respiratory tract bacteria that are not a result of contact with animals or consumption of animal derived foods.

Macrolides are though indicated for treating human Campylobacteriosis which of course can be of food-borne origin. However, since the inception of the NARMS program macrolide resistance rates have consistently been low, not exceeding one to three percent in both poultry and human isolates.

Furthermore the Centers for Disease Control and Prevention continue to report decreasing rates of food-borne illness that they attribute in part to decreasing overall rates of pathogen contamination in animal carcasses after processing due to the specific pathogen reduction measures associated with HACCP implementation.

I would also point out that this committee can review a quantitative risk assessment that was just published in the last year in the Journal of Food Production on both tylosin and tilmicosin. That quantitative risk assessment came to the conclusion that the use of macrolides in food producing animals is of low risk.

It is critical that veterinarians have available to them a wide range of antimicrobials to prevent and treat animal diseases. This is important not only for maintaining

the health of livestock and poultry resulting in a more wholesome and safe meat supply but is also important in mitigating resistance by reducing selection pressures from the overuse of a few antimicrobials.

We appreciate the opportunity to comment on this very important proceeding. One that continues to aid in formulating a sound scientific and risk based approach to dealing with potential concerns for transfer of antimicrobial resistance. We trust that the committee will provide sound guidance to the agency so that the availability of safe and effective animal health products will be assured while adequately protecting the public health. Thank you.

MS. SINDELAR: Thank you Dr. Carnevale. Would you be most kind to provide a copy of that to our transcriber here for the record. Thank you very much. Dr. Paul Sundberg, please take the stand.

DR. SUNDBERG: Good afternoon. I am Paul Sundberg. I am a veterinarian with the National Pork Board and I am the Vice President for Science and Technology for the National Pork Board.

The Board is based in Des Moines, Iowa and represents through their checkoff contributions the 75,000 pork producers that are in the U.S. We have in our system a variety of ways for producers to provide direct input to the programs, to the education and to the research that we have.

And that is primarily through, one of the ways is primarily through a committee system.

We have a swine health committee and a pork safety committee that are made up of producers from across the country that come in and again direct their programs for their checkoff dollars.

The swine health committee is primarily directed at swine health. I mean that is their deal. And they have named swine respiratory disease, I want to make sure that it is clear that they have named swine respiratory disease as one of their primary concerns. And one of the primary things that affects their production.

The pork safety committee has under its purview the antibiotic use and the responsible use of antibiotics for the industry as well as the pork quality assurance program and now our new, our soon to be released responsible use program that talks specifically to producers about using antibiotics in production in a responsible manner.

For the pork safety committee they have said that the timely availability of cost effective products is critical to the animal health and to the animal welfare and a variety of products is important in maintaining the effectiveness of all of those products.

My comments, I have are two questions, one and four for the committee in referencing --. Question one in

reference to the exposure assessment. The review of the risk of exposure to Campylobacter is consistent with our already submitted comments on 152 that were provided back in 2002.

That is that the post harvest processing of meat products will and should decrease the potential for exposure to these bacteria. So it is consistent and the review that the sponsor provided is not surprising.

However, there is a caveat to that I think that needs to be addressed. And that is that there will be a need to take into account the epidemiology of specific pathogens that include the possibility of contamination during packaging and during handling.

To question four, allowing extralabel use gives the veterinarian the flexibility to use their professional judgement on a case by case basis. Pork producers depend on that judgement and their relationship with their veterinarian to provide timely and cost effective care for their animals.

Ensuring producers are fully aware of the importance of working with their veterinarian is a focus of the PQA program and of our responsible use programs. And we feel that the ability and flexibility of the veterinarian to use antimicrobials with their professional judgement is an important thing to the health and welfare of our animals.

And one final point before I stop, just for clarification as well. Last year we processed approximately

104 million pigs in the U.S. That was last year. So just to clarify the numbers that you heard from this morning. Thank you.

MS. SINDELAR: Thank you, Dr. Sundberg. And thank you. If you would please provide a copy of your comments as well to the transcriber. Yes, sir.

DR. ANGULO: My name is Fred Angulo. I am from the Centers for Disease Control. I would like to give a comment. I understand why the purpose is of this VMAC meeting is to review the overall process of Guidance 152. And I think the great news is we see that it works. That we can achieve consensus on the overall risk estimation of a submission for new drug approval.

However, as a model for how to do it I think that this application falls short. I think the model is less then adequate, particularly in the risk assessment, I am sorry, in the release assessment phase of this submission.

Their suggestion that the release, overall release assessment is low and the main reasons are given that the pH diminishes the activity. That is the first reason. They give four reasons.

They also acknowledge in their application that this decreased pH, that pH diminishing activity has been recognized in other macrolides. But we know the resistance is emerging or has emerged or is present in other bacteria.

And so I don=t understand. I think the suggestion that pH is important is mainly related to susceptibility testing of the organism, not as a statement that resistance will not emerge in vivo.

The second reason that they give for an overall low release assessment is they state that there will not be transferable resistance. Well as was stated one important reference is given was the reference given by Jensen in --- up in Denmark which looked at 54 erythromycin resistant Campylobacter isolates and concluded that they were all due to mutations.

That is hardly a large enough sample size to conclude that there is no transferable resistance for macrolide resistance amongst Campylobacter. We need more molecular characterization of erythromycin resistant Campylobacter isolates.

Number three reason is that they say that the overall point mutation frequency would be infrequent. The reference given, I think it was their research, cited looking at 57 strains of Salmonella, E. Coli, entercocci, and Campylobacter. I think that might mean, although not stated, they looked at 15 strains fo Campylobacter and concluded that the mutation rate for 15 strains of Campylobacter is low.

Clearly there is not enough work done to conclude that the mutation rates of a Campylobacter put under

selective pressure in the laboratory has a low mutation rate. I would argue more studies need to be done.

What kind of studies need to be done? The study that needs to be done is a in vivo mutation rate study that has been done by Pat McDermott and others at CVM in which you take some swine, colonize the swine with Campylobacter, treat them according to the label indications with this drug and see if the resistance emerges. And the difference --. This is very reminiscent to the discussions for fluoroquinolones in the floxycin approval process where people said interfloxicin has a low point in mutation possibility. But we know that happened in vivo when interfloxicin was used.

The fourth reason is that they said that there would be low release assessment is they say that according to the way the drug will be used on the label there will be lower selective pressure. That is critical because they clearly state there would be low release potential if used according to the label. But supposed it=s used outside or extralabelly? It would be hard to conclude that there would be low release potential.

Finally, in the way the Guidance is written the sponsor is supposed to look at all the parameters in the release assessment and rank each parameter separately as to low, medium, and high. And then give an overall assessment.

I would urge that you look at each of the nine

parameters that are stated in the document and tell us whether you think transferable resistance is low, medium or high or whether the mutation is low, medium or high. Rank them all so it can be transparent to see how you get to the overall ranking of a low release potential.

Exposure assessment, I think that is less than adequate. In Guidance 152 that was written, it was written with judgements as to the prevalence of contamination at carcass, not at retail. I think when you talk to many consumers they would judge a five percent contamination level in the retail case is not a low rate of contamination.

The breakpoints for low, medium, and high were based upon carcass contamination rates not retail contamination rates. I think if you are going to use retail data for the exposure assessment you need to replace the breakpoints for low, medium, or high for contamination.

Well the good news despite these misgivings on the release assessment and exposure assessment the overall risk estimation is appropriate. It=s worth pausing to see what this risk estimation really means.

It means there is a high risk for human health to be adversely impacted with the use of this drug under the label indications as stated. High risk of public health impact.

Clearly you need to mitigate that risk. One way to

mitigate that risk is to deny the approval. There hasn=t been much discussion about that but that is an option. I think though we can, I suggest that you can adequately mitigate the problems by following the restrictions that are laid out in the Guidance doctrine.

In particular it should be recognized, the key public health discussion I see is how do you implement extralabel prohibitions with this drug. Because if --. My concern is although this is an injectable only drug there is a technology currently available in the poultry industry with broilers in which you can inject tens of thousands of eggs in ova the day before they hatch using the EmBrex technology. And that is an injectable only technology.

I don=t think it would be wise to use this macrolide to inject the eight billion broilers that are produced a year. Nor do I think it would be wise to use this drug in turkeys in a similar high level of use.

So how do we get around this extralabel? How do we implement, or how would you operationalize a restricted use? Well one option is to on the label for this drug state not to be used in lactating dairy cattle. Not to be used in broilers. Not to be used in turkeys. And not to be used in laying hens.

Then I would be more comfortable with the label approvals because if it is used extralabelly in cattle it may

be of limited extralabel use. But I would be concerned about its potential extralabel use in broilers in particular.

I think there is a clear need to review the use of macrolides use across the board and see if there is a need for a class wide extralabel prohibition for macrolides.

MS. SINDELAR: Thank you Dr. Angulo. And I believe I saw Dr. Gary Weber.

DR. WEBER: Thank you. Dr. D. Griffen, who is a professor and veterinarian of beef production medicine and management of the University of Nebraska expresses his regrets for not being able to attend. He had a last minute change of schedules. And he wanted me to comment for him on his observations as the person responsible for supervising the health and microbiologically significant information produced to the United States Meat Animal Research Center.

