

Veterinary Medicine
Advisory Committee Meeting

Import Tolerances

January 22 ~ 23, 2002

Tuesday,
January 22, 2002

Held at the
DoubleTree Hotel
Rockville, Maryland

Audio Associates
9537 Elvis Lane
Seabrook, Maryland 20706
301/577-5882

I N D E X**VMAC Meeting****January 22, 2002**

	<u>Page</u>
Procedural Comments by Aleta Sindelar	4
Welcome/Introductions by Dr. Stephen Sundlof	7
ADAA 1996: Legislative Overview by Jarilyn Dupont	10
Food Safety by Dr. Mark Robinson	23
Questions and Answers	37
Setting Tolerances for Drug Residues by Dr. Lynn Friedlander	44
Questions and Answers	57
Codex and International Aspects by Merton Smith	67
Questions and Answers	83
Seafood: Safety & HACCP by Dr. Kim Young	85
Questions and Answers	99
Compliance with Tolerances for Imported Meats by Dr. John C. Prucha	107
Questions and Answers	125
Public Disclosure and Environment Assessment by Dr. Mark Robinson	140
Questions and Answers	144
Open Public Session by Dr. Jim Heslin, Moderator	145
Presentation by Dr. Bob Livingston	146
Questions and Answers	155

I N D E X (cont'd)

VMAC Meeting

January 22, 2002

	<u>Page</u>
Presentation of Questions by Dr. Stephen Sundlof, Moderator	162
Committee Deliberations by Dr. Cory Langston, Moderator	165

Keynote: --- indicates inaudible in transcript.

P R O C E E D I N G S

(8:40 a.m.)

Procedural Comments**by Aleta Sindelar**

MS. SINDELAR: Mr. Chairman, members of the committee, invited guest speakers, FDA staff, and public participants, I would like to welcome all of you to the Veterinary Medicine Advisory Committee Meeting.

I am Aleta Sindelar, the executive secretary for this committee. I will be providing information regarding the public information made available at this meeting. The advanced notice of proposed rulemaking for import tolerances, and read the conflict of interest statement for the public record.

First, the Veterinary Medicine Advisory Committee Meeting will be open in entirety to the public. Thus, all information presented at this meeting is open to the public.

At the back of the room, you will find a spiral bound book containing the information provided to the VMAC members in anticipation of this meeting. All comments provided for review to the committee prior to this meeting are also made available.

A new agenda reflecting the speakers for this meeting has been copied for your review. All Powerpoint

slides of speeches presented today, as well as the aforementioned materials, have been transmitted for posting on the CVM website.

The comment period for the advanced notice of proposed rulemaking for import tolerances has been extended to March 11, 2002. Additional information for submitting comments can be found on the CVM website, and, in particular, the CVM update dated December 12, 2001.

And, finally, the conflict of interest statement for the public record reads as follows:

"The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made part of the record to preclude even the appearance of such at this meeting, January 22, 23, and 24, 2002.

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 from exclusion is granted by the agency.

Based on the submitted agenda for this meeting, and a review of all its financial interests reported by the committee participants, it has been determined that all interests in the firms regulated by

Center for Veterinary Medicine, which have been reported by the participants, present no potential for a conflict of interest at this meeting with the following exceptions:

In accordance with 18 U.S.C. 208(b)(3), a waiver has been granted to Dr. Robert Holland, Dr. Deborah Kochevar, Dr. Alexander MacDonald, and Dr. John Waddell.

Under these terms of the waiver, Drs. Holland, Kochevar, MacDonald, and Waddell will be permitted to fully participate in the discussions and deliberations, which will involve human and veterinary medical issues related to the import tolerance in the context of the Food and Drug Administration's mandate from the Animal Drug Availability Act to establish these tolerances.

They will also be permitted to participate fully in discussions and deliberations pertaining to antimicrobial drug effects on pathogen load in food producing animals, as it pertains to the preapproval process of new animal drug applications.

In the event that the discussions involve specific products or firms not on the agenda, for which FDA's 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.

Screenings were conducted to prevent any appearance, real or apparent, of conflict of interest in today's committee's discussions. Copies of this waiver statement and the waivers addressed in this announcement are available by written request under the Freedom of Information Act.

The guest speakers have also been screened for potential for a conflict of interest or appearance thereof. Dr. Scott McEwen would like to disclose that he is negotiating a contract with Vetrepharm, a subsidiary of Bioniche to do a field trial on a matter unrelated to the issues to be discussed at this meeting.

Dr. Thomas Shryock would also like to disclose that his full-time employment is with Elanco Animal Health, a division of Eli Lilly & Company, and he holds stock in Eli Lilly & Company.

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 on." Thank you.

Welcome/Introductions

by Dr. Stephen Sundlof

DR. SUNDLOF: Well, good morning, everyone. I

Audio Associates

301-577-5882

am Steve Sundlof, and I am the director of the Center for Veterinary Medicine. And I would like to take this opportunity to welcome everybody to this Veterinary Medicine Advisory Committee.

This committee is very important to the deliberations of the Center for Veterinary Medicine. We rely heavily upon the expert advice of this committee to give us guidance as we try and deal with some of the issues that are, in many ways, the most complicated and difficult.

We need this advice in order to be able to make positive progress towards resolving some of the, again, very difficult issues that face the center on a day-to-day basis. So, again, welcome everyone.

We originally had proposed to talk about import tolerances back in September, and the terrorist attack of September 11th caused us to reschedule that meeting. We were able to put this advisory committee meeting back-to-back with another one, in which we are going to be dealing with another very important issue to center, which is pathogen load, and how we deal with that particular issue in the evaluation of antimicrobial drugs.

So it is good to have the opportunity to have everybody come together. We think we will have a very

productive meeting during the next three days. If there is anything that I can do personally to make people stay more comfortable, please let me know. We will try and do everything we can to accommodate everybody's needs.

I would like to then introduce the Veterinary Medicine Advisory Committee. I will start with our chairman, Dr. Cory Langston, who represents the Discipline of Pharmacology; Dr. Alicia Anderson, who represents Public Health in Epidemiology -- thank you for raising your hand so that people will recognize you -- Dr. Wanda Haschek-Hock, who represents pathology; Dr. Ann Parkhurst, who represents biostatistics; Dr. Debbie Kochevar, who represents companion animal medicine; Dr. Robert Holland, who represents minor use in minor species; Dr. John Waddell, who represents food animal medicine; Dr. Dennis Wages, who represents avian medicine; Dr. Tom Carson, who represents toxicology; Dr. Barbara Glenn, who represents animal science; Dr. Richard Wood, who represents our consumers; and Dr. Alex MacDonald, who represents chemistry.

So, thank you all, panel, for coming. Some of you I know had a little difficulty in getting here, but we are glad you all made it. And, with that, I am going to turn it over to Dr. Mark Robinson, who will talk about food safety.

Oh, I am sorry. I am a little out of order here. It is Jarilyn Dupont, who is going to talk about the legislative history behind import tolerances.

ADAA 1996: Legislative Overview

by Jarilyn Dupont

MS. DUPONT: Good morning. Dr. Sundlof asked the Office of Legislative Affairs -- excuse me -- Office of Legislation, actually, to come in and provide sort of a background on the legislative history, with respect to the Animal Drug Availability Act, particularly, the Section 4, which is the important tolerances.

So I am going to go through this very, somewhat dryly, in one sense. Because, as most of you know, legislative history has an official history and an unofficial history. What I am going to give you is the official history, because the official history is unfortunately all that matters to bodies as yourself and to the court.

Of course, there is an amazing unofficial history, which I am sure Dr. Sundlof would be glad to relate to people during the break, and all of the lobbyists involved, and the individual companies who wanted something.

But, unfortunately, this will be a little bit dryer than that, and won't be as interesting. But we

will go through it. Part of this is published in the ANPR, which has some information about that.

Let me just start with something that is kind of not on the chart here.

(Slide)

This became law in 1996. But, if you will recall, previous to this, I believe it was 1994, was signed the Animal Medicinal Drug Clarification Act, which sort of started the ball rolling with respect to improving the review process with respect to animal drugs.

Subsequent to that session -- that was the previous Congress before this particular Congress -- before that came about then they decided that they wanted to try some more. So quite a few bills were then subsequently filed the next Congress.

That was also the time when we were doing what was called FDAMA, the Food Drug Modernization Act, which is the big sort of revision of all of the activities at FDA. So this sort of became part of that, even though it was a separate track and did get signed separately.

The ADA was designed, you know, to increase the number of animal drugs on the market. This was sort of generated out of a whole collaboration of the unofficial history with respect to industry, with

respect to FDA, the administration, manufacturers of drugs.

It was passed with extremely strong bipartisan support. If you look at the debate and stuff, there is not a whole lot of discussion that indicates that there was any sort of controversy with respect to this.

