

Veterinary Medicine
Advisory Committee Meeting

Import Tolerances

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I N D E X**VMAC Meeting****January 23, 2002**

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P R O C E E D I N G S

(8:39 a.m.)

Committee Deliberations**Dr. Cory Langston, Chairperson**

DR. LANGSTON: If everyone would take their seat, we will begin just shortly please.

Good morning. And, again, my name is Cory Langston. I am the chair of the VMAC. And I want to begin the deliberations that we left off with yesterday afternoon relative to the various issues of import tolerance.

The plan, at this particular point, I would like to just shortly reopen for any questions of clarification to any speakers or experts we might have heard from yesterday, also any additional comments that anyone would like to make relative to discussion.

Following that, I will ask each committee member to address their views on the issue at hand going sequentially with each issue through the whole panel first, and then moving to the next issue; and then I will try to come up with a summarization of the panel comments with your help, and we will move from issue to issue in that regard.

So if there are no procedural comments to be made for anything, I would like to open this for any

additional questions and/or comments.

DR. WAGES: When we were discussing the issue number 3, disclosing the information to the public regarding import tolerances, there was a comment made, and I believe it was from Richard, that following the disclosure and the -- placing it either in the federal register or the internet, wherever it was, there should be a public comment period.

Richard, could you explain the reasoning why, if we are potentially going to look at, in setting import tolerances, basically, kind of how we are doing our domestic residue tolerances, which does not require a public comment period, why do we need one now, I guess, with the new ones please?

DR. WOOD: My thinking on this was that -- and continues to be, as we discussed yesterday the setting of import tolerances, is in some respects a different -- it is a different circumstance than setting tolerances within a new animal drug approval process because the drug has already been approved, and the question is whether or not we should allow it at what tolerance level to enter the U.S. market.

And so, the question at hand, the series of questions at hand really is only one. It is not a question of what is the impact on the herd or the flock

or the individual animal. It is not a question of what is its impact on the environment.

You know, all of those other series of questions that are a part of the normal NADA process, are not before us. There is only one question primarily, and that is what would be its impact on human health at that tolerance level.

So, as we were discussing this yesterday, it seemed then that at the appropriate time in the process, not undercutting the integrity of the process -- and this came out of discussions that I had with a couple of other people here -- that it would be appropriate for there to be a public input on a question for which there is only one question. And, that is, what is affecting their health?

And it seems appropriate to me that the public would have opportunity to respond to that question in that regard, so that -- but it seems, as I looked at it, the reason for public comment was that you just do not say -- I did not think it was appropriate to simply say to the public, "We are making this decision," and not provide the framework for their response to that decision, or a way for them to respond.

When I was a pastor in local churches years ago, I learned very quickly that you do not just make

people feel guilty without providing a way for them to respond. And it seems to me that that was what we were doing here, is by simply informing them that we would like to hear from you, or we are making this decision, but there is no framework by which you can respond to this decision, that then called for a need for there to be an opportunity for public response, and then a final decision by the FDA.

I do not know if that is clear or not, but that is where I was coming from.

DR. LANGSTON: Still on issue number 3, it is particularly relative to confidentiality issues, and that sort of thing. I was curious about the procedure for public comments. A little clarification might help.

For example, if you put like a six month period, or a three month period, whatever it might be, to respond, could that be used to delay the establishment of a tolerance?

In other words, if a competitor or group opposed to the establishment of that tolerance, wanting to gum up the work, so to speak, could they wait till the very last day of that and submit some controversial item that would have to be responded to and tied up in any matter like that, kind of transgential, but I wondered if that is an issue at all?

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Could someone from CVM respond to that perhaps?

DR. SUNDLOF: Yes, well, I will try and respond. Since nobody else jumped up to the microphone, I will do the best I can.

The decision that we make on whether or not to set an import tolerance is based on scientific data. We cannot take into account other things like, you know, whether or not it is popular or unpopular.

I think the question before the committee, I mean, if we do not announce it until we have made our decision, then it is too late to have a comment period. And the question I think before the committee is:

Should CVM be announcing, some time prior to the actual decision, whether or not there exists an application for an important tolerance?

And that people would be, as I understand the issue here, that people could at that point be given the opportunity to provide any additional data which would help the agency in making its decision. And we could take all of that into account, would be my guess.

This all is going to have to go before the attorneys anyway, so the whole issue of confidentiality will certainly be raised again at that point.

I think we are asking for the committee to

give us their best judgment as to whether or not they feel that, in the interest of transparency and openness, should we be able to acknowledge the existence of an application for an import tolerance prior to our actually making the final decision?

I hope that helps.

DR. PARKHURST: So you would need time to assess data that was presented, is that right?

DR. SUNDLOF: Yes, yes.

DR. PARKHURST: So that would have to enter into the issue of when?

DR. SUNDLOF: Right. Generally, we try and require -- we have everything on a time clock. So, whatever the final regulation comes out for, import tolerances would also put some timeframe on after the submission of the application for the import tolerance by some date certain we would be required to respond back to the petitioner as to whether or not we agreed, disagreed, or needed more information.

And, generally, that is on 180 day time clock, so that is consistent with the six month window. That would mean that we would acknowledge at the time that we received the application.

DR. HASCHEK-HOCK: Richard had suggested yesterday or proposed the possibility of setting a

provisional level at the time the announcement is made. Is this feasible to do, so that imports could begin at the provisional level, and then if additional data was submitted and evaluated could be changed to a final tolerance?

DR. SUNDLOF: Well, that would be unique I think. We have not done that in the past. But then, again, we prohibit the use of, or the sell of the drug in the United States until we have final closure on those issues.

So I think if there were, I mean, there are provisional tolerances set by EPA. There are provisional MRLs set by the Codex Alimentarius. We have not done that in FDA. It is not to say that it could not be done.

If there were provisional import tolerances set, they would probably be on the conservative side, that we would take extra precaution to make sure that public health was protected; and then a final import tolerance might be something that was higher than what we had set for provisionally in the interest of public health.

DR. WOOD: But, based on what you earlier said just moments ago, is there a time in the normal decisionmaking process where people be given an

opportunity to provide additional data without jeopardizing the integrity of the decision?

DR. SUNDLOF: Yes, well, I mean, I think that is the question is, if we are going to announce it prior to our having made a final decision, then we would accept any information that was provided, and that might help us in our decisionmaking process.

DR. GLENN: I want to ask a question. In your experience, remembering that these are for drugs that are not approved in the United States, so I would say there would be some public interest perhaps. In your experience, what kinds of input are we going to get?

Are we going to get confidential data from other industries that have tried to look at this drug? What are we going to get?

DR. SUNDLOF: Well, my sense is we will get all kinds of information. Some of it will be, you know, factually based; some of it will be more on the --

DR. GLENN: The principle.

DR. SUNDLOF: Yes, would be more on the values issues, why we should not, or we should approve this.

DR. GLENN: Okay.

DR. KOCHEVAR: It seems like we maybe have -- we are talking about two different plans. I think yesterday, at least the way I understood it, the

suggestion was not that the application be announced when it comes in, but sort of the FDA process go forward, import tolerance provisional.

I do not know if that is the right word or not, but some tolerance that FDA thinks is correct is then announced, and there is a comment period, rather than when the application comes in, you say, here is this application. Anybody bring us data that you want to have us look at.