He has been at this job since 1991 and so he basically has 12 generations of cattle that he has provided supervision for. And oxytetracycline and tylosin macrolides as we have talked many times here today are the principle medications that are used in that setting for respiratory disease control and management and treatment.

Every year over 65 hundred calves are weaned and moved into feedlots at MARC. All the replacement cattle at MARC are raised from these groups. It=s a closed herd. And in the 12 generations of cattle that he has supervised in

13 years there he wanted you to know that based on antimicrobial resistance studies he has conducted there has never been a change in antimicrobial resistance associated with tylosin or oxytetracycline.

And in addition since being closed and the heifers from the feedlot phase go back into the cow calf operation this is important because research at the National Veterinary Services Laboratory in Ames strongly suggests that these respiratory pathogens isolated in calves have their originals from their mothers, from the dam. And so in this closed system he just wanted everyone to be aware that there has been absolutely no evidence in the development of resistance in any of the hemoletical isolates or Pasturella multocida

And so he just wants the information here for the record to say in the real world even with pathogens being targeted by tylosin there has been no change in the 13 years he has been the veterinarian for that facility. And I will provide this for the record. Thank you.

MS. SINDELAR: Thank you, Dr. Weber. Are there any additional comments at this time?

(No audible response.)

MS. SINDELAR: If not, we will proceed to the VMAC questions for clarification. Dr. Jeff Gilbert.

VMAC Questions: Clarifications

by Dr. Jeff Gilbert

DR. GILBERT: All right. Good afternoon. I want to get to the questions that we have developed for the VMAC. These are sort of, you know, overall of the whole process what we have been through. These are some questions that we came up with to sort of provoke your thoughts and maybe get some input on these from you.

Very quickly, question one.

ADo the findings presented in the sponsor=s qualtiative4 risk assessment demonstrate that tulathromycin is safe with respect to the potential for transfer of antimicrobial resistant organisms to humans?@

This is one question that we have thought about and would like your input on.

(Slide)

The second question touches on some of the points that people brought up today maybe. And I think there was one actually from the VMAC already about other species. But,

AAre there other issues to consider relative to this class of antimicrobial agents, that is macrolides or triamilides, these types of drugs?

For example are there other species for which the drug should or should not be approved? What about routes of administration that are or are not acceptable?@

With the routes of administration of course being injectable, feed, water. That sort of thing. This one is an injectable of course.

AAre there indications that are or are not appropriate?@

We certainly heard some comments on that.

AAnd are there any other relevant issues tot this question?@

(Slide)

Finally the third question and then final question is:

AAre the risk management recommendations appropriate, or should they be modified?@

Dr. Brown, myself and others have gone through those risk management options at the end with respect to --- advisory committee and so forth. That table from Guidance 152 is basically example risk management considerations. Are there others that we missed or were those the ones that were appropriate. And that is what we would like to hear.

So with that, those are the questions that we have for you this afternoon. Let me put them back up all on one page. And if I can clarify any of those for you or, Linda, if anybody else has any questions for any of the speakers at this time.

DR. TOLLEFSON: Yes. If anyone on the committee has

any follow up questions feel free to ask those now.

(No audible response.)

DR. GILBERT: All right. Thank you.

VMAC Deliberations

by Dr. John Waddell

DR. WADDELL: All right. We will go around the table and we will address the questions one at a time. And I would like each and everyone of your comments. And we won=t go in any particular order or maybe we will start in one place and then reverse so somebody is not always first or last. So with that I would like to start with Dr. Leggett. If you would give us your opinion on the first question.

DR. LEGGETT: I think as far as it goes I would have to say yes, if it=s used only in the manner described. So with all the limitations to that. And I want to talk about the potential for transferred antimicrobial resistance was sort of brought up and may be beyond the scope here but we are appreciating more and more that emergence of resistance is not just due to the tonnage of antibiotics that you give in the ICU or in a country or in the world. And we have seen the decline of resistance when we have cut back the tonnage.

The other more important way that has actually been

studied by Bob Keato and his group in Spain started off is the transfer of resistance from a pathogen to a commensal agent or from more importantly that it is recognized from a commensal bug in the colon to a human pathogen.

So I think that while we have the data that we have looked at is fine, it=s just the tip of the iceberg. So I am really worried going forward that we will see this sort of maybe even one pathogen to the other as Dr. Powers mentioned earlier. So that while you don=t see it in --- you do see it in the Enterococcus that then goes to that question.

And the quality of risk assessments and some other statements is I think that we need better data about the emergence of resistance to go along with this. It was mentioned that the NARMS data is insensitive. I would like to see larger numbers or other sort of studies done looking at the emergence of resistance.

Just like VRE wasn=t a problem until it was here. So what we are trying to do I think or when we talked about this last year and then they wrote the Guidance, we are trying to avoid that situation. So it=s an attempt to look forward to not face that problem.

DR. WADDELL: Dr. Reller.

DR. RELLER: I would answer this that tulathromycin can be used safely if appropriate bounds are put around its use that I will speak to as others will in questions two and

three.

DR. WADDELL: Thank you. Dr. Thielman.

DR. THIELMAN: Yes. There is a buzz there, but can you all hear me? So I would agree that the preponderance of the data that has been presented here suggests that the probability is that tulathromycin is safe with respect to the potential transfer of antimicrobial resistant organisms to humans.

However, history, politics, and public health has a checkered history of unintended consequences decisions. And I think it behooves us to consider those. In particular with respect to question number three. And so perhaps I will reserve my thoughts for that later on.

DR. WADDELL: Dr. Ohl.

DR. OHL: In regards to question one I would answer yes. I do believe that this is safe with respect to the potential for transfer of antimicrobial resistant organisms to humans. And I think we will get more in question two and three some other issues but would like to bring up now that there still is room for work in this area. Particularly in relationship to Campylobacter and cross resistance. I will leave it at that.

DR. CRAIGMILL: As a toxicologist I don=t like to use the word safe. But I will talk about acceptable risk. And I think in this regard that I think the data that are

currently here show that there is an acceptable risk although it=s a societal decision with regard to what is acceptable and what is not or an agency decision.

But I think based on what we know at this time we should probably go ahead and fill in the blanks as we go along.

DR. PAPICH: With respect to question one I think based on the data that we have been presented today, yes, I would agree with the others that it is safe with respect to the transfer of resistant organisms to humans. Especially under the conditions that have been outlined today.

I also am a little --. The data that we have or the lack of data for problems that have occurred with existing macrolides and considering their widespread use I have not seen any evidence that is very strong at least to convince me that those drugs that are already on the market have posed a problem. That further convinces me that this drug is potentially safe.

DR. WADDELL: Dr. Mealey.

DR. MEALEY: It is Mealy by the way.

DR. WADDELL: Sorry.

DR. MEALEY: That is okay. Yes. The sentence is safe. I guess I would rather reword that a little bit. Just to cover myself. And I would say that tulathromycin from the data is shown represents no additional risk to the potential

transfer of antimicrobial resistant organisms to humans as compared to other macrolides that are currently on the market.

DR. WADDELL: Dr. Sams.

DR. SAMS: Yes. I am also bothered by the use of the term Asafe@. But I think it is fair to say that the drug appears to have relatively low risk with respect to the potential of transfer of antimicrobial resistant organisms to humans when used under the conditions outlined by the sponsor.

DR. WADDELL: Dr. Aref.

DR. AREF: Yes. I will go along. It seems to be reasonably safe. Not that different from the other macrolides. However, I would like to see some restrictions on those and hopefully in the future for the other macrolides.

DR. WADDELL: Dr. Nolan.

DR. NOLAN: Thank you. Yes, I thought the findings presented by the sponsor demonstrated that this drug is reasonably safe in respect to potential transfer.

DR. WADDELL: Dr. Jaffe.

MR. JAFFE: The lawyer in me would also quibble with the word Asafe@. The problem with the word Asafe@ without have real definition of the word Asafe@ because I think safety is an absolute. It=s relative. And we don=t

really have a context in this question what it is related to.

With that in mind I think that the, I think the other problem I have here is that we are trying to piece out to these questions both the risk assessment from the risk management.

And I think that is hard to do. Especially when you are trying to talk about safety, to separate those out here. And I think as some of my other colleagues have said that really is impossible to do in this case.

So I would say that you know this is a, I would agree with the assessments, characterization that this is a critically important drug. That there is a risk, it is category one and a high risk. And so I think the only way I can answer this question is in the context of what the risk management measures are for it. And I am not sure I am yet comfortable with what at least the sponsor has proposed on that.

DR. WADDELL: Dr. McGlone.

DR. McGLONE: Yes. First, I would like to compliment the FDA and the others for taking this approach. I think it=s an interesting and healthy approach to add to the arsenal of tools that you have. I don=t have any problem with the word Asafe@ because I am not a toxicologist and I am not a lawyer.

(Laughter.)

DR. McGLONE: But to answer the question specifically we were not presented any evidence that indicated there was an increased risk of safety of any sort by this drug.