(Slide)

These are the different sections, evidence of effectiveness, limitation on residues.

(Slide)

Then we have the import tolerances, which is Section 4; veterinary feed directive, which is Section 5.

(Slide)

And the feed meal licenses, which, as you know, has become a very big issue now also, with respect to the BSC issues.

(Slide)

This is a path to passage, and this what I am going to concentrate on, and I will go through each of these individual things. Prior to the bill that actually had Section 4, which was the import tolerances, you had S.773 introduced.

That actually was from Senator Kassebaum, which is the first part of FDAMA. That did not have in

there anything to do with import tolerances, but it started the ball rolling with respect to the issue of trying to move forward on animal drugs, and sort of reinvent animal drugs. That was introduced in 1995.

(Slide)

Now, between May of 1995 and October of '95, nothing happened on that particular piece of legislation. Nothing happened officially. What was happening behind the scenes was is there was a lot going on with respect to the reinventing government initiative by the Clinton Administration at the time. There was a lot going on with, you know, lobbyists, whatever. And there were negotiations going back and forth with Congress at this time and the Administration.

In October, another bill was introduced which also was sort of ADAA was reformed, and that again did not have anything about import tolerances in it.

Let's see. Hold a second there. Well, that was it. Hold on. This is what happens when you hit the wrong button, as you can see. So bear with me one second, and I will get back up to the one I was at. Okay. Okay, here we go.

(Slide)

As you see, neither one contained an import tolerance provision but there was effort. They really

wanted to improve "the drug review process" with respect to animal drugs.

(Slide)

In December of '95, you then had 1477, which was introduced by Senator Kassebaum again. And this was the result of a lot of negotiations, which was the first FDA reform bill, and it again contained animal drug reform provisions.

(Slide)

In 1996, we had the REGO initiative, which as the reinventing government, with Clinton Administration, and it was reinventing food regulations. And in the National Performance Review Standards, they included a proposal for FDA to focus its review on the safety of drug residue in an imported food products, and including and other animal drug initiatives.

That was sort of the first written explanation of exactly what they wanted. And if people would like to look at that, I think it was published in January 1996, Reinventing Food Regulations, under the Clinton Administration REGO initiatives.

And part of it was is that -- let me read you part of this, what it included. It says, "Currently, FDA establishes legally accepted tolerance levels of veterinary drug residues in food only through its drug

approval process. Thus, even for drugs that would not be used domestically, for example, because they are intended to treat diseases or pests that are problems here, and for which the only domestic health concern would be that the residues in food be safe, the sponsor would submit, and the agency would review data demonstrating that the drug is effective and safe for use in animals. This requirement is burdensome, both to agency and industry, and adds nothing to the public health or safety of American consumers."

(Slide)

Subsequent to the REGO initiative, subsequent to all of these bills, they started having hearings with respect to the FDA reform initiatives, S.1477.

Dr. Kessler testified and briefly mentioned the effort to improve the animal drug review process.

In March of that year, it passed committee; then in March of '96, you all had another bill, H.R. 3200, which sort of became the vehicle for the Animal Drug Availability Act. That was introduced by Representative Klug.

It was one of the three different reform bills that were going on at the time. Title 2 had evidence of effectiveness and limitation on residues, and it was picked up the provisions from the REGO initiative that I

just read to you. So that is the first sort of public evidence that they were interested in this issue on the Hill.

(Slide)

We then had the House Commerce Subcommittee hearings that happened over different period of time, Dr. Kessler testified again. Then, in May of that year, you had the reinventing the regulation of animal drugs REGO initiative, in addition to the food on that was issued in January, then again repeated the effort that they wanted to do with respect to the import tolerances.

(Slide)

The only Congressional history we get on this, you have a special order on FDA reform bills, and in those they briefly mention the effort to get rid of the cumbersome regulatory process, that type of thing. But there is nothing very specific that speaks to what did we mean by this issue of import tolerances?

There is nothing that direct. There is nothing that, you know, steps out and says, this is what we meant, or this is the legislative history. But let me also point out that the language itself of the bill is not exactly unclear. It is fairly specific, and it is plain English, and it does pretty much tell you what it means to tell you.

You then have it in June being reported to the Senate. And between June and September, is when a lot of the unofficial sort of lobbying and nego -- I mean, they are official, but that is where the bulk of the effort gives when the committees in industry and everybody is working together to come up with the final bill with respect to these issues.

(Slide)

You then have the committee mark-up in September of '96, and it was discharged from the committee on September 19, and it included the import tolerance. It was passed by voice vote in about a week, within a week.

(Slide)

It was then discharged and marked up. They marked up S.773 in the committee and the Senate. They discharged that. It then was passed in Senate, as you can see, on the same day, so that was a very quick process, not a whole lot of discussion.

(Slide)

Then within a couple of days, it was presented to the president, and then in October it was signed, it became law.

(Slide)

The provision, which everyone I am sure is

familiar with now, and is repeated in the ANPR is, like I said, very self-explanatory, and it is Section 4.

(Slide)

Now, the only type of Congressional intent that we can tell you that actually occurred was is that we had only three members and one Senator actually mentioned these in the floor remarks during passage. You know, things like: Finally, the bill authorizes FDA to establish import tolerances.

Not exactly explanatory as to what they meant by any of the language in the section, they are just pleased that it is done.

(Slide)

Same thing with Mr. Manton. It just talks about, oh, this will allow us to establish import tolerances.

(Slide)

Mr. Deutsch spoke about how it would implement the REGO initiatives, which is probably the best information you can get for background on this, because then the REGO initiatives go into a little more about why they intended this to be done. The bill permits FDA to set import tolerances.

The House Commerce Committee issued a report when it did pass the bill and when it went to the floor,

and it had two references.

(Slide)

The most significant reference is probably from the Congressional Budget Office. As you know, the CBO does a cost estimate of these bills when they pass. And in doing their cost estimate, they discuss what it means to have this bill actually implemented, and in this it talks about what they thought it meant.

Now, this does not, you know, is not the absolute last word, but it certainly gives you some guidance with respect to what they intended. It talks about how USDA monitors residues, sometimes in consultation with the FDA.

Well, that sort of sentence, you know, points out that, well, this is the background. If USDA has been doing this at all, if they have done anything at all, then you would interpret that what they had done before was supposedly somehow going to be subsumed into what you are doing now.

They did not do anything. Well, then there is no background there, but that gives you sort of a clue as to the type of things that probably the committee may have been looking at. CBO talks to these committee staff. They say, well, what did you mean by this? You know, what did you do?

They talk to the FDA. They say, well, what goes on now? What do we do? And they come out with this type of thing. And so, that gives you a little bit of guidance about exactly what was intended with respect to the bill.

Again, it is not the gospel, but it certainly would have credence if you were challenging this in court or something, as to what the legislative intent was. But let me stress again that the court is not inclined to look beyond the statute if the statute itself is clearly written, is in English, and they do not need to look to legislative history.

(Slide)

When they do a report with respect to this Congressional bills, you have a section-by-section analysis, and that is done by the committee, and it is the committee's interpretation of what they meant by the bill, and it talked about Section 4. But, again, it did not very much discuss it, other than it did repeat pretty much what was in the REGO initiatives.

And, again, it talks about, you know, they intended that it be able to be brought into the United States, or diseases or conditions that do not occur in the U.S., and we should not prevent food from coming in even if they have a residue, if they have drugs in it.

So that is the type of thing we have there.

It talks about establishing a safe tolerance. It does not define what safe tolerance is. It let's FDA decide that. It talks about they may rely on data. It does not talk about the type of data, but just says where the data can come from.

If it is an international standard which we rely and it changes, it gives -- it sort of implies that FDA is the authority to then reject that standard afterwards if it turns out that it is not appropriate.

(Slide)

And then last year ANPR was published, which is moving this forward. So that is it. I think that gives us about five minutes, if anyone had any questions.

(No response)

MS. DUPONT: It was that clear? Okay. Well, good. Thank you.

(Pause)

DR. LANGSTON: Just a note to the committee members that while Dr. Robinson is setting this up, that while you will have a chance to ask additional questions during the committee discussion period, obviously, if you have anything that needs answering right now or could be answered that would be preferable probably.

DR. HASCHEK-HOCK: I do have a question. In the one of your notes, it says that currently, under current law, the Department of Agriculture monitors residue as an imported animal food products. And I was wondering, how is that done? And how extensive is the monitoring?

DR. SUNDLOF: Well, I will try and answer that one. Right now, unless we develop methods, or if FSIS develops methods for certain drugs that are not approved here in the United States, for the most part, they do not monitor for those other drugs.