Is there a difference between -- I mean, is one of those feasible and the other one not?

DR. SUNDLOF: I think it is not very feasible for us to wait until we have examined all of the data, made our decision, and then ask for comments. That does not seem to make a lot of sense.

What makes more sense, if we are going to announce it, and if there is a -- we are going to allow a comment period, we would like that comment period to be during the time that we are actually reviewing the data and taking into account any other information that might be provided.

DR. LANGSTON: What about the possibility that you could look at the data submitted and say, okay, they have the carcinogenicity studies; they have the rats acute toxicity. But, you know, there is probably decent

data. So there is a chance we can establish a tolerance and release the information to the public or the decision that it is under consideration.

DR. SUNDLOF: That could also be a recommendation from the committee. And it is probably a good one, in that, if we received an application and we did a cursory review and recognized that it was wholly inadequate in order to support an import tolerance, should we go out and announce it without getting back to whoever the petitioner was and say, you know, you need this, and this, and this, and this, in order for us to make a determination of whether we can establish an import tolerance. So that is certainly another flavor to this whole issue.

DR. LANGSTON: Any other questions or comments about issue 3?

DR. PARKHURST: Would it be fair to say that you are asking for data not -- the emphasis is you are asking for data not comments?

DR. SUNDLOF: Right. When we go out for a call for data, we would be fairly specific in what we ask for, so it would be clear. That does not mean that is what we get back, but we would be very clear in what we were asking for.

DR. KOICHEVAR: So where in the process, for

example, if the drug has been approved in Europe for awhile, and there are adverse event reports, and those kinds of things, are those -- those normally are not considered in the tolerance process.

So what would you do with that? You would probably get that kind of information back on comments wouldn't you?

DR. SUNDLOF: Right, but it would not be part of the process for establishing import tolerances. It would just be ancillary information that -- I mean, again, I think we are trying to limit this.

The problem that we have is that everything is kind of interconnected to everything else. And, before long, we get out too far, we are going through the entire drug approval process.

So, although adverse reactions may be an issue in the where the drug is actually being administered to animals, it would not be something that we would normally consider in establishing an import tolerance.

DR. KOCHEVAR: And I guess I should have clarified, not adverse reactions in the animals, but adverse reactions associated with public health concerns.

DR. SUNDLOF: Oh, definitely, definitely, we take that into account.

DR. KOCHEVAR: But in our tolerance process, there really isn't -- I mean, because those drugs have not been approved that data is not there, so the packet would look somewhat different.

DR. SUNDLOF: Right. When we set tolerances though, we ask for all literature that had previously been reported. So we get a lot of historical information on a lot of the products. Because some of them have been approved in other countries for a number of years, and so we rely on --

DR. KOCHEVAR: So you do look at that?

DR. SUNDLOF: Yes, we do.

DR. KOCHEVAR: Okay.

DR. WAGES: Steve, if a package is submitted by a company on a generic compound to set an import tolerance, and there is six companies that make that product, do they have some kind of a proprietary -- or would any of that be for whatever comes into the country from whatever generic drug used, they would be allowed.

The import tolerances is for the drug itself, correct?

DR. SUNDLOF: That is correct.

DR. WAGES: So, if there was five or six companies making a generic drug, one company wanted to actually have that drug accepted in the United States,

they would all get the benefit?

DR. SUNDLOF: Okay. I am not exactly following you, Dennis. So you have a pioneer company that actually has the data for establishing a tolerance, the human food safety data, and then you have several different generic companies who are --

DR. WAGES: Demonstrated bioequivalence, and all of that.

DR. SUNDLOF: Right.

DR. WAGES: And then can they come in on that same import tolerance? Do they have to submit anything to the United States?

DR. SUNDLOF: My sense would be, no, they would not.

DR. KOCHEVAR: Except that that ends up being different from here.

DR. SUNDLOF: Yes. In fact, this is where things become pretty complicated because a single country may petition or -- may petition for an import tolerance. We may grant that import tolerance.

But, as I understand it -- and correct me, folks, if I am overstepping -- but that would apply to imports from any country, and we can't -- should be chasing down all of the world's manufacturers of generic products.

DR. LANGSTON: Any other questions?

(No response)

DR. LANGSTON: Other issues?

(No response)

DR. LANGSTON: I have one that, since a few committee members have mentioned this to me just prior to the meeting, let me make it part of the public record.

Just to comment relative to issue number 1, and good agricultural practices, I think several of the committee members thought they would have benefitted from greater explanation of what that actually constituted in making their deliberations.

One argument I did hear for considering good agricultural practices in a tolerance limit is that those tolerances set by countries looking at good agricultural practices are typically more conservative than the ones we use on just a food safety issue.

The thought was why not have one tolerance for international harmonization purposes. I can understand the rationale for that. My concern on that would be that that would be fine, as long as the product was never introduced for approval in the U.S.

But should that occur, as often is the case, the drug will be released in Europe or elsewhere first

before it is submitted to the U.S. You would have one tolerance set on good agricultural practices, and then we would have the dilemma of setting a different tolerance based our usual food safety, and how do you go about resolving different tolerances for the same formulation.

So, that was my concern about adopting good agricultural practices into setting of tolerances. And I just wanted to make that public, and would ask if anyone else would like to comment on that or other issues.

DR. WOOD: The only other thing that I heard us discuss or mention briefly yesterday about agricultural practices, and it is more veterinary practices I guess is the concerns related to the injection site. And if the drug is not administered properly that the tolerance -- or the residue at the injection site would be higher than in the other tissues.

DR. WAGES: Whose definition of good agricultural practices do we use?

DR. LANGSTON: I am not answering that. I think it was meant rhetorically.

DR. HOLLAND: Does anyone know if these are equivalent to our various quality assurance programs

that we have for the different commodity groups in this country?

DR. WAGES: In poultry, that is what we currently use, those programs set out by National Chicken Council and National Turkey Federation and quality assurance as our framework, at least, for a good agricultural program, or best management practices, more appropriately called.

DR. HOLLAND: But does anyone from CVM know if they are equivalent to the quality assurance programs that we have in this country?

DR. SUNDLOF: It is highly dependent upon the country obviously. But when we are talking about good veterinary practices, or good agricultural practices, generally, what we are talking about is how the drug is labeled.

Just to kind of recap the discussion yesterday, that certain countries first look at the ADI and set the tolerance base totally on the ADI, the toxicologic endpoints; then they look at how the drug is actually used as labeled. And if the residues would fall well below the tolerance as established by the ADI, they move that tolerance down to be consistent with what they call good veterinary practices or good agricultural practices.

The other things that we look for when we talk about evaluating other countries, good veterinary practices, or good agricultural practices, is do they have systems in place that will actually help ensure that the drugs are used as labels.

Do they have a residue program, residue monitoring program that is somewhat equivalent to ours, so that they can determine whether or not drugs are being used as in accordance with the labeling?

Do they have enforcement strategies out there? Do they have people out there that are following up when there is a residue violation?

You know, there is a whole big infrastructure out there that needs to be in place in order to ensure that country's are actually following the good agriculture or good veterinary practices that have been established by the competent authorities in labeling these various drugs.

DR. KOCHEVAR: So would that imply that if you are setting tolerances, that again the package would look different, and that you would have to have that information? No.

You would have to know what the country's system looked like, or is that already in the system somewhere else?