DR. WADDELL: Dr. Jack.

DR. JACK: I basically tend to agree with everyone at the table. I think the answer to the first question should be yes. Despite all our worries about specific language.

DR. WADDELL: Dr. Wages.

DR. WAGES: You know like everyone else I believe the answer is yes. But I think it=s based more on, at least I didn=t see anything presented by the sponsor that alarmed me of the future or the potential for the transfer of resistance from animals to humans. So, on that basis it=s yes.

DR. WADDELL: Marguerite.

DR. PAPPAIOANOU: I basically have come to the point where I don=t know whether this drug is safe or not. I have heard a lot of comments on what appears to be the case or based on what we know at this point or we have not seen any evidence.

And there is a huge difference between a negative finding versus a situation where definitive studies have not been carried out. And what has been seen in vitro does that

really relate to what might happen in vivo.

And given how the importance of the drug was determined, which was independent of any of this, which I really applaud, and that it is a critically important drug in the absence of not demonstrating definitively I believe a more conservative approach should be taken.

And so if I guess if I had a third column to say I don=t know, it would be there. Since we have two columns I will put it in the no column.

DR. WADDELL: And the chair will answer the question in the affirmative also. Okay. We will move on to question number two. And I think the way to approach this might be to separate two into the four parts and go around each time on each section. So, at this time we will start with Dr. Mealey to answer the first part of question two.

DR. MEALEY: That was to punish me for correcting you.

(Laughter.)

DR. WADDELL: You notice I avoided this last name.

(Laughter.)

DR. MEALEY: My first name is Katrina by the way.

(Laughter.)

DR. WADDELL: You can start next time too.

(Laughter.)

DR. WADDELL: Just kidding.

DR. MEALEY: That is a tough one. Other species for which it should or should not be approved. I think there are enough questions out there that I would probably feel safest having it be approved only for the species in which it has been studied to this point. So no additional species.

DR. WADDELL: Okay. Everyone is in suspense as to which way we are going to go. Dr. Sams.

DR. SAMS: I agree completely.

DR. WADDELL: Okay. Dr. Aref.

DR. AREF: I agree also.

DR. NOLAN: I don=t think we know enough for approval to other species.

MR. JAFFE: I mean I guess my question is here the sponsor has requested its approval in cattle and swine. They haven=t requested approval for anywhere else, any other animals other than that.

I am assuming this question deals with not just approved uses but also extralabel uses. And I don=t see any reason at this point to, I haven=t seen any evidence to suggest that it should be used extralabel. I haven=t heard any evidence of where it would be used and what animals it would be used in and whether it would be safe in those animals.

So, I guess I would say that. And I guess I would also question whether we have limited the use in cattle and

swine to the proper use. I know that in Europe this drug is used in a more limited, has been approved in a more limited capacity than is being requested here. And I think that might be something to consider.

DR. WADDELL: And Dr. McGlone.

DR. McGLONE: I hate to be contrary. Okay. No, really I don=t.

(Laughter.)

DR. McGLONE: But generally, it=s clear we haven=t been presented evidence from other species, from a lot of species that the product is safe. But, we have to consider the bigger picture. And the bigger picture involves for example animals with diseases that are difficult to treat that include minor, what might be called minor species. And I would hate to have animals suffering when there is a drug that might be available that might be effective.

I would hate to think that this committee would cause suffering in animals by not approving a drug that might be effective. And because of the way the world works and budgets assigned to safety and efficacy testing it=s unlikely that minor species and also rare infectious diseases will ever get the dollars needed to demonstrate safety and efficacy.

And if reasonable people use special drugs, let=s just call it a special drug for the moment, in a professional

manner I think that the net outcome might be relief from suffering and I would hate to prevent that.

So I think that the FDA ought to use some logic and make a good faith effort to allow a drug like this or this class of drugs to be used in minor species and for unusual conditions as a way of reducing suffering in the world.

And I think the risk associated with limited use in unusual circumstances to reduce suffering the risk in terms of food safety is minimal since we are talking about a minor species and a minor event.

So I hate to disagree with all my colleagues and maybe we want to go around one more time on this question to find out what people think about relief of suffering in species that never will be studied.

DR. WADDELL: Dr. Jack.

DR. JACK: I guess I don=t hear what everybody said is so contradictory. I don=t think we have been presented with data specifically to this question unless we are willing to extrapolate from other macrolides. And there are a couple of other species that we have been told you shouldn=t put macrolides into. And from that standpoint I tend to agree with Dr. McGlone.

DR. WADDELL: Dr. Wages.

DR. WAGES: I guess I look at this not from the extralabel part. I guess I would address the extralabel in

number three. But I can=t sit here and I don=t think this committee can sit here and be predictive about how things are going to evolve and what diseases we are going to be faced with in the future, to categorically look at FDA and say never approve this in a certain species.

You know what if we find out that this is the --- chicken with this product it will act, basically eliminate Campylobacter in a poultry house and eliminate the contamination that occurs. So I just am uncomfortable making blanket statements on we should never approve something. I agree with the minor species.

You know you have sheep and goats out here that are kind of left in the, even though the MUMS bills are out there, still it puts a stamp on a product that I believe that if you look at categorically saying that we should not look at other species or should not be approved.

So I don=t think at this point there is enough information to say no, it should not be approved for other species.

DR. WADDELL: Marguerite.

DR. PAPPAIOANOU: I am a major fan of evidence based on decision making as people could tell probably already. And again I don=t feel there is evidence. And again given this critically important drug for human public health purposes I would have to say no.

DR. WADDELL: And I would say I would have to agree with Dennis that we don=t, I mean we weren=t asked, I mean I certainly wouldn=t feel qualified to tell a sponsor what other species he should go after or shouldn=t go after. Let him bring the evidence if there is a need. And you know they find something that does work. Dr. Leggett.

DR. LEGGETT: I will address these questions as a human veterinarian because otherwise I know nothing about it.

(Laughter.)

DR. WADDELL: Is there any other kind?

(Laughter.)

DR. LEGGETT: With human use drugs you can, once they are on the market you can use them for other indications than what they were approved for. But if the company wants an actual approvable indication then we need to see the data. So the comments about the minor species I interpret it in the way macrolides are used in people. So they are used for staph and strep infections. The only thing we looked at here was this part of stuff and maybe there are other admission if they have that data.

So, I would have no trouble in a cow with mastitis or with rot foot or whatever was, foot rot.

(Laughter.)

DR. LEGGETT: That I don=t see why you couldn=t consider a drug like this. But I would definitely limit it

for the time being to these species of poultry as we talked about being that and ground water, and eggs being the major sources of Campylobacter which is the second most common resistant pathogen in food-borne illness as was pointed out in the American Health, The American Animal, AHI last year.

DR. WADDELL: Okay. Dr. Reller.

DR. RELLER: I appreciated Dr. McGlone=s comments. So I would approach this a little differently. And if, though it was not done here, and we were not asked, but the constraints of that first question, I mean we are sort of put in a difficult position. Because is Asafe@ without the potential, I mean we are put in the position of prophesying what was going to happen. And I am very uncomfortable with that.

And in light of Dr. Thielman=s comments it=s sort of like the investment houses past performance is no prediction of future performance. So consequently if I were to take one group of animals and did the risk exposure consequence assessment I think that this product should be proscribed for use in poultry.

And by looking at it with that strong statement and a little more latitude you have got some flexibility in some other arenas. Because I think if we were to have the discussion many people would feel quite strongly about even considering the use of this product if there were no other

erythromycin or macrolides out there and it was a question of using it in that food animal.

So I would answer this, for now I would proscribe it for use in poultry, all poultry period. For any purpose. If we were in the approval process approve it to be used safely with the constraints that will eventually come out for the indications requested. And not box us in on professional by prescription only for therapeutic use in other situations. Akin to what Dr. Leggett said.

DR. WADDELL: Dr. Thielman.

DR. THIELMAN: Hello, testing. Can you hear. Okay. So, yes I actually agree with the comments of Drs. Reller and Leggett. The data that were presented to us for swine and cattle I think are pretty clear. The risk assessments have been made.

I am extremely uncomfortable with the use of tulathromycin in poultry without a similar risk assessment. But understand that there may be other orphan indications in minor species for which the judgement of a veterinarian should prevail. So that would be the nuance to my response.

DR. OHL: I had to have Art help me out and tell me what a minor species was. I think I have a list here at least of the major ones and can assume the rest are minor.

I am not a veterinarian and so I can=t directly address the questions of the use in some of the other species

and what the need is there. And so I will stick to what I would be concerned with as a doctor of humans. And one who is concerned with antibiotic resistance. And where the issues lie. And for Campylobacter which is a food-borne organism of most concern here.

Clearly poultry is where we believe most of these infections arise. And some from ground water. And I would think that for any use to be used in poultry we would need to sit down and do a different risk assessment. Because it=s completely different. The categories would all be completely different here. And I would be very uncomfortable with its use in that species.

DR. WADDELL: Dr. Craigmill.

DR. CRAIGMILL: When we talk about which species whether it should or should not be approved in, and I will start from a number of angles. From the first one I think it=s really up to the sponsor to determine where it wants to go after. Which species for which they want to get the drug approved.