Now, they do have agreements with the foreign countries that they are not supposed to be using drugs that are not subject to approval in the United States. So the USDA monitors foreign slaughter plants, and basically ensures that they meet the same standards as the U.S. slaughter plants meet.

But we are aware, I think just about everybody is aware, that there are drugs that are being used in other countries that are not being used in the United States, and either we do not have the methods, or we do not have the toxicology data to have the same kind of assurance that we do in the United States for domestically produced products.

Now, we do monitor for some chemicals,

especially things like chloramphenicol, that is part of the monitoring process. But there are very few drugs that are actually on that.

This gives us the opportunity to, if we know that a country is using a drug that is not approved in the United States, to require that they provide us the information that is necessary for us to be able to establish to our satisfaction that any residues in the meat or animal products that come to the United States are safe.

DR. WOOD: But just to clarify, when you say we, are you talking FDA or USDA at this point?

DR. SUNDLOF: This is FDA.

DR. LANGSTON: Any other questions?

DR. ROBINSON: Could we have the chandelier and the wall sconces down just a bit?

Food Safety

by Dr. Mark Robinson

DR. ROBINSON: My name is Mark Robinson. I am the director of the Division of Human Food Safety in the Office of New Animal Drug Evaluation. And, as you know, we are here to talk about import tolerances. I would like to thank Ms. Roberts for the legislative exposé.

As she pointed out, we are here specifically to talk about the establishment or the process of

establishing tolerances for those residues of drugs which are used in food animals, but which may not be approved for use in the United States.

The primary reason to establish import tolerances is to protect the public health and to facilitate trade. Currently, there is a de facto tolerance of zero for any residue found in imported food animal commodities.

And, theoretically, this de facto tolerance would protect the public health. But I think it is arguable as to whether this would actually facilitate trade.

More importantly, if there is data available, particularly from other regulatory environments, which would demonstrate that something other than a zero tolerance is warranted, then it seems reasonable that we consider this data in our examination for tolerance other than zero.

In my association with the Division of Human Food Safety, I have the pleasure and the privilege of working with some of the best scientific minds in the evaluation of new animal drugs. One of the products of these evaluations is a tolerance.

A tolerance is simply a benchmark and an upper limit for the level of residues in a food animal

commodity that we consider to be safe. We do not say that a residue above that level is unsafe; we say that we do not have data to characterize it as safe.

I am a relative newcomer to the FDA, having been here just short of two years. In my previous lives, I have had a fair amount of activity with the FDA.

One thing that I learned quite quickly was that the best way to put off an audience was to begin quoting chapter and verse from the Food Drug and Cosmetic Act or the code of federal regulations. So I am going to show you this next slide with a little bit of apprehension.

(Slide)

The Animal Drug Availability Act of 1996, modified the Food Drug and Cosmetic Act in Section 512(a)(6) to read, in part:

"In establishing such tolerance, meaning the import tolerance, the secretary shall rely on data sufficient to demonstrate that a proposed tolerance is safe based on similar food safety criteria used by the secretary to establish tolerances for applications for new animal drugs filed under subsection (b)(1); (b)(1) is the section of the Act that applies to new animal drug applications in the United States."

I think the important things to take from this slide is that the data and the decisional criteria used to establish safety need to be comparable for import tolerances, as to those used for determining drug safety in the U.S.

(Slide)

The things that are evaluated in our evaluation of new animal drugs in the United States are principally sponsor-generated data that demonstrates the effects of defined concentrations of an active ingredient, formulation component, metabolite, or drug product, in relation to specific public health endpoints.

The majority of the history of the Division of Human Food Safety in the evaluation of new animal drugs has been concerned with an evaluation of active ingredients or the metabolites.

However, there have been exceptions where in a formulation component such as a solvent, a matrix, or some other excipient, has caused us more concern than the actual active ingredient or its metabolites. Therefore, we have also asked the sponsor to examine those.

Most recently, in the area of decreased drug susceptibility to antimicrobial, and the introduction or

potential introduction of transgenics into the new animal drug application pipeline, we have begun to consider the entire drug product as well.

However, the policy and the guidelines for transgenics for antimicrobial resistance are yet to be established. So it is a little premature to talk about import tolerances in those domains. We will focus principally on the chemical drug residues for the rest of this talk.

(Slide)

The reason for evaluating this data is captured in Section 512(d)(2), in which it says, "In determining whether such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof, the secretary shall consider, among other relevant factors, the probable consumption of the drug and of any substance formed in or on food because of the use of such drug, also the cumulative effect on man or animal of such drug."

Now part (b) alludes to chronic exposure. We also consider potential acute exposure problems, but the emphasis is on chronic exposure. Part (a) alludes to the obvious, which is that after the first pass of this drug in the animal, there will probably be residues left in the edible tissues, and we need to consider what the

potential effect might be on the consumer.

But it also opens up a door to another area, which is as big or as small as you want to make it, which is any substance formed in or on food because of the use of such drug.

The various considerations in the public health and the technology sectors are dragging that part of the Act around such that a definition as to we consider and what we do not is a matter of open debate.

(Slide)

The point of the evaluation is to identify any potential adverse human health effects that may be caused by the consumption of new animal drug residue in edible tissues from food animals, and when one is identified to try to mitigate any potential adverse human health effect.

Now, this is really a binary function. The data presented by the sponsor either will indicate that something may happen or it may not. There is no gradient, either qualitative or quantitative, in this evaluation.

We need to make a determination that if an effect is observed, we need to find out if we are concerned about it in relation to other observed effects. If we are that becomes a focal point of our

evaluation and tolerance establishment, and we need to find out if there is a way to mitigate that effect.

(Slide)

The previous slide highlighted the word "residue," so I thought I would throw up again from the code of federal regulations the definition of a residue. It is any compound present in edible tissues of the target animal which results from the use of the sponsored compound including the sponsored compound, its metabolites, and any other substance formed in or on food because of the sponsored compounds use.

Now, again, this harks back to 512(d)(2), and opens up that big door of in or on food because of the sponsored compound's use. This definition was derived principally in order to cover the issue of carcinogens, but it has been applied in a wider arena such that we use it basically as the standard definition of residue today.

As I said before, because we do not have policy or guidance for other issues like antimicrobial resistance or transgenic animals at this time, it is premature to consider those areas with regards to import tolerance. And so, we will focus on the chemical residues.

(Slide)

The objectives of the human food safety evaluation are to determine the concentration of total residues in the edible tissues of a food animal that when consumed daily by an individual over a lifetime will cause no harm.

This, in effect, is what we refer to as "the acceptable daily intake" or ADI, and that is what I will cover. I will actually take this one step further to the derivation of what we refer to as a safe concentration.

In the next talk, Dr. Friedlander will carry on to define the concentration of a marker residue in the edible tissues of a food animal that will be indicative that the edible tissue is safe. This is a tolerance.

(Slide)

Underlying the evaluation are a number of factors that I think are important to keep in mind. The factors that need to be constant are the purity, strength, and identity, including the identity of the active ingredients and the formulation of the drug product.

If we are evaluating something other than that which is going to be marketed and used, then we are operating in a vacuum and the evaluation has no sense.

Also, in the human food safety evaluation, we assume that good agricultural practices have been applied, in that enough of the drug is going to be used to achieve whatever purpose is intended, but that only enough of the drug is going to be used.

This is actually transgential to our evaluation, but it becomes important in establishing the tolerance with respect to the residue chemistry and depletion studies.

(Slide)

A bit of historical perspective. Originally, in the United States, we did not accept any detectable residues in food animal commodities. This is the no residue or zero residue tolerance. This was technologically limited in the sense that zero changed over time.

(Slide)

As we learned more, a universal truth was established, and tolerances for all drugs except for carcinogens were established at 0.5 part per million. This again included minimal, if any, hazard assessment.

(Slide)

And, as we gain knowledge about the effects of residue levels of drugs, the CVM moved to a risk-based assessment, which is effectively stated as the set risk,

which is a reasonable certainty of no harm, would be equal to the evaluation of the hazard mitigated by a control of human exposure.

(Slide)

Put another way, the public health risk is regulated by assessing the potential hazard posed by the drug in controlling the exposure in order to meet the standard of a reasonable certainty of no harm.

(Slide)

The hazard assessment, which will be the subject of the rest of this talk, is composed of -- this is for chemical drug residues. It is composed of a number of toxicological studies including a genetic toxicity battery, 90-day feeding studies in rodents and other mammals, multi-generation reproductive studies, developmental studies in rats, and an evaluation of the potential effect of antimicrobial residues on the human gut flora.

In certain cases, special studies are called for where a subchronic 90-day study is in completely reviewing, we may ask for a lifetime study, or a carcinogenicity studies may be called for based on the results of the genotype studies.