DR. SUNDLOF: If the committee feels that taking good agricultural practices into account is going to -- is what the FDA should do when establishing an import tolerance then, yes, we would have to investigate that.

If the committee feels that we should not be taking good agricultural practices into account in establishing a tolerance, import tolerance, then it becomes a moot point.

DR. KOCHEVAR: But it goes back to the other discussion that we had about GMP, that if you do not have any information about whether the system in a given country has any checks and balances for people following GMP, then you do not have any way to judge it.

DR. SUNDLOF: Right. Remember though that the USDA requires equivalence for countries that are going to be importing meat into this country. So they are looking for things like residue control programs, and how drugs are administered. So they kind of make that determination before meat is ever allowed to enter this country.

DR. KOCHEVAR: What about seafood?

DR. SUNDLOF: Seafood, they all have to comply with HACCP, so it is covered there as well.

DR. PARKHURST: Before you sit down, what do

you see as the advantages of using good agricultural practices?

DR. SUNDLOF: Well, in 1996, we, with the passage of the Animal Drug Availability Act, we said that we are no longer going to take that approach. The U.S. had previously had virtually the same approach as the European Union does now, which is to set the tolerance on the toxicologic endpoints, and then adjust it if the labeling of the drug was such that it would never reach those tissue levels.

And it gets very, very confusing when you try and do that, because now all of a sudden the tolerance is not a food safety. It is not established on the basis of food safety. It is really established on the basis of something else.

And for years we tried to explain this to the public, and the public does not understand this at all. When they are looking at a tolerance, they are looking at a safety endpoint.

The other thing was that we started a program called Professional Flexible Labeling, where we allowed large dosage ranges on the label, so that veterinarians could use their professional training and knowledge and experience in selecting a dose from a whole wide range of doses.

Once you start allowing that kind of flexibility in there, and then it is very hard to know what the -- how to set the tolerance based on good agricultural practices because it can vary all over the place.

We just, again, people look at this as ways of finding out if veterinarians or producers are using drugs illegally -- or using drugs off-label, even if there is no human safety.

It is just very hard to try and make one tolerance do two things; that is, in one case looking at the safety of the public health, and then trying also to use it to find out if veterinarians or using, or producers are using drugs in accordance with the labeling.

We have taken what I think is a much cleaner approach, is that the tolerance is a safety, is a food safety value that we can take regulatory action on.

Some of the other problems that we get into is that when we take regulatory enforcement action against a producer who has repeatedly caused residue violations, and we have a number of these, and there are people in jail right now that continually have sold animals that had residue violations.

When we go into a court of law on that,

generally, our case has to be based on public health. It cannot be based -- it could be, but it has never been done -- based on something other than public health.

The chances of us prevailing in a case where the -- you know, it was not a public health issue. But, clearly, the producer or the veterinarian had used the drug inappropriately is a very difficult case to make in court.

And so, and yet at the same time, if you have a producer or a veterinarian who has consistently violated the law and you are not able to take the appropriate regulatory action against him, it undermines the public confidence in the systems.

So this is the approach that we have taken, and those are some of the reasons why.

DR. GLENN: I have a question too. Are good agricultural practices, under any definition, are they a requirement of a new animal drug application currently?

DR. SUNDLOF: The only time that anybody is allowed to use a drug in a manner that is not consistent with the labeling, which is what we are calling good agricultural practices, is under AMDUCA provisions, which are very limited.

They are only for veterinarians only under very specific conditions. If they result in a residue

violation, then the veterinarian is at fault. So, yes, we expect that when we approve a drug, that it will be used according to the label with the provisions of AMDUCA.

DR. GLENN: And is it called GAP? That is what I am trying to get at.

DR. SUNDLOF: No, no.

DR. GLENN: Okay.

DR. SUNDLOF: It is not called that. This term comes from kind of the international Codex process, where there are good agricultural practices, documents out there. It has been picked up in the area of foods, The Center for Food Safety and Applied Nutrition, in developing some of their HACCP programs and how they are going to evaluate agricultural production in the United States, and then apply that to products coming in from overseas as well.

DR. GLENN: Thank you.

DR. WOOD: Related to that, with regard to -- in light of what you just said about the impact of good agricultural practices, with good manufacturing practices, would taking those practices into consideration also have an impact on tolerance level setting or not?

DR. SUNDLOF: Well, it probably would be a

yes/no. If we felt that drugs -- that the drug was not approved under good manufacturing standards, it would be very difficult for us to set a tolerance because we do not know you know.

If the system is out of control, we have no control over the potency, we have no control over excipients or contaminants that might be in it, that might be also a public health effect.

So having some kind of prior knowledge that the drug is produced under standards of good manufacturing practices that we have in the United States or an ISO standard that is in Europe, or some other standard that we feel comfortable with I think is important in our ability to establish a tolerance.

We may just say, you know, we have no assurance that this product is produced under a quality system, and therefore we would be reluctant to establish an import tolerance.

DR. HASCHEK-HOCK: One other question, in regard to conditions of use of the drug, the labeling of the drug. How important is that in relation to tolerance established on the basis of food safety?

DR. SUNDLOF: Well, the drug, when used as labeled, should not ever produce a residue, violate a residue in an animal. I say never, but there is

99 percent assurance, with 95 percent competence that it won't.

When establishing a tolerance, we do not look at the mean of the residue depletion curve. We look at the 95th percentile confidence interval and establish it based on that. So, even if the drug is misused, there is still a high likelihood that it will never -- that that animal will test negative unless it is grossly misused.

But we have a fairly wide cushion in there to allow for some additional use outside the label and still will be falling within our tolerance. So the labeling is very conservative in that respect.

DR. LANGSTON: Other questions or comments?

(No response)

DR. LANGSTON: Are we ready to move into the actual issuance of your opinions?

(No response)

DR. LANGSTON: Okay.

Committee Response to Question 1, Issue 1

DR. LANGSTON: We will start with question 1 then. And the question is: There are different approaches that we could use to find the safe import tolerance. We could look at toxicity and residue data and build in a conservative safety factor.

I am going to simply designate that as the food safety approach. Alternately, we could also review conditions of use such as good agricultural practices, route of administration in dose, which may result in a different safety factor or factors, which I will designate as good agricultural practices approach.

Additionally, we could consider manufacturing information such as that required for domestic application, which also could result in a different safety factor or factors, which I will designate it as simply manufacturing issues.

Also, I would like for you to address the issue of handling muscle residues, if you have any comments. In case you have not organized your thoughts in that line, and certainly you do not have to. That is simply the way I view it in my own, as far as issues.

I will take the lead on this particular one and give you my views, and then we will rotate through; and on subsequent questions other people will start the discussion.

First off, as to approaches, I definitely favor the food safety approach. I believe it does have to be based on adequate quantity and quality of data. And if that data is not sufficient, then a tolerance should not be set for that particular drug.

While I understand the concept of incorporating good agricultural practices, I have too many reservations about problems that might be encountered. So I tend to discount the good agricultural practices as an approach.

I do feel that we do need some sort of GMP-like quality assurance relative to manufacturing that should accompany the issue in salve tolerance.

On the last issue of how to address muscle residues, I would offer three options in that regard. It is a difficult question.