If we are going to talk about extralabel use I am very glad that Dr. McGlone covered all the minor uses. Because I think there are some extremely important ones, particularly for a drug with these characteristics.

For some of the non-food animals or some of the food animals that are wild life this is a drug which could be

a God send where you could give it once and it will keep them, you won=t have to corral them in again or treat them.

So I think in terms of the minor uses and the extralabel uses those things should be left open for us to explore. Maybe we will find out that it=s as bad as tilmicosin for goats, which goats don=t like tilmicosin. Steve is that right? Is that the one that they don=t handle very well? I was just making sure he was awake.

(Laughter.)

DR. CRAIGMILL: But anyway those are the kinds of things that will shake out with treatment. I think once we know withdrawal times for this particular compound which are proprietary at this point based on the long half life I suspect the withdrawal time will not be short. It may preclude the use in poultry because poultry grow so fast you may not ever be able to get it into them in time before you slaughter them.

I would like to just say we ought to keep our options open for this, allow extralabel use, and see how it shakes out.

DR. PAPICH: I agree with the comments of many others that have been made already that at this point I think it would be premature to exclude it from other species until we have other data that tells us otherwise.

I would rather wait to give the sponsor the

opportunity to present data to us, much as we have already heard today in the case of the cattle and the swine. The sponsor should have the opportunity to present data that makes their case before we sit here and make a judgement prematurely to exclude it from one species or another. I think that would be unfair.

And a number of comments have been made about the minor species. We can=t exclude it, I don=t think, from the minor species until we have better data because it potentially could be valuable for some of those indications. It perhaps could replace drugs that do pose more of a risk. And that would be another opportunity where this drug could possibly be helpful.

We can=t predict adverse effects and that may exclude some uses. But that can=t be predicted because we don=t have the data. Art mentioned the tilmicosin situation. The thing that limits the use of tilmicosin in some species is a cardiovascular toxicity. It has nothing to do with the antimicrobial effects. And that won=t be determined until work is done with this drug in other species.

So I think there are many reasons that stand out that at least convinces me that we can=t at this time exclude other species without other data.

DR. WADDELL: Since Dr. Wages represents our feathered friends, it seems he has got his feathers ruffled

here in this discussion. So he would like to make additional comments.

DR. WAGES: Just put some people=s minds at ease here. If you look at our number one pathogen that we deal with from a disease standpoint it=s E. Coli and this product wouldn=t be high on our list if you gave it to us tomorrow and it was free.

The other potential on a product like this would be necrotic enteritis control or treatment for a break. You know the old erythromycin, tylosin, all work fine. So this product is not even a, if it came to us we wouldn=t even tell them to waste $5 on trying to get it.

As far as an injection, you know the only approved injectable antibiotic in poultry was removed voluntarily from the market. And that was actually fluoroquinolone that the industry said we are not going to do this because of the fluoroquinolone issues.

The only things used in egg are the ones that are already approved for day old injection which are gentamicin, ceftiofur. You know the people that spout that we will go out here and do that has never raised a chicken or dealt with a chicken in their life. And its all what they read or hear or want to. So that is just not what we do.

The only things that are put in the egg, and I will say by the majority of the integrated which represent

95 percent of what gets done in the United States only the injectable in the egg through the EmBrex is done because they took a product that was already in day old sub-q and it makes it easier labor. You cut down people injecting it. And that is why it is done like that. Thank you.

DR. WADDELL: Okay. We will go onto part B of question two. And that addresses the routes of administration that either are or are not acceptable. Why don=t we start with the attorney down on the end. Greg.

MR. JAFFE: Well the sponsor has suggested that it will be injectable. And I think that that is the only way to go here. I think if you based on the Guidance 152 and the fact that this is a critically important drug and that comes into category one I think especially at this point without more information that it should only be in the injectable form and not be allowed in feed or water at this stage.

DR. WADDELL: Dr. McGlone.

DR. McGLONE: Well, I don=t feel like I have enough information to really address this question. I would be uncomfortable with using it as a sub-therapeutic antibiotic at this point just because we don=t have, we weren=t presented with data. And we haven=t been presented with data on abscesses from injection sites and to know whether it=s caustic or whatever problems might exist. So, I would suggest, at least I don=t think we have been presented with

such information.

So I think we don=t have actually any information to answer this question at this point. So, I can=t give you an answer. Sorry.

DR. JACK: Ditto.

DR. WAGES: I guess it=s, I kind of agree. I guess I am a little concerned that in my mind if we have already classified this as a category one drug determining whether it goes somewhere else other then in individual animal treatment is a moot point. So I don=t understand why we are even talking about this, in my opinion, because based on what we have decided how were are going to look at a category one this was --.

You get an extralabel it could be may and might be and there is some wording. But I think it was pretty evident that mass medication or low level use, et cetera was not going to be done. So right now the way it=s used as individual animal is what I would buy.

DR. PAPPAIOANOU: I would agree with that. Injectable only.

DR. WADDELL: Ditto.

DR. LEGGETT: Nothing to add.

DR. RELLER: Injectable only. I appreciated Dr. Wages= comments including about the poultry. But I think one of the purposes of the discussion of some things that

might be self evident is to get them in the record about how strongly the views are.

I mean there may be for legitimate reasons a range of perspectives from those entrusted with caring for animals as veterinarians, but from the human infectious disease practitioner side it was pretty strong. And it was unanimous. And it=s in the public record.

Prevention is very important. And I think there is potential risk in assumptions that are not publicly articulated. And consequently the emphasis on that and also even though to emphasize parenteral injection use only based on currently available data even though it may be self evident. And that was all that the sponsor requested.

DR. THIELMAN: I would agree. Injection only based on the data that are presented. And just to add to Dr. Reller=s comments further, if it=s not an issue in poultry then there shouldn=t be a problem with putting it in the record or package insert or whatever.

DR. WADDELL: Dr. Ohl.

DR. OHL: With regard to tulathromycin and it=s injection is what it=s been presented for. But I look at the questions. Is this a question related to, it says to this class of antimicrobial agents and I am wondering if there is another angle on this. So I might just address that.

That from the standpoint of how much particularly

oral or adoral macrolides are used there really is not, does not seem to be a lot of data to me to know what this means for the risk to humans.

Specifically we need more information on resistance in Campylobacter. Both how, from transferable elements as well as to phenotype. We need more data on how Campylobacter is and how much of it is really in the retail meat market. I saw ground beef. I saw pork. And so for this angle, but I don=t know about the chicken angle. I have seen some other work on it.

So I think that for the class of antibiotics I think we need to get more information on macrolides and should start thinking about what routes of administration mean there as well. And I can=t answer that question for the class without having that data presented to me.

DR. WADDELL: Dr. Craigmill.

DR. CRAIGMILL: I believe under AMDUCA that it would be illegal to use this drug in feed. Is that true for water also?

DR. SUNDLOF: Nodding of head Ano@.

DR. CRAIGMILL: So it could possibly be added to water under AMDUCA, which doesn=t sound like a very good idea at this point. I will just leave it at that.

DR. PAPICH: Much like my answer to the last question at this point I wouldn=t feel comfortable with

excluding it from other routes of administration. We just don=t have data in front of us that tells us much about other routes of administration. I would be surprised if it was given orally that it would be active. It=s probably not absorbed very well.

But if the sponsor came forward to develop some sort of a topical formulation for it I don=t think that they should be prohibited to do that as long as they can present data. Perhaps there are intra-memory uses or other topical uses of this drug. And at this stage I wouldn=t want to exclude that.

DR. MEALEY: I have a question for clarification. The pharmacokinetic data, it just lists that a parenteral injection was administered. But I don=t know if that was IM or sub-q.

DR. BROWN: That is correct. We have chosen not to disclose the route of administration specifically. It is parenteral injection not intravenous.

DR. MEALEY: So I guess, so the routes of administration, parenteral injection, includes two different ways. And I guess I would even limit --. I have concerns because if it was given subcutaneously we don=t know what IM is. If it was given IM we don=t know the pharmacokinetics of the subcutaneous route of administration.

So I would even say that the parenteral is a little

bit vague. And we don=t know what the other --. We don=t have enough information even about the other form of injection.

DR. SAMS: I agree. We have very little information about other routes of administration. Even though this drug is a macrolide it does differ chemically from the others with the addition of two amino groups. Therefore oral bioavailability is likely to be much different from the other drugs in the group.

Therefore concentrations of the drug within the GI tract probably are much different from those that we have heard about today. So we just don=t have sufficient information to make any conclusions at all about the acceptability of other routes of administration.

DR. AREF: As a decision I would rather have some results to decide from rather than get the results backdoor. So I would say you would have to go with what they already have studies about.

DR. WADDELL: Dr. Nolan.

DR. NOLAN: Yes. I don=t think we have any data on which to base a decision here on the use of the routes.

DR. WADDELL: Okay. And we might get a lot of the same answers with the next one too. I think in Nebraska we call that beating a dead horse.

(Laughter.)