(Slide)

All testing is conducted through oral exposure

in surrogate species. We do not have the luxury of using human exposure data except in very limited circumstances due to the ethics involved with testing animal drugs in humans. So we look at surrogate species and expose them orally.

(Slide)

The objective is to define the concentration of drug substance that produces no effect in the toxicological assay of greatest relevance to human exposure, the no observed effect level or NOEL.

Now, as kind of a loaded statement there, the toxicological assay of greatest relevance -- well, this is a matter of expert opinion. We run a full series of tox tests with no prejudice as to which might be the most relevant.

The data often speaks for itself, but we also may need to consider what is the purpose of the drug in the animal and what may its potential worse case effect be in the human? That may drive us also. At this point, we introduce something that can only be explained as expert opinion.

(Slide)

The NOEL, or the appropriate NOEL is divided by a safety factor to obtain the acceptable daily intake, which is the amount of drug residue per kilogram

body weight per day that can be consumed daily over the lifetime of a human without harmful effect.

(Slide)

Now, where do these safety factors come from? Again, back to the Act, Section 512(d)(2) says in part:

"In determining whether such drug is safe, the secretary shall consider, among other relevant factors, safety factors, which in the opinion of experts qualified by scientific training and experience, to evaluate the safety of such drugs are appropriate for the use of animal experimentation data."

(Slide)

In our evaluation, we generally consider that the variability in human response is 10X. Now, you would have to speak to a cultural anthropologists, or someone else who understands this better than I, in order to understand why we are focused in-base 10 on factors of 10X.

But these are tried and true, in the sense that if you can prove a negative, these have worked over the years and have been accepted internationally, not just within the United States.

Also, because we work in surrogate tox species, there needs to be some compensation for the potential that a study in a rat will not be totally

revealing with respect to what happens in a human, or in a beagle, or in a non-human primate.

So, another factor may be introduced for the inner species extrapolation. Further, if we are relying on a subchronic exposure in order to establish what might be the chronic exposure effects, we may or may not add another factor of 10, so that the total possible -- and there is a mistake here. I apologize.

The total possible safety factor that could be applied to the NOEL is anywhere from 1 to 10,000. We have examples of both extremes. But, for the most part, the vast majority of drugs evaluated fall somewhere in between.

(Slide)

So what does this all add to? As I have tried to show you the NOEL, which is micrograms per kilogram per body weight daily, divided by a safety factor, determined by expert opinion, results in generation of an acceptable daily intake, which is also in micrograms per kilograms body weight per day.

The final step before going into the residue chemistry evaluation, is to define a safe concentration. The ADI is related to the total chemical residue exposure.

This is multiplied by the average weight of an

individual in the United States, which is currently considered to be 60 kilograms, and then divided by a consumption factor in order to determine the safe concentration for the total chemical residues in that edible commodity.

These consumption factors are mutually exclusive. They are listed at the bottom. We consider, maybe not quite accurately, but we consider that if a person consumes 300 grams of skeletal muscle that they are not going to consume liver, kidney, or fat during that same day. They will not be exposed to the residues during that same day.

The only point at which these are not mutually exclusive is for milk and eggs. If you have a drug which is for use in laying hens, the sponsor has a choice of partitioning the ADI so that some of it is for the egg, some of it is for the hen.

Similarly, for a lactating dairy cow, if a sponsor is concerned about milk discharge, they can partition part or all of the ADI to the milk, one-and-a-half liters of milk consumed per day, and the rest would go to the other edible commodities.

I know you all are hanging on the edges of your chairs waiting for the rest of the chemistry part. I think you will have to wait until after the break.

(Slide)

One last point that I would like to make is that the underlying assumptions that I illustrated before are not actually part of the human food safety evaluation as we have it divided up administratively in the CVM.

The purity, strength, and identity issues are really in the chemistry and manufacturing control. We do not deal with them. We assume that they are being done and have been done, and history shows that they are done very well.

Also, the good agricultural practice considerations are handled by the division, either the Division of Therapeutic Drugs for Food Animals, or the Division of Production Drugs for Food Animals, so that this is an area in which are not directly concerned.

But, again, the evaluation that we do relies on these factors being constant, so that the drug that is used is the same one that we have evaluated. Thank you very much. Questions?

(Applause)

DR. LANGSTON: Any questions for Dr. Robinson?

Questions and Answers

DR. KOCHEVAR: How problematic are those assumptions in facilities that the FDA has no knowledge

of in other countries in terms of good manufacturing practices, the purity, strength, identity issues?

DR. ROBINSON: Problematic, as was alluded to earlier, we deal with imports, principally, USDA deals with imports, but also FDA does on the basis of equivalency. There is equivalency for slaughter house operations. There is also equivalency with respect to the standards used in other regulatory environments.

So it is a big problem if there is no regulatory environment in which the drug is being used. If there is a regulatory environment, and the drug that we are talking about is approved for use in that regulatory environment, which is really, if I can shade this, that is the only way that talking about import tolerances really makes sense, and we need to be aware of what are the standards in that environment.

But the fact is that most of the environments, the regulatory environments of which I am aware, have similar standards for chemistry and manufacturing control. We would need to probably become more aware of the effect of those standards.

DR. WOOD: In your underlying assumptions, one on the list is good agricultural practices. Is there a clearly identified list of good agricultural practices for approvals in the U.S.? And how can that be measured

as we review imports from other nations? Is there a code of practice that is universal? And how easily and carefully can that be evaluated, is one of the assumptions, or parts of one of the questions that are before us.

DR. ROBINSON: Right, and I think it is in question 1. This is an area that I cannot speak to well. There may be others who can. We have no list that we can hand you. The basic GAP that we live by is that through the evaluation of the new animal drug in one of the animal divisions, either production drugs, or therapeutic drugs, that they will look at the efficacy data.

If the sponsor has proposed a concentration of a drug, or a frequency of use of a drug that achieves a purpose that can also be achieved by a lower concentration or less frequent use of the drug, based on their own data, then we will suggest strongly that they go for the lower concentration or less frequent use. That is really the extent of our participation.

DR. WOOD: Does that same subjective principle apply for good management -- manufacturing practices as well? And that is not on your list, but it is a part of the question before us.

DR. ROBINSON: No, GMP is very strict, very.

There is books full of information on GMP's that need to be adhered to.

DR. HASCHEK-HOCK: My question is: I assume that most countries also that do the ADI and the safe concentration, and if they do, do they use the same formula like 60 kilogram person?

I could think of maybe some Asian countries where the average weight might be less. And the consumption factor, I would also assume that in some countries it would be a different consumption or a different ratio between those different types of products.

DR. ROBINSON: Those are both valid points. The consumption factors would not make sense in other cultures in the average weight of an individual could vary. There are differences in different regulatory environments already.

What is important to remember is that we would not take the product of the work in another regulatory environment. We would take the data that is presented to another regulatory environment, the EU Japan, and do our own analysis based on our own standards.

So, to the degree that it is arguable that our average weight and consumption factors are relevant, it is kind of an abstract concept. But, to the degree that

they are relevant, they are the standards that we would apply in the United States even to an import tolerance.

DR. LANGSTON: And relative to that data that they provide to you, do you have any feel for the amount and quality of the data such that you can drive a NOEL?

DR. ROBINSON: We have had a number of submissions for drugs which have already been approved for use in other regulatory environments. And the quality of data, honestly, has been as variable as the quality of data that we received for new animal drug applications that are just for drugs used in the United States.

We look at it with the same eyes. This is for sponsors who have come in. They have a drug product approved, what's hypothetically in the EU, and they actually want to get new animal drug approval in the United States for use.

The consistency of the data is generally good, and is generally revealing enough to establish a NOEL, sometimes not. Sometimes we need to ask for more.

DR. KOCHEVAR: I wonder -- and this may just be a point where I need clarification. When we establish tolerances here for drugs, it has to be on the formulation that is actually used in that animal. Is that standard the same for drugs coming in, or can the

data be related to just the active ingredient or the marker residue?

DR. ROBINSON: That is really one of the questions to the committee. It is a bit of a circular argument. We establish a tolerance which is for a substance, and that is what is codified in 21 CFR 556. So I won't use any specific substance.

Substance X may be an active ingredient in drug product use produced by a variety of companies in a variety of different formulations, but the tolerance is for that substance. But each drug product receives consideration for a tolerance, so the tolerance actually ends up being linked to the drug product.

We need to figure out a way, if there is a way, to reverse engineer the relationship that we currently have, so that the detection of a chemical drug residue in an imported commodity could be related with some certainty to the use of a drug product over which we have some knowledge.

DR. LANGSTON: The issue of the safety factors has always interested me, and as you alluded to that they all seem to be units of 10. And while I agree you have not had a problem, actually I do not know of human health consequence from a human ingesting a drug residue unless it was grossly high, such as no withdrawal time

applied at all, for example.