First, I would offer the consumption factor approach; that is, if you drive your tolerance, whereby, you are taking your ADI times a 60 kilogram human, and then dividing it by a consumption factor, I think it is arguable that you could use the consumption factor strictly for muscle rather than for all of the edible tissues as occurs presently in the U.S.

As it was pointed out yesterday, the whole carcass is not entering the U.S. food chain, it is simply the muscle. If necessary, you would argue for development of an analytical technique. That is my first preference.

My second preference and third preference could best be explained with a graph. So let me skip up

here just shortly.

(Overhead)

My second preference would be to designate muscle as an alternate target tissue, where if your assay is capable, you would extrapolate down and drive a tolerance base at this level, which would be analogous to the safe concentration relative to total residues. That is dependent on your assay methodology.

And then, lastly, my third approach would be an operation of the safety factor such that if your analytical technique is inadequate to reach this lower level, you would come in at a point at the limit of detection, or, quite frankly, more likely at the limit of quantitation; and then you would be able, if you detect that, to come up and establish what that total residue is at that particular muscle concentration, and then see if that operation in the safety factor is significant enough to be a public health issue.

In this particular example, if you deem the total residues normally with an organ target tissue is 25 parts per billion roughly. In this example, it would be 75 parts per billion, would be what would be your total residue in the muscle, or 3x decrease in the safety factor, which in the scheme of 10 to 10,000 safety factors is probably insignificant.

Granted, it is probably going to be a lot more of a change in safety factor. It will depend on the slope of those lines, and also will it falls out.

So, again, in summary, my first -- or my third approach would be the operation or examination of a safety factor approach. The second would be if methodology exists, use of an alternative tissue for designating muscle, relating it to total residue.

And the third would be, and my preference, would be the consumption factor approach, basing the needs consumed strictly on muscle. Okay.

So, Alicia, would you like to?

DR. ANDERSON: I also agree that using what you called the food safety approach would probably be the best one. Because I think whatever approach we choose should be one in which we are able to verify it, and I am just not really clear how we would be able to verify either using good agricultural practices or manufacturing information.

Even though USDA and HACCP could probably ask for that information and receive it, I am just not sure that is something that we could do quality control on.

And I know that FSIS, the gentleman from there has spoke that he did have teams that would go over and do inspections in other countries, which to me just

seems extremely labor-intensive.

And also, you would never be able to do a surprise or a drop inspection because you have to notify the government as soon as you arrive I am sure. So I also agree that using the residue data, or the food safety approach would probably be the best one.

DR. HASCHEK-HOCK: I agree that tolerances should be established on the basis of food safety. I think it is important the data submitted for import tolerance setting be deemed equivalent to those required for domestic tolerance setting, in respect to toxicology, radiolabel chemistry, and analytical methodology. Additional GMP equivalence should be present -- I mean, additionally, GMP equivalence should be present.

As far as the residue data, I had not gone into it as extensively as Cory. But I felt that where muscle data is not available, organ data could be used conservatively to set tolerance, which is basically I think the same as what you were saying, right. And the international standard should be considered while determining the import tolerance.

DR. PARKHURST: Well, I too agree with the food safety approach. And I think the issue of being consistent with the domestic criteria is very important.

And it should be a criteria that is clear, and that can be enforced without giving loopholes where we do not really want to do that.

And the idea of using muscle tissue, it is my understanding that in some situation we do have information with the target tissue that is collaborated with the muscle tissue.

In those cases, where we do not, and we do have the target tissue, there maybe some ways in which your statisticians can look at the calibration problem and calibrate using the muscle tissue, calibrate that. Excuse me. Using the target tissue, calibrate that to the muscle tissue, which is something along the lines you have indicated.

DR. LANGSTON: Any comments relative to GMP or GAP? You do not have to.

DR. PARKHURST: Well, it is not clear to me what advantages there would be in the GAP, or the other two approaches. And I think that the big issue of consistency with the domestic criteria is overriding.

DR. KOCHEVAR: I would agree that consistency is very important that we have to keep the standard as equal as we can for producers in this country versus those that will be coming in for import tolerances. So that is a larger principal.

But I also think that GMP has to be considered because there are issues that have been brought out a couple of times already that impact public health. And so, in some way, shape, or form, the data that is received for determination of import tolerances would have to have some mechanism for us to at least evaluate those in some way.

I also think -- and this may not be the place to express this -- but there is an issue regarding banned substances that has to be considered. And I do not know where that follows in this list of questions. Would it be better to address that later?

DR. LANGSTON: I think in question 5, issue 5.

DR. KOICHEVAR: Okay, okay. The notion of harmonization, especially if we consider that many times the tolerances that are already set by Codex are more conservative than the ones that may be set here; that there should be some consideration given to harmonizing as much as we can so that producers do have, as often as possible, one standard to deal with.

I think producers also are going to have to have information about values in target tissue and muscle. And, Cory, I think the second alternative that you gave, if analytical methods can be developed, is a good one, is preferable.

DR. LANGSTON: So, if I am paraphrasing, you believe that in the issue of harmonization GAPs should be, at the least, somewhat considered?

DR. KOCHEVAR: I think that we cannot evaluate GAP effectively. And so, someone -- I think Alicia might have said that, you know, if we cannot enforce something, then it becomes difficult to put it as part of your criteria for selection.

So, no, I think I was voting less for GAP, and more for a sense of, in general, as we approach import tolerances and tolerances, that we try to harmonize the way we set the final number.

DR. LANGSTON: I understand. Thank you.
Robert.

DR. HOLLAND: I support fully the food safety approach using U.S. CVM standards. I think for me that is fairly clear, primarily; secondarily, take into consideration the Codex Alimentarius activities. Now that I am a bit clearer on what good agricultural practices means to CVM, it is basically labeling.

And I think if there is confidence in labeling that it should not be thrown out totally. But it can be under certain circumstances probably used, particularly, if it is in the framework of the Codex negotiations. So, across the board for me, use CVM standards.

DR. LANGSTON: Any issues relative to manufacturing GMP?

DR. HOLLAND: For me, again, that would come under CVM standards.

DR. WADDELL: I think whatever approach or combination of approaches that they choose should just be that we maintain a level playing field with the U.S. producers versus the exporting countries.

And so, if the food safety approach, you know, does that, that is fine. But there might be situations where they will have to include, you know, the good agricultural practices and the GMPs.

And I think the same thing goes, you know, with the muscle residues. Whatever approach best fits what we are doing here requiring of our U.S. producer should be where we should go, not necessarily to make a higher bar, but to make a level playing field.

DR. WAGES: I guess I am in favor of kind of a combination of the food safety approach and the manufacturing approach; and then come as close as we can to be consistent with our domestic residue policies.

I have somewhat of a problem with the good agricultural practices. Because if we look at it as by definition a subject of labeling, there can be many times when you extra label and off label. And probably

the majority of times it does not result in violative residues.

And so, just trying to put an import tolerance and at least give a lot of credence to the way they either do or do not go on or off label, I do not feel is too appropriate. So I am kind of in favor of both the combination of the food safety, as well as manufacturing information as included with domestic applications for residue.

As far as muscle residue, I do not have really anything to add. I guess my first preference will be the consumption, where you take the average daily intake times the weight divided by a consumption factor. However, if we do have methodology that would go to a very low level and detection in muscle, then I think that would appropriate also.