DR. WADDELL: So, let=s go around quickly. I will start with the indications. And the same thing goes there. I mean there might be potentially some great other indication out there that hasn=t been brought forth. We just don=t know.

DR. PAPPAIOANOU: Yes. Again, I reiterate. I agree with everybody that we haven=t seen a lot of really relevant information and so again I think the most conservative approach is one given the importance of this drug in human health. So.

DR. WADDELL: Dennis.

DR. WAGES: Ditto.

DR. JACK: Ditto.

DR. McGLONE: I don=t want to repeat but I agree.

(Laughter.)

MR. JAFFE: I am not going to repeat. But I do think, I mean I look at this, you know FDA did say this is a critically important drug and so when we get to all these risk management, or we consider these things risk management measures that are, if it is critically important we should be erring on the conservative side and using this drug as limited as possible.

So, I think for all of these things it should be done where it is absolutely necessary to be used and used in a way that will limit the possibility of any adverse impact

on human health.

I think one of the things I have been missing here is some of the efficacy data. I know the sponsor probably has it and it=s given it to FDA and it=s proprietary. But I mean part of the question here is, I mean, when we get these kind of --- issues you are getting to tradeoffs here.

And the issue is, you know, is this, I don=t know how much more effective this drug is compared to other drugs that are out there to treat this disease that it=s worth doing and what the trade off is between using this one and another one.

Will it replace one that is more harmful potentially more harmful or replace one that is less harmful. And so not having that information given the fact that it is critically important we should be erring on the conservative side and using this as limited as possible.

I am not sure the sponsor yet has met the burden to show the difference. I had raised the question earlier about the difference between cattle and swine. And why one is being used only, for cattle it=s being used not just for treating the animals with the disease but also for control of ones who might get the disease.

And as I understand this drug is being used in Europe in a much more limited capacity of some sort. And I guess the question in my mind to this one is can it be

crafted more conservatively how it is being used at this point. Until we get more data, until we see how it is used in practice, see how many doses are really used in practice to see what effect it might have.

DR. NOLAN: I don=t think we have enough data on which to base a recommendation for other indications. Other then the ones that have been presented.

DR. AREF: I agree.

DR. SAMS: Agreed.

DR. MEALEY: Agreed. But I have a concern that I don=t know what is going to happen with these recommendations or anything. But, and I am sure that the human veterinarians over there would agree that if we limited drugs to use only for what they were indicated for, if we limit those choices I don=t think that we are practicing at the level of the standard of care for veterinary medicine and public human medicine as well.

I don=t know how many, you know, erythromycin probably approved for upper respiratory tract infections probably gets used for a lot of different things. And I am concerned that if we make some recommendation that actually gets accepted that this drug will be limited in its use for ever and ever and ever.

Is there any kind of clarification there as to what would happen? I mean if it does ultimately prove to be safe

and not increase risk for antibiotic resistance in human medicine or in human patients, would then the company actually have to go back and prove those? I have concerns about that.

DR. PAPICH: At this point I would want to limit the indications because we just have a lack of data.

DR. CRAIGMILL: I agree with Mark and also Dr. Wages has already told us that E. Coli in poultry it=s probably not a great idea.

DR. OHL: In regards to the question -- is this on? In regards to the question is this particular compound tulathromycin I believe the indications that were presented are appropriate.

In regard to the possible question as to the class of antimicrobial agents as stated on the slide I would have to see more information related to those particular labelings. And I would add to the record that I am concerned that some of those indications may not be appropriate knowing what I know now.

DR. THIELMAN: I have seen a lot of data on the microbiological effects that we were trying to extrapolate to human health but very little efficacy data. So it=s very hard for me to speak to what an appropriate indication is or is not for this drug.

DR. RELLER: The answer here, I will reserve most

of my comments for when we get into the risk management, flushing that out. But to me somehow getting in the indication that this is for the therapy of sick animals by prescription of veterinarian for bovine foreseen respiratory disease, sick animals.

Now that logically could encompass, you know, intervention in a cluster of sick animals before getting in a larger group. I mean it=s not necessarily one by one. But avoiding the whole concept of mass or larger numbers treatment to prevent something. I mean this, the indiction is for therapy of the sick not prevention of economic catastrophes is the concept I would like in the record.

DR. LEGGETT: I answered in regarding the specific drug, I sort of answered it when we were talking about the 2A part of it. In terms of the macrolide class -- before I go on.

It was pointed out to me earlier in the day by a veterinarian that the time window for bovine respiratory disease is very short. And once you are -- and after that there is no problem. So I could understand why you would want that in cows as opposed to the way swine are grown.

Now in terms of the class of macrolides, based on what I heard today I am worried that the macrolides that are already on the market are more dangerous than this one. Because of the ways that they are used in the long run when

they are used for 161 days or whatever now and then used as growth promoters.

So not knowing anything about it that would be my concern about the class. But I state I am not an expert.

DR. WADDELL: Okay. One more part of this question. Are there any other relevant issues? I can=t believe there is going to be a lot that comes up on this but let=s go around the horn quickly and just address that portion of question two. Why don=t we start with Dr. Thielman.

DR. THIELMAN: None.

DR. OHL: That is one way of passing off of who talks first. I think the relevant issues have already been addressed peripherally with the other questions. And I will leave it at that.

DR. CRAIGMILL: I can=t think of any at this time.

DR. PAPICH: Neither can I.

DR. MEALEY: No.

DR. SAMS: No.

DR. AREF: No.

DR. NOLAN: No.

MR. JAFFE: No.

DR. McGLONE: I hate to be different.

(Laughter.)

DR. WADDELL: No you really don=t.

(Laughter.)

DR. McGLONE: I have a big one. And it has to do with something that was mentioned by the sponsor, by the FDA, and by several of the people asking questions today. What we really are talking about in this risk assessment is two things. One is the risk to people. And the second is the benefit to the animals. And what is missing is the benefit to the animals. That is not in the equation.

And if you can cure a million animals of three days of agony before they die and change the food safety risk point 001 percent, then that is the way a risk assessment should be done. The benefit versus the cost. And if the cost in terms of human health is zero, then you might want to prevent that suffering.

So I don=t think there has been enough, even though it=s been mentioned by all of the people, I don=t think there has been enough qualitative or quantitative data presented on the positive side.

Because if the drug were not effective for example, if it didn=t improve the welfare of the animals, then there also, and it was, or only a slight improvement and yet there was huge food safety. The balance hasn=t been addressed except on just one side of the equation.

So I find the overall assessment really good for about 50 percent of the equation. And the other part I think

is missing. And I would encourage the sponsor and the FDA to fill in the rest of the equation.

DR. JACK: With the assumption that this VMAC group was asked to look at the introduction of microbial resistance organisms into humans or the concern of, and I don=t think we were asked to look at the risk of getting the antibiotic itself into humans. That is not really our issue.

I think there are a lot of other issues that we haven=t addressed around this table but I am not sure that they are really our bailiwick. So from that standpoint I think we are in pretty good shape.

DR. WADDELL: Dennis.

DR. WAGES: Yes. I would agree. The majority, I agree with what was said earlier. But that is not what we were asked to do. You know we were pretty focused on the transfer of resistance basically through the use of this antibiotic to humans either through, predominately through the food chain which is why the 152 document was originally put in was for the antibiotic use and approval process for food producing animals.

So I agree with you but with what we have got, ditto or something.

DR. PAPPAIOANOU: I agree that a lot of issues have been brought up. I am not --. And as long as they get catalogued in the report as having been so, such as some of

the environmental issues that were brought up earlier. A lot of the comment about, especially when we are talking about this class of antimicrobial agent, what the issue is relative to all the other ones that were brought in before 152 was put into effect.

Issues of having data from in vivo studies in addition to in vitro, whether we are not left with a single anecdotal report I think would be very helpful.

DR. WADDELL: I would have to agree with Dr. McGlone that there are other things. But actually we had a fairly narrow focus here today.

And I mean another thing I would like to add and see is that with approvals of new tools like this with our producers we may end up actually reducing the number of colds and chronics. And there will be a healthier product actually coming to town and going to slaughter in the end.

So, those are things that I guess are I accepted as a given that this product will, or any new tool will help us with. So we are more or less focused on the safety issue and the risk evaluation.

DR. LEGGETT: A couple of comments. Nothing really exists in a vacuum. And I think that we got around to Guidance 152 because we had been too lax in the use. And there is going to be a yin/yang. So but I think going forward we just have to keep trying to in an iterate fashion

make it tighter and make it better.

I also think that in the human antibiotic realm there have only been two new classes of antibiotics in the last 20 years. And it=s because the drug companies do their own risk analysis. And their own risk analysis how much money do I make and is it better to give an antibiotic that I give at one shot at one time. Or is it better to make some sort of cardio-protective drug that all cows are going to have to take for the rest of their life.

(Laughter.)

DR. LEGGETT: In terms of, I got the impression that you were worried sort of about the quantity of risk analysis. This is a qualitative process and is always going to have a problem with that. But I don=t think we can do quantitative risk and the statistician can remind us but we are talking about very little incidence of events.

And more important we don=t know what is going to happen going forward. So I think we would be fooling ourselves saying that we can get a very reliable quantitative estimate.