But, back to my point, has anyone ever looked at, for example, using two or three standard deviations of the NOEL instead of 10X? Or, in other words, what is the basis for these units of 10?

DR. ROBINSON: I will answer the second part first. I think the basis for the units of 10 is that we have 10 of these things and we think that way.

Yes, a lot of people have used a variety of means, and there are people here who can speak to this much better than I can on the risk-based approach to basically eliminating safety factors as a consideration.

But, so far, we do not have the proof of the pudding or any standardized method so that we are sticking with the process that we have in place, and which has so far served as well.

Yes?

DR. WOOD: Just so that I am real clear, currently, as the FDA looks at tolerance levels for residues, then based on your earlier comments, there is no consideration or evaluation when it is an antimicrobial of resistance capabilities or dynamics?

DR. ROBINSON: No, I am sorry if I gave you the wrong impression on that. We have been for the last four years considering the effects on changes in

bacterial drug susceptibility due to the antimicrobial drug product. It is just that we do not have policy and guidance established for that.

We have handled it on a case-by-case basis for the last four years. So it would be putting the cart before the horse to establish a process where describing an import tolerance when we do not have the same mechanism in place for drug approvals in the United States.

DR. LANGSTON: Thank you very much. I believe that we will break until 9:45, if you could please assemble back here. Dr. Lynn Friedlander will take you the rest of the way to the derivation of a tolerance.

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

MS. SINDELAR: Okay. Why don't we start the meeting back again?

And let me introduce Dr. Lynn Friedlander, and she is going to speak on setting the tolerances. Thank you very much, Lynn.

Setting Tolerances for Drug Residues

by Dr. Lynn Friedlander

DR. FRIEDLANDER: Good morning, everyone. Can you hear me all right?

(No response)

DR. FRIEDLANDER: I am Lynn Friedlander. I am currently the acting team leader for the Residue Chemistry Team in the Division of Human Food Safety. And our team is responsible for evaluating the scientific data that comes in to support the new animal drug approvals in food animals, specifically, the data that is used to establish tolerances and for our domestic approvals to set meat and milk discard times if they are needed.

(Slide)

Now, as Dr. Robinson pointed out, we are going to focus on chemical residues in this part of the presentation, as he did in his. There are potentially other benchmarks that could be used. But since we do not have guidance in place, I am going to stick to the chemical residue aspect.

I kind of feel like I am getting a class of students back from their winter break or something, and I cannot tell how much you forgot while you were having coffee. So, the first thing I am going to do is I am going to sort of very rapidly rehash the material that Dr. Robinson went over.

Ah, mood lighting, thank you.

(Slide)

This is our definition of residue. It is in

the regulations. It is the same one you saw before. It is any compound in the animal tissues of the target animal formed as a result of the use of the sponsored compound. It is the parent drug. It is the metabolite. It is anything else basically.

(Slide)

We have already talked about the toxicity data that is generated as part of a domestic approval. I am not going to talk about the microbial safety data. As Dr. Robinson mentioned, this is an evolving area. The guidance is not there yet.

So I am going to skip right down to the residue data in the food producing species. I am going to talk a little bit about analytical methodology, because that ties into the whole process. And then I did want to remind you that all of our food safety studies are done to conform to good laboratory practices.

Dr. Robinson talked about the basic toxicology package. If we need it, we can ask for additional special toxicology studies. The end goal here is to calculate the no effect level, to assign an appropriate safety factor, and then to calculate the allowable daily intake.

(Slide)

There is the little formula.

(Slide)

We do a safe concentration, which is basically a way of spreading out the ADI over the kinds of food people eat so that consumption value is what we think people eat for any of the food animals derived commodities.

(Slide)

And the safe concentration is the amount of residue that can be eaten in any of the edible tissues each day for the entire life of the consumer without exposing them to more than the allowable daily intake.

(Slide)

Here is our risk equation. You have seen that before. And the goal of the residue group in the tolerance setting procedure really is to mitigate the hazard that has been identified by the toxicology studies.

In a domestic approval that is accomplished by assigning tolerances, and, where necessary, withdrawal periods from meat, milk discard periods for milk, and eggs are a little special. They have a zero withdrawal that they have to comply with, or they are not approvable.

(Slide)

Dr. Robinson talked about the basic studies that go into doing tox. We also have a fairly defined set of studies that are basic to the tolerance setting procedure, the residue chemistry procedure. We look at comparative metabolism in the toxicology species.

This is basically our link to everything that was done as part of setting up the ADI in the safe concentrations. So we do a little bit of work with rodents, or whatever the appropriate toxicological species is.

We do total residue and metabolism. For the residue chemistry group, total residue means radiolabeled. So we are talking about drugs that have been appropriately labeled for a study, and then this is basically a mass balance kind of thing, and a metabolism study.

The analytical method comes into play because it is a little hard to track metabolites if you do not have some sort of method. Total residue, it is easier to do without a method or an analytical method, a chemical method. But the metabolism actually requires that you have an analytical method, and so that is also part of the residue.

The residue depletion withdrawal study is something we do for domestic approval, but it is not

particular relevant to import tolerances because that will have been taken care of in the regulatory environment from which the food product originates. So that won't be something that would really fall into the import tolerance discussion.

(Slide)

The comparative metabolism study is done in usually rodents, and it is a way to decide whether the toxicology evaluated the right stuff. You feed drug to the toxicological species, but people do not eat rats, people eat cows.

So the rat is serving as a surrogate for people, and you want to make sure that the rat has been exposed to the same sorts of things that people will be exposed to when they eat food.

Generally speaking, we are looking at profile matching, making sure that the profile is comparable. If you come up with compounds that are not matched, if there are compounds that are found in -- that are not found in the toxicological species, that are subsequently found in the food producing animals, then we are probably looking at additional testing to cover that deficiency.

(Slide)

The total residue and metabolism study is

probably the linchpin of what we do for food safety, in terms of the tolerance setting procedure. As I mentioned, this is a radiolabeled drug study. It is usually conducted at one to one-and-a-half times the proposed dose.

This ensures that we see a full dose to the animals. We require that the company that sponsors the drug, administers the drug by the route of administration that will appear on the label.

Now, this is in direct contrast to the toxic studies which are all conducted orally. If a drug is going to be administered by subcutaneous administration, then we see total residue and metabolism study in the food producing animal by the subcutaneous route of administration.

We also want to see the same kind of dosing that is going to be on the label. So if it is a three injection dosing regime, we want to see a three injection dosing regime.

If it is feeding in the diet for an extended period of time, we are usually looking at a determination by the sponsor that they have attained steady state, and that keeps them from having to do studies for six months, or ten months, or whatever.

We also want to see it in the intended

species. What this means is that every time a sponsor comes in for a new species indication, they are looking at doing this total residue and metabolism study again. So you do it for cattle; you do it for swine; you do it for chickens. There is not very much material that crosses over for another species.

We would like to see it in both male and female animals unless there is some peculiar reason why that would be inappropriate, say, a drug is only approved for one gender.

The total residue and metabolism study does two things, two very important things: It determines the marker residue; and it determines the target tissue. The marker residue is the residue that will be used to monitor depletion of total residues in all of the tissues. The target tissue is generally the edible tissue that depletes most slowly. It is not always the case, but generally that is true.

And, most often, it is liver or kidney, and that should be no surprise to you. The organs of elimination are usually pretty well-loaded with drug on the way out. Very rarely, we find that the target tissue is muscle or fat.

The total residue and metabolism study also provide a metabolism profile in the food producing

animals. This is what we are going to go back and compare to the toxicological species. This is where we are going to do our comparative matching, make sure that what was in the rat is also in the cow, or the pig, or the chicken.

We use this total residue and metabolism study to establish or marker to total ratio. The marker to total ratio is what is going to allow us to calculate a tolerance.

(Slide)

Analytical methodology is a little hard to fit into the talk because it sort of comes in very early, but a lot of it is not completed in its final form for regulatory purposes until somewhat later.

We are basically looking at two kinds of analytical methodology: A determinative method, something like HPLC, will measure concentrations of drug residue in the edible tissues; and then we are also looking for a confirmative method, something like LCMSMS, that will verify the identity of drug residue.

This is important when we take cases to court and we need to be able to say that what we found really is what we say it is. Screening methods are important because they are rapid, but they are not required for an approval.

General speaking, what we ask is that drug sponsors show us how their new drug is going to perform in existing screens, so we know if something is not going to continue to function the way it has functioned in the pre-approval process.

(Slide)

This is one of, I think, only a couple of pictures I have got for you, but pictures usually at least wake people up a little bit. What we are basically doing a plotting of total residue and the marker residue.