DR. CARSON: As a consumer, I guess I want assurance of safety and minimal risk. And I would like to see it based on the scientific data like others have as well, where it is going to be equivalent to the same domestic procedures, and the scientific data that we use for a food safety approach.

As far as the good agricultural practices, or the labeling issue, as it has been redefined I guess, is I guess I tend to think or feel that if we have a

residue it does not make any difference how it got there, whether it had good labeling, or it did not have good labeling.

So I guess I would put minimal emphasis on the labeling there. I do think manufacturing issues should be taken into account. And I think I like the muscle as an alternate target similar to your option 2, I guess, Cory.

DR. GLENN: Establishment of import tolerances should not differ from currently established processes for establishment of domestic tolerances. So, therefore, I support the food safety approach that you mentioned as a science-based approach.

In the absence of a good definition, although I appreciate, I understand this better, of good agricultural practices, I think it is difficult to support inclusion of those at this time.

However, for good manufacturing practices, it appeared to me that these were very specifically defined within domestic approval processes, and probably within this equivalency that we have assessed for 34 other countries.

So, therefore, it seemed to me that that would be useful to include and sort of level the playing field as was mentioned earlier.

Then, lastly, from what I understood yesterday, it appeared that an approach to include muscle or non-target tissue tolerances is consistent with current procedures for domestic tolerances.

I thought I heard Dr. Friedlander say that sometimes there are two tolerances. The processes that are used therein, I would support currently, based on what I know.

DR. WOOD: Well, first, thanks for giving us the night to think about this as we were watching Jay Leno.

I strongly support the use of the food safety approach as the overarching paradigm by which to set import tolerances. And this is consistent with supporting the use of existing FDA CVM tolerance process, and I think that is what needs to be applied in setting import tolerance levels.

To use a modified approach I think would be to undercut FDA's primary mandate to protect human health in this process.

Based on the discussion, even that we had this morning, and the information received from CVM regarding good manufacturing practices, I think that I would hope that CVM would continue to assess the good manufacturing practice potential from an exporting country, as it set

its import tolerances.

And with that as a factor, but not the determining factor, that continues to be a food safety approach in my mind. And I share a concern about the agricultural practices and its meaning outside of what we briefly raised regarding concern about the injection sites.

Fourthly, in response to muscle tissue, from what we learned yesterday, where the USDA's enforcement focuses on testing muscle tissue primarily, I do believe this committee should call on the FDA to explore tolerance level for animal muscle where appropriate, identify it in relationship to the target tissue.

I do not have the scientific expertise to choose among the options available, but certainly would want to support this committee's encouragement of the FDA to set some kind of tolerance, appropriate tolerance level in relationship to the target tissue related to muscle.

Finally, there is an issue that perhaps belongs to question 5. But, in talking further with FDA CVM, it seems like it is appropriate simply to mention it here, and that has to do with how antimicrobials are addressed in this tolerance setting process.

In talking further with them after our meeting

yesterday, I found that as tolerance levels are currently determined, the impact of an antibiotic on the gut flora is examined. And so, it simply encouraged the FDA to continue that aspect of their tolerance setting.

DR. MACDONALD: I support the current system in place at CVM for establishing tolerances for domestic applications for any import case. Whatever is being used at a given time point should be used for both domestic cases and import cases.

In that data package, of course, is a question about the drug, the drug characteristics, purity, product, et cetera. In that data package, of course, all of that is clearly specified as to what the product is, the purity, the crystal in form, et cetera. It is totally specified. And, of course, that is the reference point for any future use.

The specific use conditions are also specified in the data package, and usually they are presented at a maximum case. In other words, if there is a projected range of use, the residue work and metabolism work is always done at the top end.

And a contemporary application, of course, unequivocally deals with both the target tissue and the muscle tissue. And, at this time and place, a methodology has to be provided for both the target

tissue and a methodology also for muscle.

So, in terms of good agricultural practices, the usual situation there is the values obtained under those conditions are from products whose residue, actual residue levels are considerably lower than that projected from an evaluation of either a straight tox or in combination of a tox microevaluation.

This is the case usually on non-absorbed materials. So I think the GMP issues are covered as part of the data package, and the good agricultural practices is an application that can be applied if necessary.

DR. LANGSTON: Thank you for your views on this. Let me try to summarize. It would seem that there is overwhelming support by the committee relative to the use of the food safety approach, as now implemented by CVM.

Relative to good agricultural practices, the majority opinion by far was that this should probably not be part of the evaluation. However, there was a minority opinion that under certain circumstances it should be considered.

Manufacturing of the product is of extreme importance. There were concerns relative to the implementation of this, but it still seems to be a

concern of the committee that it be included in some form within the process.

And, lastly, that the tolerance for muscle should be established by some methodology, to be left by CVM, some expressing views that using muscle as an alternate target tissue was a good approach or changing to a consumption factor. But, obviously, that will remain the prerogative of CVM and analytical chemists.

So would anyone like to amend or comment on my summary?

DR. HASCHEK-HOCK: The only thing, several of us did mention that international standards or harmonization levels set by other international organizations should be considered in setting this. And I feel strongly that that is important.

DR. LANGSTON: Thank you. You are right. Several people did mention that. Anything else?

(No response)

DR. LANGSTON: Okay. In that case, will move on to issue number 2.

Committee Response to Issue 2

DR. LANGSTON: Although we have already had the opportunity to ask questions, I will open it if anyone has thought of anything else relative to this.

(No response)

DR. LANGSTON: All right. The question reads:

"Only the drug marker residue for the drug substance, not the production formulation, or the sponsor of the import tolerance can be determined by the type of analytical method that is typically used to assay imports.

Are there analytical techniques or other approaches that would allow us to determine whether a residue is due to use of the drug product for which the tolerance is approved?"

And, Dr. MacDonald, since I started one before, how would you like to begin this one?

DR. MACDONALD: To my knowledge, at the residue level of the concentrations we are dealing with, I think it would be extraordinarily difficult to have an analytical method that could distinguish between different sources of a given drug.

This type of work goes on, but it goes on on the bulk level. In fact, the FDA has a lab in Cincinnati that is devoted to, if you will, forensic drug analysis to look at sources of drugs on the human side, as to where they came from.

And they use a variety of exotic techniques and comparative isotopes, et cetera, to determine whether the drug was made downwind of Chernobyl or in a

country that uses a given solvent versus another solvent.

But to try to distinguish at the residue level when you are looking at per million concentrations between different sources, I just do not think that is a doing entity.

There are cases where manufacturers do put, or have in the past put tracers into monitor their product versus a competitor's product. And this has been done down to the feed level, to the dose form level, the premix level, but not at the residue level.

So, to my knowledge, there is no workable methodology that could be put in place to distinguish different sources of a given drug from different locations. That is just I think analytically not doable.

DR. WOOD: I do not really feel like I have the expertise to select among analytical techniques, other than to state that from a consumer perspective, any technique that is used, you want to rest upon why the acceptable scientific practice and experience, and that this is not a place to try some kind of new approach.

I hope that the analytical techniques that have been used with domestic tolerance setting will

continue to be used in this regard unless there is sufficient scientific evidence to determine another approach.

DR. GLENN: Based on discussion, it appears very difficult to identify use of different product formulations by analysis at the residue level.