And finally I think that given that very, very low incidence we also have to allow industry to come forward and develop drugs. And by making it more quantitative it would make an enormous cost to them. And they would just say no, it=s not worth it.

And then finally I assume in terms of other relative issues, I assume there is no polypharmacy in cattle or swine so we don=t have to worry about QTC.

DR. RELLER: I didn=t have any comments until Dr. McGlone raised his. So maybe I will use this as a sequel to that question three. And recognizing the importance of treating the animals appropriately and I think it=s, the comments made earlier about the other preventive measures that are, you know, deserve increased emphasis that were not so reliant upon antimicrobials.

But very specifically I would be concerned about giving a drug three days before slaughter and a drug that has a half life of 90 hours which is the seque into the next question of the importance in my mind in risk management of having a wide exclusionary period before slaughter in these two food animals.

Now how wide that should be, you know, in terms of exact days, but a very wide margin. I have given the reality of when, or some of the things we have heard earlier about when the animals are at greatest risk and how they are treated it may not be an issue. But again I think it=s very important to articulate whether it=s 30 days or 60 days or whatever days it is. There are people more expert than I on that.

And then there are other things that will come up

in the risk management when the time comes.

DR. WADDELL: Okay. I believe we made it around the table on that one. And we are on the home stretch. Question number three. Are the risk management recommendations appropriate or should they be modified? Dennis why don=t we start with you and go that way.

DR. WAGES: I think the only one that if we look at, the one that I guess has not been addressed to the point of my comfort is looking at the extralabel drug use of the product. I think the NARMS, the VMAC committee meeting in evaluating this, you know NARMS was actually put in place based on the fluoroquinolone approval in poultry, which was a VMAC recommendation in >95/=4, >94, with its restrictions on extralabel drug use and prescription only.

I think when you look at it in an individual injection of an antibiotic like this regardless of its importance the question whether you are going to use this extralabel.

And in my mind I think of extralabel in two ways. One is when I go, and I know you shouldn=t, but in my mind you can go extralabel and just go to any species and just throw out. Verus extralabel use for different diseases in that same species that it is approved for.

And I am comfortable with using this product in beef cattle or in swine extralabelly for a variety of other

conditions if they would be indicated. But if we look at the information that we have been presented today and through the risk assessment I don=t see any overwhelming evidence that says we should restrict the extralabel one way or the other.

If you look at Guidance 152 it tells you we may restrict extralabel use. It might be beneficial to do that. It really doesn=t give you a clear cut that if it=s a category one you are not going to use this product extralabel. That is what I was in favor for. I was in favor if you were going to call this a one, is that being darn important.

DR. WADDELL: That was close.

(Laughter.)

DR. WAGES: Whew. If it=s that important you know let=s call it and let=s go right down the line that it is not going to be mass medicated. It=s not going to be extralabel use and go right down the --. There is nothing that has been presented that tells me that it=s a risk to go extralabel.

But I am more comfortable with we have called this important. It=s a category one. I am fearful that we are going to wind up calling anything that ever gets approved from here on out a category one. It will lock us into that. That concerns me somewhat.

But I think if you call it important then by golly you go down the line and it=s a yes, no checkoff and they

have to, the sponsor presents compelling evidence to change that. There has not been anything in my mind to show that. So I think the risk management that has been identified as originally in 152 where it=s the monitoring the VMAC meeting and no extralabel drug use, I am going to call that acceptable.

DR. WADDELL: Okay. Dr. Jack.

DR. JACK: I would love to say ditto again, but I am not sure I understood what he said.

(Laughter.)

DR. JACK: Now I think from the challenge, I have to admit to you, you know call me simple, but here we are presented with a drug that is to be used for respiratory disease in cattle and swine. And all the evidence we were presented was Campylobacter and GI disease. And I have to admit that confused me a little bit.

But the risk management recommendations, again like what my colleague here said about individual animal use, the issues of withdrawal I think are left for another group or somebody else to describe. But from what I have read, what I have heard today, the risk management concerns have been met as far as introducing anything microbial resistant pathogens into people. So I would answer that question yes.

DR. WADDELL: With no modifications?

DR. JACK: Not that I could recommend.

DR. McGLONE: Okay. As I understand it the question relates to this table that has risk management recommendations being marketing status by a prescription extralabel drug use. One graph said no. The other said restrictions. Which one is appropriate? Do you know?

MR. JAFFE: The sponsor has suggested.

DR. McGLONE: Restrictions. And the other one is no.

MR. JAFFE: No, no. The sponsor has suggested no restrictions.

DR. WADDELL: No restrictions on extralabel drug use.

DR. McGLONE: Oh, no restrictions. Right. Okay. And then so restrictions on extralabel drug use and low extent of use post approval monitoring, yes. And VMAC review, yes, which we are doing. So I agree with that.

But I think that the risk management model is inadequate as I have said before in that the other side of the equation is what is the benefit to the animal. And is it high, medium or low. And if it=s high then it changes this a little bit. And then that gets to the extralabel use because if you have a sheep that is dying, an individual animal now I am talking about, not flocks of animals. And I think this determination ought to be made on an individual animal level.

If you have a sheep or a dog, but we will say a sheep, and it=s doing very poorly with a respiratory problem and you have this bottle of antibiotic in your hand, why would you not want to use it? You would want to use it.

And so you don=t want to -- if reasonable people viewing data for multiple species but not that species in similar situations would come to that conclusion, then I think we shouldn=t hamstring, which is a big term, we shouldn=t hamstring people and prevent them from using their professional judgement in the matter in which they have been trained to reduce suffering in the animal. And in some cases to reduce the food safety burden as well. Because if that animal were sick and then killed and eaten there might be a bigger problem than if it were treated, made well, and then eaten.

So I think as far as the table goes the question is that if the data are appropriate. But I don=t think the equation is complete.

MR. JAFFE: I would agree with my colleague next to me. I also think that -- to my left. Dr. McGlone. I also think that it=s been very hard to do this today because we haven=t seen some of the data or information about the efficacy of it. What this is going to replace if it is going to replace something. What it does to the animal.

And I think without that it=s very hard to assess

really the value of this and therefore the tradeoff that one makes to the potential. Because this is a critically important, identified as a very, very important drug and because it is in category one, the high risk category.

So without that data it seems to me we need to have as much risk manager measures as possible to limit the use of this out there and only to use it where it really is absolutely necessary to be used. So in my mind that should be, it should be a single injection.

I mean I think the sponsor has done a good job of trying to address some of that by decreasing the total use of it by doing the single injection and by limiting it to a prescription. I think those need to stay.

I would, you know, I think that it should be limited to only the animals with the disease that need it, the swine and the cattle and not done more in terms of control or treatment, or preventive, as a preventive measure. It should not be done that way.

In terms of the extralabel use I mean I guess at this point I would also say that again that that is something that shouldn=t be used. I understand the argument that has been made about the minor use or minor species. And I guess maybe if they are not food animals, if you could make a distinction between using it in a food or non-food animals that might make a difference.

But I think especially in food animals are using it for other indications. But again that is just going to increase the use of this critically important drug which may have no benefit to that animal, and clearly is presenting a risk here according to this risk assessment to humans.

I know that that may raise some legal questions about whether they can do extralabeling or restrict extralabeling here. Based on the Guidance it=s sort of unclear and the discussion we had this morning whether the agency can say no to extralabel use as a risk management tool for a newly approved drug because they don=t know what extralabel, we haven=t been given any evidence of what extralabel uses, what animals it might be used on, and where it might be used to do a risk assessment to say that it will affect public health.

So it seems somewhat tautological to me that we are even talking about extralabel use when it=s unclear whether the agency can actually restrict extralabel use. Although the sponsor did talk about the fact that, talked about not using this, I think it was in lactating cows and so forth. So it does seem to me that there can be restrictions put on how this drug is used. So I think there may be ways to do that.

The other thing I would add is to the extent that it is going to be used and approved by FDA for other uses, I

mean I have looked at all these questions not so much as --. I mean, the sponsor can always come back and get additional approvals for it. By saying here we don=t, I don=t think of us here saying you can never get it approved for chickens or something like that. We are just saying don=t automatically approve it now. They can come back for that.

I think that if you are going to have any extralabel uses or any other uses other than for the disease I think the sponsor should be required to do some additional monitoring and collect data about what uses the drug is going to be used for. What it is actually used for. The efficacy of it. But also how much is used and what effects it might have.

Because if the agency is going to at some later point be able to restrict extralabel use, they need to have data about that. And so to sort of just say well we will put it out there and let veterinarians prescribe it and don=t do any follow up to see what animals it gets prescribed for and what quantities how can one do a risk assessment to see later on whether that in fact may have some detrimental effect.

So I guess I would say that the agency at a minimum should set up some strenuous monitoring programs for the sponsor to go out there and collect data on uses other than respiratory disease for this drug to find out where it=s being used, what animals and so forth. So that they can

collect data to actually do a risk assessment at some later point if there would be a need to restrict the label at that point.