We have identified the marker residue. We have identified the target tissue. We have plotted total residue. This is the radiolabeled component. What we are looking to do is find out how long it takes total drug residue to deplete to the safe concentration.

Remember, the safe concentration is the allowable daily intake adjusted for food consumption. What we want to see is when that happens. When does total residue deplete to the safe concentration?

Now, in this graph I have got it coming off just a little bit after three days. We also want to know what the concentration of the marker residue is at that same time because this is what is going to allow us to establish the tolerance.

The concentration of the marker residue in the target tissue at the time the total residues have depleted to their safe concentration is what we call the tolerance.

(Slide)

So here it is, all the word, and the pink tolerance.

(Slide)

You can establish a tolerance for any tissue for which you have the appropriate data. In the past, we have done it for just the target tissue; sometimes we have done it for all of the edible tissues; sometimes we do it for target tissue and muscle.

You have to have the data to support your assignment. The good news is that most of the time these data are already available as part of the package. So, in many cases, you are not asking for additional information or additional work.

(Slide)

Graphically, you see it here, the tolerance and its relationship to the safe concentration and total residues.

Now the target tissue tolerance monitors all of the edible tissues of the entire carcass. When the concentration of the marker residue in the target tissue

is less than target tissue tolerance, total residues in all of the edible tissues are less than their respective safe concentrations. This is the one true statement we can make.

(Slide)

If we have set a non-target tissue tolerance in addition, say, we set a tissue tolerance for muscle. We cannot guarantee that the muscle is speaking for the entire edible tissues from that animal. What we can say is that when the muscle tolerance has depleted to the muscle, when the concentration in the muscle has depleted to the muscle tolerance, the muscle is safe.

We cannot make any assumptions beyond that. We make it very clear that the muscle tolerance speaks only for muscle and no other edible tissues, unless it is one of those rare cases where in fact the muscle has been determined to be the target tissue.

(Slide)

Now, the important part about the tolerance is it forms the link between the toxicology, the ADI and the safe concentrations, that are handled by the radiolabeled studies to cold residue studies. And that is important because we do not market radiolabeled drugs. We market final formulation, and we need to have a regulatory analytical method that can track the marked

residue from those marketed products.

(Slide)

Here it is graphically, toxicology results, radiochemistry results tie into a tolerance in the analytical method. On the right-hand side, you see withdrawal time and milk discard time. These would be important for a domestic approval, but they would not be important for an import tolerance.

(Slide)

What is important is that the withdrawal time and the milk discard time appear on the product label in the United States. They appear in the relevant sections of the CFR. The tolerance is always in 21 CFR 556.

(Slide)

Now, one of the questions that has been asked of the VMAC Committee is, I believe it is question number 2, and that has to do with linking data from products to tolerances. As Dr. Robinson pointed out, we assign tolerances based on the chemical, but we do so having reviewed a product package.

From this little graphic, which is where I am going to finish, you can see that for domestic approvals, we have a formulation that comes in formulation A with an original data safety package. From that, we calculate a tolerance for that, and then

anything relevant to it such as withdrawal time.

Subsequent approvals in the United States, and these are very often generic approvals, must link to that original tolerance. We do not have multiple tolerances in the CFR for the same chemical.

And so, formulations that are approved following what we would call the pioneer must either link to the original data, and this is usually a bioequivalence study; or they must confirm the original data with studies of their own.

This is probably the trickiest part of question 2, because in the international arena we may not have a mechanism to confirm this linkage the way we would normally have it in the domestic approvals because we would have seen not only the package for formulation A, but for all of the subsequent derivatives of formulation A.

That is about all I have for you. I am glad you were able to stay awake after the coffee and the muffins. If we have time, I will be happy to answer any questions.

Questions and Answers

DR. HASCHEK-HOCK: I have a question in regarding to the formulation. Can you give some examples or indicate what percentage of cases there are

where the formulation has affected the tolerance?

DR. FRIEDLANDER: Most of the time where we see multiple formulations for the same chemical, we are seeing it as generic products. And generic products buy their way into that original safety package. So they can literally buy their way into that package; or they can do, for example, blood level bioequivalent studies.

So, in many cases, we do not see the same package for one of these second, third, fourth compounds. What we see is blood level bioequivalent study. And then, in all likelihood, we see a final residue depletion study to either confirm or assign a withdrawal time for that second, third, fourth compound.

So it is a little difficult to say whether or not they would match the package completely, because we do not see the same package for them. They have certainly demonstrated equivalence by what we consider a suitable package, in terms of bioequivalence.

DR. HASCHEK-HOCK: That answers part of the question. But other examples, would companies not submit packages where formulations do not show blood level equivalency?

DR. FRIEDLANDER: As part of the review process, we are entitled to see, and are supposed to see data packages that both support and do not support

whatever a company is offering as a product.

So if they have studies that, perhaps, are truncated for some reason, a blizzard wipes out a herd of cows or something, we are supposed to see as much of that study as there was.

Similarly, if there are data from Europe, whether or not that data supports the position they have, in terms of their pending U.S. approval or not, we are supposed to see that. Data which are not supportive of whatever you want in the United States are not supposed to be hidden from us.

DR. KOCHEVAR: I think also on the second half of her question, has there ever been a case where products have been shown to be bioequivalent, but then showed different data at the end of the road for a tolerance level? Has that ever happened?

DR. FRIEDLANDER: When you demonstrate bioequivalence with blood level studies, or clinical endpoint studies, that essentially gives you the tolerance. You do not repeat the studies to support the tolerance.

DR. KOCHEVAR: But I thought you said there was one study they did have to do.

DR. FRIEDLANDER: They have to do the residue depletion study that sets the withdrawal time.

DR. KOCHEVAR: Okay. And so, has that ever been different between bioequivalent products?

DR. FRIEDLANDER: I could not say specifically. The calculation of the withdrawal time in many cases gets down to the exact conditions of the study. This is particularly true if the withdrawal time is long, because we will only assign withdrawal times that are whole days. We do not assign three-and-a-half days. We do not think anybody would follow that in practice.

When you get to more extended withdrawal times, the statistics associated with setting the withdrawal time can throw out numbers that are slightly different, so we can get numbers that are like -- maybe the pioneer number is 30 days.

Because of the statistics involved in the calculation, you can throw out numbers that are like 29 days, or 31 days. We would consider that essentially the same, and it is just that they did not have the exact same animals, in the exact same feedlot, on the exact same days. That is the number crunching part that is throwing out those numbers.

DR. MACDONALD: Alex MacDonald. The residue hazard assessment for the total residue looks at that total residue with two assumptions: (1) that the total

residue is available to the second species, i.e., man; and (2) that that total residue retains the bioactivity of the original drug, the biological profile.

There is a provision that, in effect, to evaluate that residue in terms of its bioavailability to the second species, the bioavailability to man, as to that portion that is absorbed or not absorbed, and the second part is to evaluate that portion that is absorbed in terms of retained the bioactivity of the original molecule upon which the ADI and the tolerance is set.

This is in place. The provision is there. This was not mentioned in any of either Dr. Robinson's presentation or yours. How is this viewed today, in terms of evaluating residue exposure to man?

DR. FRIEDLANDER: We generally assume that all of the residue is equally toxic. We generally assume that all of the residue is equally bioavailable. If a sponsor wishes to conduct the additional testing to demonstration otherwise, that is certain their option.

What we are looking at is for drugs that are not readily available by the oral route, essentially, a demonstration by the sponsoring firm that this is the case, that it was an overly conservative assumption on our part that everything was available and toxic. If they can provide the data that shows us otherwise, then

we will certainly consider that in our evaluation and our assignment of the tolerance.

I would anticipate that if these data were available for a compound that was being considered for an import tolerance, we would also evaluate those data at that time.

DR. MACDONALD: It is interesting that the bioavailability of residues is an integral part now, in fact, a required part for a contemporary application for an MRL in Europe.

DR. HASCHEK-HOCK: I need to go back to my original question. And maybe, obviously, a company does not need to present a formulation which does not reach blood level equivalency because they would perhaps just go back and reformulate.

But is there any information available that formulation really does affect the toxicity of the compound?

DR. FRIEDLANDER: We see a number of formulations in the course of product development. Often these are presented to us as -- we do not know what the formulation is. But it is going to be so much active ingredient, and plus or minus this inactive, and plus or minus this inactive, and we will see a range.

Often those data are subsequently fine-tuned.

And, in many cases, all we see will be the single, the winner formulation, if you will. I think part of the reason for that is that the drug development process is very expensive, and most companies do not want to follow formulations that are not going to be successful. And, of course, success is defined in a number of different ways.

DR. LANGSTON: I might comment on that. Typically, I would presume that if it is not available, meets those criteria, it would have equal efficacy and toxicity. The only exception to that, relative to a formulation that I am aware of would be if there is a difference in isomers that were not detected by the assay, where you have one active isomer and different ratios.