DR. CARSON: I agree with previous comments. I am not sure. And, again, based on my background at a veterinary diagnostic laboratory, where we are always looking for residues of different materials on, it seems like, on a daily basis, I am unaware, at least with chemicals, that we can do this kind of tracing.

Certainly, in the vaccine world, where we can use monoclonal antibodies and some tags like that, that we can look at some antigens; barring that, in the chemistry, in the drug area, certainly, I am unaware of any methodology that is going to allow us to look at those, verify that at the residue level.

DR. WAGES: I do not have really the expertise in analytical chemical analysis. But it appears that unless we find a way that we can have some kind of a tracer labeled marker, at a very, very, very minuet part per million or billion level, that to be able to trace a drug, based on its use patterns, will be next to impossible.

DR. WADDELL: I have nothing further to add.

DR. HOLLAND: The only thing I would say is just provide the verbiage to support research and development by the agencies that are involved with this, these activities. Because I certainly do not have any expertise in this area to suggest anything other than that.

DR. KOCHEVAR: I guess I am bothered a little bit by just the inherent inconsistency here. When we say, you know, analytical techniques used to determine whether a residue is due to use of the drug product for which the tolerances is approved, but didn't we just decide that, in some sense, if we followed the plan that has been laid out for import tolerances, one tolerance will serve for multiple drug products?

So, why would it matter if that is the way we are going to go at it, which product the residue was relate to? So, to me it is not consistent with what was apparently the approach we opted for import tolerances.

And I guess the second issue there is I am still bothered in principle by the fact that this is inherently different from the way we would do a domestic tolerance determination.

So, the analytical method aside, there is some sort of inconsistencies with the question, based on what

we have already talked about.

DR. LANGSTON: But relative to the analytical techniques available?

DR. KOCHEVAR: I would agree the opinion.

DR. PARKHURST: I have no expertise in this area.

DR. HASCHEK-HOCK: I agree with Dr. MacDonald that there are basically, at this time, no feasible methods available to determine whether the drug residues are from a specific drug product.

DR. ANDERSON: I also do not have the background to really comment on the type of analytical techniques that could be used. But, as someone said earlier, to me it is not a question of how it got there, but is it there or not?

I do not even really see that it is FDA's job to determine, you know, is the residue there due to the use. I would think that would be up to the drug company. So, I do not even think that that would be FDA's position. But I do not have the expertise to comment on how the analytical techniques could be done.

DR. LANGSTON: I have considered whether metabolic ratios or profiles could be used, but I think the practicality of it would be very difficult to implement. My view is that there would be no practical

way at present to decide what formulation was used. And I agree with Dr. Holland's recommendation that perhaps this would be an area to consider for research.

So, in summary, I think the overwhelming majority of the panel that expressed comments was that there is no analytical technique that could be used to differentiate a formulation.

Several opinions were expressed, or a few opinions were expressed, relative to the need for perhaps further development of this technique if it is a big issue for the FDA in the whole issue of consistency for domestic versus international tolerances.

But, the basic bottom line, no, there is no analytical technique to differentiate at present.

DR. MACDONALD: Excuse me. Specifying at the residue level.

DR. LANGSTON: Good, thank you.

Committee Response to Issue 3, Questions A-D

DR. LANGSTON: Issue number 3. We are considering how we should inform the public of the import tolerance process, while also ensuring that we do not disclose trade secrets and confidential commercial information.

And, John, why don't we start with you, and go this way? And we will come back to you, Robert, and

come this way.

DR. WADDELL: I think this boils down to really a legal question. I think the lawyers are probably going to decide what can be disclosed and when. I mean, I have no problem, you know. They would open up for public consideration, you know, two or three months ahead of their decision, but I think the lawyers are going to decide this.

DR. LANGSTON: Dennis.

DR. WAGES: The answer to the first question: Should we disclose to the public we are considering an import tolerance?

I think we have probably all agreed that the answer to that question is, yes, in my opinion. That is correct.

If so, when?

I guess I kind of agree with John on the legalities of such a timing period might be out of this committee's hands. But when the package is delivered to CVM, and then they are looking at a six month time period, when they would be getting back to the applicant.

You know, maybe a 90 day post receiving of the package might be at least a place to start for recommendation of when that should be disclosed to the

public; but, again, maintaining the integrity of the process, as well as any confidentiality would again probably be decided by the legal term versus this committee.

How should we do it?

I think the federal register, as well as the CVM webpage could be appropriate avenues. My priority is with the federal register, being that is the ultimate document in disclosing information.

And, as far as the detail, again, I would defer with the legal department. But we have to make sure or ensure the integrity of the process, as well as any proprietary information and confidentiality is maintained at all levels in the disclosure.

DR. LANGSTON: Thank you, Dennis. I just noticed I read the issue, but not the specific questions. And Dennis did a good job of addressing those questions.

So, again, the actual questions are should we disclose? If so, when, how, and how much detail?

DR. CARSON: I concur with John and Dennis. Certainly, there are a lot of advantages of the public's right to know, of industry's right to know that these processes are started and initiated. But it is going to be a balance between the confidentiality, proprietary

information, and the public's right to know.

So, I also agree that probably the lawyers are going to decide the timing of this, and the exact detail that can be allowed. But I can see a lot of advantages of having information available ahead of time. One thing we talked at, I guess, coffee break yesterday, that maybe there could even be some collaboration between countries.

If one country initiated a process or requests for a tolerance that other countries that might also be using that drug could combine with them and have the advantage of either collaborating or coming in on the coattails, so to speak, of that action.

So there certainly are some advantages of that, but it is going to have to be balanced with the confidentiality.

DR. GLENN: If we are adopting the food safety approach, I do not believe that public health is better protected by public disclosure of an application for import tolerance. However, there are many reasons for public disclosure and transparency in the processes that we are using at this time.

One thing that would be different here regarding the availability of additional information appears to be that the previous regulatory package in

that foreign country would be available, I would presume. Also, other data may be submitted from public, as was mentioned previously.

So, therefore, in that framework, public disclosure, I think of an application for import tolerance seems to be acceptable and using any means necessary.

DR. LANGSTON: Any preference with federal register, how to get it out?

DR. GLENN: Well, I think both. The processes that are used currently, in terms of public disclosure, I think are quite good by the agency.

DR. LANGSTON: Well, likewise? I failed to ask you, Tom. Both methods? Okay.

Any specific amount as to when, how far in advance it should be released?

DR. GLENN: No, there was some good discussion on that. I will leave that to my colleagues.

DR. WOOD: As I stated earlier, I think public disclosure is important in relationship to setting import tolerances, because the essential question with import tolerance is one of public health, and what level of residue human health can sustain.

So, in that regard, I think there needs to be an opportunity for the public to provide scientific data

to the decisionmaking process that it feels is important in FDA's consideration of that question.

When that should happen, I, too, will leave that to my colleagues. But I would say, perhaps, more to our colleagues within the FDA CVM, I think that the bottom line importance is that there is public disclosure, and that there is an opportunity for the public to provide scientific data that it feels that is important in the decisionmaking process in a timely fashion, so that the FDA CVM has opportunity to consider that data before it makes its final decision.

A part of that whole mix though, I affirm what has been said by others here that the timing of that needs to be at a point it does not jeopardize the integrity of the whole tolerance setting process.

And so, I am not equipped to answer when that integrital moment would be, but that certainly needs to be factored in. This needs to be accomplished through the federal register, both through the federal register, which is the government medium of communication, and also through the CVM website, which is used extensively by the public to keep informed as to what is happening within the agency and its work.