DR. NOLAN: I don=t, the folks around the table made a compelling argument for maintaining the extralabel use of this drug. But until we have more data I am still a little uncomfortable with some aspects of that. So I would, I think the FDA=s recommendation on this with the modification of the sponsor=s extralabel use is what I am most comfortable with.

DR. AREF: I also think that there should be no extralabel use. If there was a restriction like that you could use it for non-food animals I would be more willing to go along with that.

DR. SAMS: In reviewing the guidance document where the extent of use for a category one drug is identified as low that is predicated on the assumption of some extralabel use restrictions. In the absence of restrictions the extent of use could very well go from low to medium. And so therefore it seems to me that there must be some extralabel use restrictions in order to assure that the extent of use is low. So I would recommend extralabel use restrictions consistent with what this group has expressed today.

DR. MEALEY: I would still hope that we could use this drug extralabelly for non-food animals. Llamas and

things like that would be safe. Everything else I agree with.

DR. PAPICH: Generally I am in agreement with the recommendations as they currently have been suggested to us. With respect to the extralabel use I have not seen anything that compels me at this time to restrict the extralabel use, at least from what I know about the drug right at this point.

But I would like to make another point. And this is a little bit related to Dr. Sams= point about the extent of use. And what I am suggesting is not necessarily pertaining to this drug but in the Guidance 152 in general that the guidelines that they provide for evaluating the extent of use poses a problem with this class of drugs.

Because even though this drug is administered just one time and it=s limited to that at this point, we know that it has a duration of action that is much longer. And we really don=t know how to deal with those kinds of drugs right now.

The macrolides have that as a characteristic and one of the reasons for some of my questions to Dr. Brown earlier was that we know that it has a long half life in plasma. We don=t know what the half life in tissue is. And more specifically we don=t know how long after a single injection its antimicrobial effects persist. It could very well be much longer then, I am looking at Table 7 in the

Guidance 152, it could be that it has a long duration of effect even though it=s administered only once.

So the guidelines are difficult, I think, maybe to apply to this drug in some circumstances. And we may run into problems in the future if there are other drugs, other long acting drugs that sponsors bring forward.

DR. CRAIGMILL: I am going to have a somewhat long answer because there are several things I want to address. But before I start I wanted to just say that I am not a lawyer.

(Laughter.)

DR. CRAIGMILL: And I think one of the things, and I like, Dr. Brown had a slide showing the assessment of critical importance or how that fit. And if it was critically important everything was high. So what I want to say is that when we look at this category it all depends on what your definition of high is, to quote one of our presidents.

(Laughter.)

DR. CRAIGMILL: So what is high? There are range of highs in there. And what we have done is we have taken this as an incremental process instead of a -- or a digital process instead of an analogue process. And I think this needs to be an analogue process where we take into account the possibility that even if it is critically important and

that ranking is high there are various levels of it. And in that regard I think that is where the extralabel use restrictions have to be viewed more carefully than the others.

Additionally I think we have, there are risk management steps that are already built in as Dr. McGlone said. Risk management is building this risk assessment process. It=s intertwined so much you can=t really separate it.

When you start making those determinations that everything is going to be high if this one is high it means you have already added a safety factor or you have decided that this is going to be the way it is. It=s a risk management step. It is not a risk assessment step.

And as such that is fine because I think you couldn=t do anything else in regard to these predictive risks at this point. I just really think we have to be flexible in this regard. And in that regard I am in favor of keeping the extralabel uses available to the veterinarian until we know more.

I think they are going to be very important particularly for our minor uses. If I look at sheep and goats, how many antibiotics are there approved for goats? There is one. There is one.

DR. : What is it?

DR. CRAIGMILL: Ceftiofur. For sheep there is a couple of them. I mean these are important. How many for rabbits, bison, deer. These are food animals. Although rabbits it=s kind of questionable now a days at least in this country.

Our human veterinarian colleague I wanted to just briefly address the issue of the withdrawal time. Since humans are not at least in America food animals --

(Laughter.)

DR. CRAIGMILL: -- the issue of withdrawal times is something that you don=t consider very often. But they are based on, and they are an entire package that has to be submitted. Probably one of the more extensive packages because it has to include an entire tox package with carcinogenicity studies, et cetera.

Residue studies, total residue depletion using radioactive tracers, establishment of what is called a marker residue so that it can be followed. And then a statistical projection so that 99 percent, or 95 percent of the time of the time 99 percent of the treated animals will be at or below tolerance. And the tolerance is the safe level at the withdrawal time.

Those are studies that we won=t get to see for a long time. Because Pfizer is not talking about the withdrawal time at this point because, well because they

won=t.

For the label that is going to be what was established. Now the question always comes up, okay, what do you do for minor species or extralabel uses when someone uses that drug in a food animal. Where do you get your withdrawal times? Well there are ways to establish, and one of these is the food animal residue avoidance data bank where you can call and get advice on that.

We have been very fortunate in FARAD to actually get proprietary data from some of the pharmaceutical manufacturers in order to help make these predictions for other uses.

The other thing is that as these drugs become available and are used there will be studies that will be done and published in the minor species that will help us to make those determinations.

So I would urge CVM no restrictions please at this point. The other issue is that the amount that would be used in the minor species is so low as to be virtually unmeasurable or imperceptible in terms of their impact. That is why they are minor and why the pharmaceutical companies don=t pursue approval for them. Thank you.

DR. OHL: The risk management recommendations were outlined in the context of two species for specific indications. And in that context I agree with all of them.

Although I might say that post approval marketing is contingent on NARMS being able to continue their Campylobacter surveillance both in humans, mostly in humans is what they do. And that would be contingent upon them being able to continue to do that.

The point as far as extralabel drug use restrictions because all of the risk management considerations that I made were for these two species. I would say that I am comfortable with extralabel use in non-minor animals. I guess that would be same in the major group of animals. And that confers a specific group.

DR. WADDELL: Say that again.

DR. OHL: I am uncomfortable, boy I use a lot of double negatives. I am uncomfortable with extralabel use in the major animal group. In the minor animal group I believe that the risk to human health because of they are minor would be low and then I am comfortable with saying that at this point.

DR. THIELMAN: I believe we were asked to make a judgement based on a sizeable body of indirect data. The preponderance of the data presented suggested to me that we will likely not see a problem in human health because of the introduction of tulathromycin.

However I think we need to be smart and we need to monitor the situation. I can best say that I know that I

don=t know it all. And I am not an agnostic about it. I don=t think that it=s not knowable. I think it is knowable. And we need to monitor the situation carefully.

The post approval monitoring scheme with NARMS may not be adequate. And I would wonder if it might not be a good idea to ramp that up in some way to look more carefully at microbiological monitoring at the retail level or at the slaughterhouse level following the introduction of this medication and to see if rates go up.

It seems to me per comments made earlier from our CDC colleague that NARMS may not pick up on problems for quite a while. And then to back track and do the epidemiologic investigations that are necessary to figure out that it=s related to the introduction of a particular medication could put us way down the line. The horse would be out of the barn to use the veterinarian metaphor.

So that is I think my major concern. Again I favor extralabel use restrictions per my previous comments. And I think those are my comments.

DR. RELLER: My query about the withdrawal time was more what is the antimicrobial or the resistance pressure affect of having at the traumatic time of, the stress time of slaughter of antimicrobial on board in a very large number of animals who are harboring Campylobacter coli or jejuni. We are not talking about --.

So there are a lot of organisms and a lot of antibiotics. And that to me is potentially problematic for resistance. And hence the exclusionary period before the animal is in the final step before getting on the shelf at the store.

My no off-label perspective has more to do with, it=s just a reiteration of not going beyond the specific indication for sick animals in the two major groups. And the absolute for the time being proscription in poultry for the reasons earlier discussed.

The concept that Dr. Thielman presented and building on Dr. Angulo=s comments earlier of an augmented NARMS approach including studies that I would like to see on the exposure of animals harboring Campylobacter that is the target animals for treatment, in terms of emergence of resistance.

And relative to other antimicrobials in this class it=s conceivable in that a first component of the risk assessment that in fact there is less pressure on the emergence of resistance with this compound versus the macrolides currently being used in food and water.

And if there were experimental data to demonstrate that that would be very important. And the last thing that, you know, in terms of management of risk that I would like to see is getting it on record even though that is not the only

nor the specific question asked.

And I think the time is, as some others have mentioned in the public comment the time is over due to revisit how other macrolides are currently used and labeled and the indications and the restrictions and so on.

Because as one of the colleagues around this table mentioned earlier it=s conceivable that the extent risk that is already out there with the use of other compounds could conceivably exceed that of this compound. But they haven=t been vetted in the same way in accord with 152. And I don=t know what the regulatory process is nor the constraints or how it is possible to go about that.

But I think if we are really serious about this problem and I think the effort put into 152 says that the community at large, all of those interested in this, the time to be serious about antimicrobial resistance has come. It=s been here a while. And the experiences in Europe can help educate us. And the mistakes of the past can help educate us with what has happened in past advisory committees as regard to fluoroquinolones.

And what I am trying to say is that all of these drugs may not be the same. And we honestly don=t know. But we need to design the monitoring systems to expand them, to design them in a way that would capture the relevant information and properly categorize the risks of things that

are already on the market that could be revised as well as to learn prospectively. And this has been a great start. But I think a lot more needs to be done.