DR. WOOD: One of the questions that we are to address has to do with the environmental impact of tolerance levels. Is that factored into any of the impact -- into any of the tolerance setting procedures?

DR. FRIEDLANDER: I think Dr. Robinson is going to talk about environmental.

Environmental is handled by a different group from the food safety group, so I cannot really address it in any extent. It is certainly part of the approval process that we evaluate the environmental.

DR. LANGSTON: Just for clarification for the committee, would it be correct to say that one of the issues we have to look at is oftentimes, we are not getting the target tissue in an import like the liver or kidney assay.

A big question for us will be if muscle is coming in, what if that we cannot detect at that level in the muscle? Is that a fair paraphrasing?

DR. FRIEDLANDER: Very often levels in the muscle are quite low. Before we could consider an import tolerance -- and I think this is very important. We are going to essentially review an entire application as part of an import tolerance, the entire food safety application. We won't be looking at target animal safety, obviously.

If there is not enough information in that package to let us evaluate the produce the way we would want to evaluate it for domestic approval, it is not going to be -- an import tolerance is not going to happen.

We will probably be sending letters back and forth that say, "This is what we need that is more, that wasn't in your package." This is an ongoing, even in a domestic approval, this is an ongoing dialogue with firms as to whether or not we have seen everything we

need to see if they could present something differently, or more raw data, you know, presented in a different way to make it more understandable for us.

I think the most important component is that for import tolerances muscle is going to be a significant tissue of import and we need to have something that allows us to address what is in muscle.

Now, it may be that the level that is in muscle is so low that it is not a concern. You do need to match up all of your numbers with your method performance, and that is a significant component in any approval domestically. The method has to perform at the level of food safety concern.

DR. KOCHEVAR: There was a portion of the notebook that we received that regarded the issue of differences between sanitary and phytosanitary measures in different countries, and how there is this -- there is a need to consider the level of development of a certain country in order to reasonably expect them to meet a standard.

At your level of the regulatory process, is that at all part of your consideration, or is that something that is evaluated totally separately, in terms of --

DR. FRIEDLANDER: Of course, right now we are

only doing domestic approval. So it is not really part of the equation directly. It certainly is part of the equation in terms of source of bulk drug. I do not know if that falls under the phyto and SPS agreement or not.

But, certainly, for a bulk drug coming in, as part of domestic approvals, the bulk drug that is subsequently formulated into drug in this country, that certainly is an equivalence issue.

DR. LANGSTON: I took that as being taken from Codex rather than the FDA. Was I correct about that in the handout?

(No response)

DR. LANGSTON: Hearing no objection, I think it is.

DR. KOCHEVAR: So, the answer is you do not. I mean that is not that we evaluate a product, and that that is a separate and not related issue in terms of how you arrive at a final tolerance withdrawal, and all of that stuff.

DR. FRIEDLANDER: Correct, but I would couch that in the fact that we are now working in the domestic arena for our approval so.

All right. Then it is my pleasure to turn the podium over to Merton Smith.

Codex and International Aspects

by Merton Smith

MR. SMITH: Thank you, Lynn. I am happy to be here this morning. This will be somewhat of a change of pace from the previous speakers. The non-toxicologists in the audience may think it is a welcome change of pace.

Because the Codex Alimentarius has adopted a number of tolerances for animal drugs in foods, we thought that it would be useful to address this group and describe the responsibilities of FDA with regard to considering and utilizing international standards, and standards of other trading partners.

These responsibilities are described in various places in international agreements that the U.S. has signed, in U.S. laws, in U.S. regulations, and in U.S. guidances and policies.

Codex Alimentarius is an international organization that sets food standards under the auspices of the World Health Organization, and the Food and Agriculture Organization, both U.N. agencies, for those of you that might not have been aware of that.

(Slide)

First, I would like to look at some of the major trends, societal trends, business trends,

regulatory trends that have caused FDA to become more involved in what I am going to call just generally international harmonization. That is not in its broader context international harmonization.

I mean by that, not only harmonizing requirements, but also looking to see if differing requirements are equivalent, assessing the equivalence, and just looking outside of our domestic activities and not working in a void, but looking outside to other countries and other organizations. That is what I mean by international harmonization.

(Slide)

First of all, if there is one thing I want everybody to get out of this, if you will look at this slide, I think it is the most dramatic and most important depiction of why FDA has moved into the area of international harmonization.

You can see that the number of imports coming into the United States has increased exponentially, particularly, since 1995. This slide was taken from a presentation given by one of our deputy commissioners a couple of years ago at the FDLI meeting.

You can see at the bottom that, at that time, our full-time equivalents, or the number of people working at FDA had changed very little; whereas, the

number of imports, as I said, has increased exponentially.

I went back and looked at data just the most recent data from the year 2001, and it continues to rise. It is up to 8 million imports in 2001. To be fair though, the FTEs, we have gained some FTEs, but obviously not enough to handle this kind of increase in imports.

So FDA's involvement in international harmonization is also dictated by the fact that we have to be more efficient with the resources that we have in looking at the safety of imports.

(Slide)

Going back to the other factors, trends that have influenced our involvement in international harmonization, the demand for quick consumer access to new products. Obviously, the internet and the media has made consumers very aware of products that are available in other countries.

This has put sort of a pressure on FDA to consider what is going on in other countries and other international organizations. The European movement toward a unified market, this began in the late 1980's. There was a program in the European Union called the Single Internal Market by 1992.

At that time, the Commerce Department involved FDA in looking at directives that were being proposed by the EU, and looking at the technical aspects of those directives to give advice to the Commerce Department, as to whether or not they made sense, and whether or not they were in accordance with what the U.S. did.

Bilateral and multilateral trade negotiations, and I will talk about this more in a few minutes. But, obviously, NAFTA, which took effect in 1994, and the WTO, the Uruguay round legislation are negotiations that resulted in the formation of the World Trade Organization, which took effect in January of 1995, are two of the most important of these kinds of trade negotiations that had an effect in bringing FDA into international harmonization activities.

New legislative mandates. This is primarily FDAMA in some of the requirements, and I will go over that in a few minutes too.

(Slide)

Recommendations for increased international harmonization. These recommendations have come from a number of sources. I won't go through all of these, but just to give you an idea of both external groups and internal FDA studies have really dictated that FDA become more involved in international harmonization

activities.

The Food and Drug Law Institute in 1988, said something about integrating FDA's policies with U.S. business policies. So that is quite a statement. The advisory committee on FDA in 1991, the so-called Edwards Committee recommended that FDA must strengthen its efforts to harmonize regulatory standards, particularly, with major trading partners.

The administrative conference of the United States a body that makes recommendations to regulatory agencies about how they do administrative law. They made similar recommendations about becoming involved and more cognizant of international standards and standards of other countries when we develop our own standards.

The White House Council on Competitiveness obviously thought that this involvement by FDA would increase the U.S. competitiveness, business competitiveness. There was a World Health Organization resolution in 1992 that supported harmonization of drug regulations.

The FDA Task Force on International Harmonization came out with a report in 1992. I have it here. We took over a year to interview -- basically interview what we thought were the most important stakeholders in this issue.

There were about 75 organizations that we went to to get opinions about how FDA should be involved in international harmonization. These were, as I said, inside FDA, as well as outside. Some of the recommendations that came out of this report are that:

- FDA should enhance its participation in activities that promote the international harmonization of standards; FDA should work to enhance international cooperation in the areas of enforcement and compliance;
- FDA should evaluate its current product approval programs for the purpose of developing innovative approaches to achieve international harmonization;
- FDA should strengthen its dialogue with outside groups concerning its international harmonization activities; and
- FDA should enhance the effectiveness of its technical cooperation with foreign governments and international organizations.

The report also emphasized that FDA needed to determine how many resources should go into this. And so, over the years we have become more involved in all of these activities, and we have dedicated more resources to doing this.

There is a couple of policies that FDA has

published in the area of international standards and international memorandum of understanding; the National Performance Review: Reinventing Food Regulations in 1996.

There is also an OMB circular that encourages agencies to use international standards that promote the desired degree of health and safety protection. There are regulations, Commerce Department regulations, that describe the responsibilities of federal agencies, in that they should use relevant guides and standards for conformity assessment practices. These are like doing inspections of manufacturers.

(Slide)

In the area of international agreements, as I mentioned, NAFTA and the WTO or Uruguay round agreements are the major ones. There are other trade agreements of course. Environmental agreements, science and regulatory cooperation agreements.

In fact, FDA over the years has had over -- currently, we have over 50 agreements with foreign regulatory counterparts. All of these support FDA's international harmonization activities in one way or another. Some of them are more prescriptive, but most of them are very general and talked about cooperating with regulatory counterparts.