DR. LANGSTON: I have failed to ask specifically as to the details. The whole things were

asked previously, such as the freedom of information summaries or equivalencies, things of that sort. I am afraid I am going to ask each of you to address those as well.

DR. WOOD: In terms of the level of detail that should be provided, I think it should -- again, should be something that is determined by the agency.

But I would expect that the detail would be comparable to what would be provided in the freedom of information responses in the normal domestic approval process, particularly, information related to its impact on public health, but nothing that would jeopardize the -- again, the integrity of the process or the proprietary nature of the sponsors.

DR. LANGSTON: I am going backwards. Barbara, any comments as to the level of detail?

DR. GLENN: No.

DR. LANGSTON: Tom?

DR. CARSON: Equivalent to the freedom of information would be I think very acceptable.

DR. LANGSTON: John.

DR. WADDELL: I agree.

DR. LANGSTON: Alexander.

DR. MACDONALD: As Dr. Sundlof mentioned, the first step, of course, is somebody applies for an import

tolerance, they submit a package. If the agency looks at that and says, "Okay. We have all of the pieces necessary to get on with our evaluation," at that point, they would go forward.

If the application is deficient, of course, it would be kicked up and additional information would be requested. If that package is adequate, if all of the bits and pieces are necessary for the evaluation, I think it will be reasonable at that point to make an announcement that an application for import tolerance has been filed and requests additional information from all interested parties to be submitted to that process at the agency.

That can go, obviously, through the federal register, but through the internet. That information can then be utilized by the agency in their evaluation, along with the formal data submission by the sponsor to provide the assessment, and that assessment would come out in a form of an FOI detailing all of the information at the FOI level of the sponsor submitted data; and, obviously, under these conditions, anything that was submitted from interested other parties.

DR. HOLLAND: Yes, part A, the answer is yes, I believe the public needs to be informed. B, I think you need to have the comment period during the time that

information is being evaluated by the Center for Veterinary Medicine.

C, how should we do this?

Go to federal register website, CVM Veterinarian. I think it is another opportunity with that publication.

How much detail?

I think that is a legal issue. We are not going to decide that point here.

One other thing, I mentioned this yesterday. I think it would be nice. I do not know how important it would be, but it would be nice to have some kind of historical perspective on tolerance-related issues, these compounds.

DR. KOCHEVAR: A, yes. B, upon filing and completion of the application. So, I basically agree with Dr. MacDonald that until they have the whole package, it is probably not worth publicly making that announcement.

C, all of the above, federal register, internet.

D, how much detail? That allowed by freedom of information. And I agree that some summary of past experience with that drug, because of the circumstances, of an import tolerance would also be very useful.

DR. PARKHURST: I agree that, yes, the disclosure would seem to be helpful to the process. B, it seems like it would be most helpful to have it after the preliminary acceptance or approval of the proposal, if that could happen.

C, I think the sources as to where we should list it, I do not have any sources to add; and then, D, I think one consideration is, is this just for disclosure, or would it also be helpful to have it as -- well, you probably do not want to go as far as saying a call for scientific data, but that is what you would like, any scientific data that is out there that nobody would overlook.

And if that is one of the goals, that people would provide scientific data, then there may be some proprietary data that people would like to share in there maybe should be some thought or provision about how to handle that.

DR. LANGSTON: So, in terms of sharing, similar to what was said before about past experience or other submitted data being provided, is that paraphrasing?

And when you said, I think you used the term "acceptance" of the package. Do you imply a provisional tolerance being set? Are you talking about a complete

package, as is Dr. MacDonald?

DR. PARKHURST: No, more along the line of what Dr. MacDonald said that the agency has determined they are going to go ahead with it.

DR. WAGES: Can I give a point of clarification real quick on something?

Were we not told by Dr. Sundlof that they would be very specific in asking for the publication information on data submission for the information, so that it would be very specific on what data they want versus, even though they would get multiple different comments? Thank you.

DR. PARKHURST: I mean, to me that is a different thing from disclosure. One thing is there is just disclosure, and the other objective is more or less a call for scientific data. They are a little different.

DR. HASCHEK-HOCK: Okay. Answer to A, yes, I think it is important that any import tolerances considered be disclosed to the public, and allow for comment because of the human health issues involved;

B, when should this be done? Again, I think this will end up in the lawyer's lap. But it would seem that there should be some reasonable assurance that the package can go forward, so at least the preliminary

review, perhaps, after a preliminary review, then the request for comment could go out;

C, yes, I think both the federal register, and the website are important; and

How much detail should we provide?

I think it is important to maintain confidentiality of the data. So, perhaps, as indicated by others, an FOI type statement, and also information on use of the drug in other countries.

DR. ANDERSON: For A, yes. For B, if so, when? I think as soon as FDA begins their own deliberations is when they should release to the public that they are considering this. So, if that is upon filing, then I would say upon filing.

For C, I think the federal register and the internet is a good idea, just whatever makes it easier for public access. And for D, regarding how much detail should be provided, I think as much detail as possible that does not compromise any trade secrets.

So, if that is what they get in a FOI, then that is what I would recommend.

DR. LANGSTON: I think that definitely it needs to be provided. I would say that at the point that the FDA has received enough information that they view it as a viable application. It should be announced

to the public.

I think all of the methods of dissemination mentioned, federal register, the web, and perhaps CVM newsletter would be appropriate. And I favor something along the line of a freedom of information disclosure.

So, in summary, I think everyone on the panel is in, more or less, agreement that some form of public disclosure is appropriate. Various opinions were expressed as to when this should occur.

Most expressed that a complete package should be available, so that it is not announced to the public, when, in fact, it stands a poor chance of being approved; nor the opinion was perhaps at the point of filing.

But I think one of the overwhelming things is it be submitted in time to allow for feedback to CVM before a decision is actually made on the tolerance.

Also, various opinions relative to the depth, acknowledging that this is likely to be handled by the lawyers. However, something along the Freedom of Information Act seems appropriate, several people noting that additional information, such as past experience reports, might be included as well, as long as confidentiality of trade secrets is not compromised.

DR. WAGES: You need to address I think part

C, for the record, Cory.

DR. LANGSTON: Oh, all of the methods, the federal register, the internet, and the -- and mention was made of the FDA Veterinarian. Thank you.

DR. WOOD: And the feedback would happen via comment period, right?

DR. LANGSTON: Thank you.

DR. PARKHURST: The idea that the agency might consider a call for scientific data, I do not know if that is liable or not. We did not discuss that, but that would be something for them to just consider.

DR. LANGSTON: I think this is going in the record. So, obviously, that now becomes part of the minutes and a consideration they can take into account.

Committee Response to Issue 4

DR. LANGSTON: Okay, issue number 4. We are considering amending the regulations of 21 CFR 25.33, to allow categorical exclusion for import tolerances under the National Environmental Policy Act, if there is information that shows that establishing import tolerances does not have a significant effect on the environment.

We are seeking information on whether import tolerances will have a significant effect on the environment. I will start off again, and that is fairly

easy. No, I do not see an impact.

DR. ANDERSON: I agree. I do not see an impact also.

DR. HASCHEK-HOCK: I agree. And, therefore, I think that a categorical exclusion for import tolerances should be approved under the National Environmental Policy Act.