DR. LEGGETT: Let me say first of all, all in all the comments have been excellent and I think for my part I would say that the current risk management recommendations are appropriate. Though I will add a few comments. Some of which echo those made earlier.

First of all, the macrolide class is currently being used widely in these animals if I understood the data that was presented here. So the FDA needs to address the benefit to the animals versus the risks to the public health of the macrolide class in general.

Even though this new fashion of going through Guidance 151 (sic) applies to an individual drug, it applies to that drug as a member of a class. And regarding the fear of making each new antibiotic, I think Dennis maybe, a category one, I would like to point out that there are only four classes of the antibiotics written in that appendix table A-1 that are considered critical out of the other things.

So if a company wanted to come in and say, and prepare a third generation cephalous born for cows there wouldn=t be a problem at all. We wouldn=t be doing this. That is my understanding.

Regarding our inability to access the risk in benefit today without the efficacy data I think the FDA should consider integrating this current meeting with the actual drug approval VMAC meeting as long as it doesn=t last a week. So that way we would have both the risk, the risk benefit management all in one place.

Regarding the worry about extralabel use, let me give you an example of drug x that we recently reviewed and then approved for human use. We saw as what in retrospect should have been an expected increase in the emergence of resistance as the drug went from what we were told at the meeting was going to be very restricted use in humans to trying to sell it to orthopaedic surgeons and everybody else.

And so that I think is a danger about using extralabel use in the major animal domains. But I don=t, from my reading of this 152 use in minor animals would not be restricted because it=s not going to have that risk of transmitting emergence of resistance to humans. And I will shut up there.

DR. WADDELL: All right. I would just say that in the years I have been coming up here and meeting a lot of times in this same room that I am starting to learn a little lawyer speak myself.

(Laugher.)

DR. WADDELL: And one of the things that has come

up over the years through all of the 152 deliberations was that the final test is they have to assure there is reasonable certainty of causing no harm to humans.

And I take a look at how much we have used antibiotics in this class in all the species, as Dr. Apley showed today, and it just occurs to me that with that kind of use it would be unbelievable that there wouldn=t be more resistance out there then what there is. You know based on past history.

Those antibiotics have been around for 30 or 40 years. And we are doing a lot of things on the farm to try to reduce the use just because of cost. But some of those things have come back to bite us too. Somebody mentioned unintended consequences.

And in the last couple of years we have created a vaccine for Lawsonia intracellularis in pigs. And it=s allowed more and more farms to remove all antibiotics from grow finish feeds. And what we found is we are starting to see a re-emergence of some of the disease and pathogens that were there all the time we just didn=t know they were there.

And so I think that if there was a great impetus to cause resistance in Campylobacter from this class of drugs let alone this particular new approval that we would be drowning in resistance out there with what little work NARMS

has shown.

So I think that I applaud the FDA for where they, and CVM, for where they have come so far. And giving us, producers and veterinarians in the field, the tools that we need. And I think that the recommendations that have been put forth today are spot on. In fact I think if anything else they should have come, you know, it would have been nice to bring this stuff sooner to the market.

DR. PAPPAIOANOU: Thanks. This is the second time I have been to, that a meeting has been held that I have been able to come to during my tenure. And in both meetings what I have noticed there is always the tremendous research agenda that has yet to be filled.

And it=s very frustrating to come and to not be able to see the actual information that one would need to make evidence based decisions on any of these questions that are posed to us.

And so I would just like to get that and agree with some other colleagues that this is research that is not impossible to conduct. It is very doable. And it would be good to start to fill in some of these gaps so that we don=t keep hearing well there is no data therefore we are going to guess. It=s going to go A, B and C.

I understood the task in looking at this Guidance as it relates to food animals, Guidance 152. Not in other

animals that are not food animals. So, I am going to comment just on food animals alone.

And given the food animal constraint in terms of how I am looking at this assessment I do think with the information we have based on the critical nature of this drug that was established by an independent committee, not worried about all the other stuff, but just looking about the importance of it to human health that there should be no extralabel use.

The other risk management modification that I do think is very important is looking at NARMS as the post-approval monitoring. I think we have learned it=s not sensitive. And by the time it shows to be a problem so that many of us around the table are saying well I haven=t seen any evidence.

Well, are we waiting for the antibiotic resistance to appear. And then oh, yeah, now we have this problem. Well the genie is out of the bottle. It can take years to detect it. It can take massive effort to reverse it. So to me waiting for that to happen before we look at it differently is a mistake.

So I would suggest in terms of finding a better way again looking at these risk management categories of trying to get to something more specific in terms of picking up early detection of problems if it should go that way.

DR. WADDELL: Okay. We made it through all the questions. And it=s time for a 15 minute break. And then Dr. Tollefson will summarize for the final meeting and then we will adjourn. So, 15 minute break.

(Whereupon, a recess was taken.)

MS. SINDELAR: Can we present the last, next steps. If everyone can -- next steps. Last steps for today. And just one notation for those of you who may have parked downstairs, for some they have asked for a coupon for parking so please see me or Anna Roy at the desk and we have coupons for those who need them for parking below. Thank you.

DR. TOLLEFSON: Thank you Aleta. We are about to wrap up but before I make some concluding remarks I want to call Dr. Sundlof back up to recognize the value of a few or our members on the committee who will be retiring.

DR. SUNDLOF: Thank you Linda. Yes, it is my privilege now to recognize some of our VMAC members who are unfortunately are going to be rotating off of the committee but who served admirably in their position and have been a great help to us at CVM.

We really value their contributions. And though it may not always be apparent, everybody that is on this committee leaves our organization changed in some meaningful way in how we regulate animal drugs and animal feed.

So first of all I would like to recognize our

chairman, Dr. John Waddell. And John, if you would like to step up here we have a commemorative plaque for you.

(Applause.)

DR. SUNDLOF: Somewhere I thought we had a photographer around here too. Well thank you very much for all your help.

DR. WADDELL: You are welcome.

DR. SUNDLOF: The next member who will be rotating off, and again we appreciate very much her contributions, is Marguerite Pappaioanou. Thank you Marguerite, it=s been great working with you.

(Applause.)

DR. PAPPAIOANOU: Thanks so much.

DR. SUNDLOF: And last but not least a member who is not only leaving the VMAC but told me earlier today he is leaving poultry, I think, too, but for a higher calling in swine and cattle, I think. Dennis Wages.

(Applause.)

DR. SUNDLOF: Thanks Dennis.

DR. WAGES: I appreciate it.

DR. SUNDLOF: And with that I will return the floor to Dr. Tollefson.

Concluding Remarks, Next Steps

by Dr. Linda Tollefson

DR. TOLLEFSON: Thank you. I want to join

Dr. Sundlof in thanking you very much for your efforts here today and your expertise. I think we have got a lot of information from you.

I realize it=s frustrating to stay so focused on our questions. But there are reasons why we limit the questions before the Veterinary Medical Advisory Committee. And we do appreciate you following that. I think our Chair is very good at it.

We heard a number of things that we are going to take away from this. One is the extralabel use restriction. We heard loud and clear that you do not want that in companion animals and minor species, which I think we can accommodate very well but that it should be considered in the major food animal species for which it is not approved.

Also expansion in the human NARMS, the National Antimicrobial Resistance Monitoring System, particularly for Campylobacter. Campylobacter has long given us trouble. And it=s a difficult organism. We have done a lot of work with NCCLS on giving the MIC the testing and MIC levels set. So we are used to that.

We are expanding our retail meat arm of NARMS just for that reason. The slaughter data is pretty much limited to Salmonella data. And the reason for that is that USDA collects Salmonella isolates from all slaughter and processing plants throughout the country which we get to test

for susceptibility.

But they only receive Campylobacter isolates from poultry from the eastern lab, so we don=t get that many. And we are hopeful that by expanding the retail meat data we will be able to culture then any organism that is on the meat. That has it=s own problems. It=s expensive.

We have been expanding over the last two years and hope to expand even further to a more statistically robust system in January. But I agree with all the comments fully that there are certainly constraints.

Also I heard that drug use information would be helpful. That if we approve this drug for the species the indications on the label as the sponsor has requested and then look at what is going on and look at possibly drug use data and try to make further decisions based on that.

Also a few of you mentioned doing specific research on administration of the drug in animals in vivo, like the Pat McDermott work on Fluoroquinolones in poultry, which I think helped us quite a bit.

So that is what I have heard. What we are going to be doing with that is taking all those suggestions, we have the transcript, under consideration and moving forward on this particular approval which is not quite completed.

I mean there are efficacy considerations and there are other human food safety considerations with the

tolerance, and method, and withdrawal period and so on. But I think we got what we wanted on the antimicrobial food safety very much from the committee. So thank you very much.

(Pause.)

MS. SINDELAR: You didn=t adjourn the meeting.

DR. TOLLEFSON: Okay. So I have to officially adjourn the meeting so that you guys can go home. Thank you every one.

(Whereupon, the meeting was adjourned at 3:42 p.m.)