DR. PARKHURST: I would like to see the emphasis on "National." Because if you just read that not very carefully, it might be on the home country as well, as we do not want to get into that.

DR. KOCHEVAR: I would agree. It does not seem like the environmental impact is significant.

DR. HOLLAND: Agree.

DR. WADDELL: Ditto.

DR. WAGES: Agree.

DR. CARSON: Agree.

DR. GLENN: Import tolerances in edible animal food products do not seem to have a significant effect on the United States environment.

DR. WOOD: I would agree that this does not have a significant impact on our environment as an edible form. At the same time, I would hope that the FDA would keep an open eye to emerging scientific evidence that might prove us otherwise and cause this to

be an issue to be brought before us at another time.

DR. MACDONALD: I agree. There is no impact on the environment.

DR. LANGSTON: I think it is pretty well unanimous that there is no impact on the environment with the notation that this relates to the U.S. environment. It is not the prerogative to address the importing -- or exporting country's environment.

The last issue is really allowing you to comment on any other aspects of import tolerance you may wish to raise. So this is a chance to bring up several things. Dr. MacDonald, do you have any comments?

DR. MACDONALD: No, I do not. I think that the approach that has been proposed we will be very thorough on them, see any additional things that need to be done.

DR. WOOD: I would like to initially raise, well, first, regarding resistant bacteria. I addressed that concern in my response to issue 1.

Secondly, and I know this is going to be probably addressed by others around the table, because of the potential for a negative health impact. If a zero tolerance were to be exceeded for substances that are banned in the U.S., I would hope this committee would ask the FDA to require a country to certify that

food animal products would not be exported to the U.S. from animals treated with these U.S.-banned substances.

Some of these banned substances cannot be tolerated in our body at any level if residues were to be exceeded. We heard yesterday that the USDA does not test for the presence of these residues in imported meat and poultry. This sort of protection would help. These substances should not be used in food animals when the food products are intended to be exported to the U.S.

DR. GLENN: I would also like to mention that it seems to me that we should not -- or the agency should not review an application for import tolerance on an animal drug that is banned in the United States. It does not seem to be consistent.

And, furthermore, the public comment period would be interesting regarding that issue.

DR. CARSON: I have no other issues to bring up on this.

DR. WAGES: I guess I would go to the point that this committee should recommend to the FDA CVM that they should solicit public comments on a proposed ban on food products imported into the United States from those countries that allow drug use in food animals that are either banned or illegal in the United States.

And, based on that comment period of the pros

and cons, an evaluation should be made whether that ban is implemented. Products that are used in countries that are simply not approved in the United States, and that is aside from illegal or banned, those should be looked at on a case-by-case or a drug-by-drug basis.

But I think it is, and in fairness to the producers of food in the United States, allowing the importation of meat product, or at least in my mind not probably fully identifying the pros and cons.

And, as I said yesterday, this is a two way street. And that is why I think it is important to get the public comment, and people who have the foresight of all of the possible ramifications of such. But I think we would at least recommend that FDA CVM look at proposing a ban on importation of those products.

DR. WADDELL: I agree with Dr. Glenn and Wage that -- I mean, this goes to the level playing field issue for the U.S. producers. And it just makes no common sense to me at all that there be products banned for use in this country, and then we allow imports, even with a zero tolerance, from countries that allow the use of those products. So, I agree.

DR. HOLLAND: No comment.

DR. KOICHEVAR: I think that it is an important issue, in that, CVM would have to come up with a

mechanism for trying to assure that those substances were not used in animals that from which the meat was going to enter this country.

I think it is difficult to say though that we can enforce anything like this if we do not in fact check for those residues. So it would have to be, it seems to me, some dialogue between FDA and USDA. And, again, maybe even the notion of Codex dialogue to deal with this issue beyond just the policies of the FDA.

DR. PARKHURST: I would like to thank my colleagues for raising the issue of the zero tolerance versus banned. And I think it has been eloquently presented as a motion. And so, I would like to really second that, that it is very important, and that if it is a banned product it should be handled the way we handle it for the tolerance in the U.S.

DR. HASCHEK-HOCK: I have an additional comment. I think the development and implementation of import tolerances will be an additional burden on the FDA, as would any additional testing that might arise if banned products were excluded for use in animals imported into the U.S.

I think there would be a need for increased FTEs and funds for analytical test of development in actual testing. And I would like to just bring to the

floor that I think additional funds should be allocated by the government to FDA in order to be able to develop and implement this.

DR. ANDERSON: No additional comments.

DR. LANGSTON: I would like to echo a couple of things already mentioned, that is, that other countries would have new or alternative drugs to use in their food animals to combat disease or enhance production, yet still be able to import to the U.S., is no doubt frustrating to producers.

I wish that were not the case. And, certainly, if the sole purpose of the FDA was to simply assure human food safety, it will be more easily addressable. And, of course, from the standpoint of those drugs being approved in the U.S., the FDA also has to establish efficacy and safety in the target species as well.

And while it may be a little comfort that those foreign countries may have either suboptimal or marginally toxic doses and/or placing their public or environments at risk, I do, nevertheless, feel that the gain in harmonization offsets those concerns.

Likewise, the issue of being able to import a food product from a country where a banned drug is used as a perplexing one, even if it is a zero tolerance, I

personally would like to see some sort of certification from those countries that that drug is not used.

The concept of either of those two, however, I realize is somewhat political. There are tit for tat things, such as Dr. Wages has mentioned. Already we face barriers relative to growth hormone issues, and growth implant issues, which may not necessarily be scientifically-based, but certainly could become an issue.

Lastly, I am going to get up on a soap box just a little bit and hit one of my topics on the issue of safety factors in the calculation of tolerance. I am skeptical as to their scientific merit. While it is true that no adverse human health effects have resulted when these tolerances have been used, in point of fact, I am not aware of any adverse health effect when any sort of withdrawal has been used relative to food residue.

All of the health effects that I am aware of adversely have been associated with grossly high levels, where not withdrawal was applied. While the human food safety factor is paramount, I would also point out that when you do set a low tolerance, you do impact that producer, and you also in certain cases impact the pain and suffering of the animal, particularly, for

analgesics, inseds, this sort of thing, relative to --- animals which will have to be held for a longer period of time, again, public health being paramount.

So, I would tilt at a windmill and say that some addressing of safety factors should be considered in future research.

And, along those same lines, stepping up on Dr. MacDonald's soap box, I also liked his approach of addressing the issue of whether those ingested foods are bioavailable in the human and/or affect the human being or his intestinal microenvironment.

So those were relatively diverse comments, which I will not attempt to summarize.

Anything else?

(No response)

DR. LANGSTON: Okay. That, as far as I am concerned, brings to a close this portion of the VMAC meeting. I understand we will reconvene at 1 o'clock, for the pathogen load issue.

I usually do not use Robert's Rules of Order, but since this is the end of this session, is there a motion adjourn?

(Chorus of ayes)

DR. LANGSTON: Second?

MALE VOICE: Move.

DR. LANGSTON: Second.

MALE VOICE: Second.

DR. LANGSTON: All in favor?

(Chorus of ayes)

DR. LANGSTON: We are adjourned. See you at 1
o'clock.

(Whereupon, the Import Tolerance meeting was
adjourned at 10:20 a.m.)