(Slide)

These are the provisions within the NAFTA, the sanitary and phytosanitary measures of NAFTA. They are very similar to what are in the SPS agreement as part of the Uruguay round. So let me just go, for the sake of time, go to the WTO provisions for SPS.

(Slide)

The first one here is a clear recognition. It is important that this trade agreement recognizes that countries obviously have a right to adopt and enforce measures necessary to protect health.

Secondly, countries should ensure that measures are applied only to the extent necessary to protect health, and measures must be non-discriminatory. We cannot subject one country's imports to different measures than another country unless there is a scientific or legitimate reason for doing that. Measures shall be based on scientific principles and not be maintained without sufficient scientific evidence.

(Slide)

The importing country must accept measures as equivalent if the exporting country objectively demonstrates to the importing country that measures achieve the importing country's appropriate level of protection.

So this is a provision that encourages the determination of equivalence between countries that have differing regulatory requirements. Equivalence means that although the requirements are different, overall they have the same level of health protection.

So this is an important concept that Dr. Robinson alluded to earlier. Measures shall be based on international standards except where they provide a higher level of protection, and then they must be scientifically justified.

This is a very important principle of the SPS agreement. SPS agreement mentions the Codex Alimentarius as a recognized international organization. There is one article, or one point that I did not put on this slide, and that is in Article 7, that member countries need to be transparent, especially where they have regulatory requirements that are more stringent than international standards.

In that case, they have that notify all of the WTO member countries. This is like 140 countries have to be notified that these standards are being changed in whatever country, and there is a process that sort of -- there is a central notification point in each country.

In the United States for SPS measures, it is in the Department of Agriculture. They coordinate all

of these notifications with other agencies throughout the U.S. government, and agencies can then comment back to the notifying -- the country that is notified of pending regulatory changes.

(Slide)

Turning to the area of FDA legislation, before 1997, that is before the FDAMA was enacted, as I mentioned, that FDA has entered into over 50 agreements. The oldest agreement to my knowledge is in 1948. I think it was a shellfish agreement with Canada.

So, obviously, FDA thought that they had authority to enter international harmonization activities. The authority that we based these agreements on until 1997, or we still base the agreements on these authorities are listed here. I am not going to go through all of them.

(Slide)

But let me turn to the FDAMA, the FDA Modernization Act of 1997. The critical language in FDAMA that relates to what we are talking about this morning is that FDA must participate with other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve reciprocal arrangements as determined to be appropriate by FDA in consultation with experts in science, medicine, and

public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.

So the verb here, "must participate," is fairly strong, but it is qualified by "as determined to be appropriate by FDA." And also, there is the transparency requirement that we consult with all of the stakeholders that are involved in setting up standards to reduce the regulatory burden on industry and harmonize regulatory requirements.

(Slide)

Also, FDAMA requires that FDA must support USTR in meetings with other governments to discuss ways to reduce the burden of regulation and harmonize regulatory requirements for medical devices. So this just covers medical devices and it is very specific.

But it is qualified by the statement that harmonization is consistent with the purposes of the Food, Drug, and Cosmetic Act. And, of course, there is no purpose section in the Act, but it is understood that the main purpose of the Food, Drug, and Cosmetic Act is to protect the public health.

(Slide)

Also, FDAMA states that, "FDA should support USTR in efforts to move toward acceptance of mutual

recognition agreements relating to the regulation of drugs, biological products, devices, food additives, and color additives in the regulation of good manufacturing practices between the European Union and the United States."

This provision is restricted to good manufacturing practices, but all of the products that FDA regulates are covered, most all of them. It is between the FDA and its counterparts in the European Union.

(Slide)

Turning to regulations that relate to international harmonization, there is a regulation that covers food standards in Section 130.6, called Review of Codex Alimentarius Food Standards. In 1997, FDA proposed, or at least published it in advance notice of proposed rulemaking that -- stated that it was planning to amend these requirements.

These requirements deal with just commodity standards, Codex commodity standards, and not the general standards that -- the so-called horizontal standards, for example, the standards that cover animal drug residues that we are dealing with today. So in this ANPR, FDA was going to amend these regulations to incorporate procedures to deal with the horizontal or

general subject matter, Codex regulations.

There has not been a proposal yet, partly, because our Center for Food Safety and CVM are trying to determine the level of resources that would be required to enact this kind of a procedure, particularly, if it, as it deals with the retrospective review of existing Codex standards; and also CAFSN is looking at their policies with regard to food standards.

These are so-called recipe standards for different food products. They have not, even over these number of years -- it is a very difficult issue, and there has not been much progress in that area yet. But it is something that could obviously affect how we will -- if we go ahead and propose something, it would possibly affect how we would deal with Codex standards in setting these import tolerances.

Part 26 is a regulation that we implemented as a result of implementing the Mutual Recognition Agreement. In the area of pharmaceutical GMP, the MRA, so-called MRA agreement between the European Union and the United States, one annex of which covers pharmaceutical GMPs, and includes veterinary drug manufacturers, veterinary drug GMPs.

There is a transition period as part of that agreement. But we thought that agreement was so

significant and placed a number of FDA resources in this area, that we thought that it was appropriate to propose the agreement.

It is the first time that in an international agreement that deals with FDA regulated products has gone through rulemaking. So we basically codified the international agreement in the area that covers FDA products.

Here is another example of draft guidance that has not been finalized yet in the area of equivalence criteria for food. There are a number of issues there that we are trying to deal with, particularly, the Center for Food Safety, that are very difficult issues, and much of the concern is based on concerns about how many agency resources will be required to do these kinds of equivalence assessments.

(Slide)

Let me just turn quickly to what other -- what my knowledge of what other agencies do, as far as looking at Codex -- in particular, Codex, the existence of Codex standards in their areas, or in the case of APHIS, the existence of standards under the International Office of Epizootics.

APHIS, in their veterinary services, sanitary international standards team, works with the OIE on

international standards for diagnostic tests, vaccines, in the safe international trade in animals.

It is my understanding that APHIS does consider OIE standards when it develops U.S. requirements, but that if there are differences they usually do not provide an explanation for the basis for those differences.

And, again, this is a concern about the number of resources that would be required to look at all of those differences and to explain the scientific basis for those differences.

The same is true with the Food Safety and Inspection Service. They obviously need to be aware and are aware of existing international standards in areas where they develop domestic standards, but they do not take the initiative to go a step further to explain why if their standards are more stringent, why that -- what the basis of that is.

The EPA is different, at least in the area of their current review of pesticide tolerances. This is based on legislation in 1996 called the Food Quality Protection Act.

Under that legislation, the Congress required that EPA consider Codex standards in the area of pesticide residues, and also required that if there were

differences between EPA's tolerances and Codex tolerances, then it had to be explained what the basis of those differences were.

So this has been a huge effort by EPA. They have relied primarily on the private sector petitioning EPA to provide that information, but it is still to review all of that information and they have had some problems.

(Slide)

So, in summary, FDA's primary goal with regard to its international harmonization activities is to preserve and enhance its ability to accomplish its public health mission including maintaining high standards of protection, enhancing regulatory effectiveness, and increasing worldwide consumer access to safe, effective, and high quality products.

(Slide)

Trade agreements permit, obviously, permit the establishment of, and enforcement of measures that provide a level of protection considered appropriate by the importing country. Measures may be more protective than international standards, but they must be science-based and serve to effect the importing country's chosen level of health protection.

Where consistent with consumer protection

purposes of the Food, Drug, and Cosmetic Act, FDA must harmonize requirements and seek appropriate reciprocal arrangements based on determinations of equivalence.

(Slide)

FDA's regulations satisfy the obligations of NAFTA and WTO because they are non-discriminatory, solidly grounded in science, and based on what the United States has chosen as the appropriate level of protection.

So, with that, if anyone has any questions, I would be happy to entertain them.

Questions and Answers

MR. SMITH: Yes?

DR. WOOD: I know that VMAC and the questions before us deal with policy. And, yet, in your presentation, you raised the concerns at several points about the ability of the agencies to respond in terms of staffing to the needs for harmonization and all.

So I guess this is just a general question. But, I mean, what are the -- will there be agency issues in terms of responding to any of the import tolerance questions that we answer here that we need to be aware of, or are we in an area again of another unfunded mandate or something?

MR. SMITH: Well, our response to date is

primarily questions that have been raised as potential trade barriers, questions that go to our U.S. trade representative, or the Department of Commerce questioning the scientific basis for some of our requirements, for example. And, of course, those agencies come to FDA.

And, with regard to resources to do that itself, without considering any kind of additional program, particularly, any kind of retrospective review of existing Codex standards, for example, that kind of program in my mind would place a huge burden on FDA, and I do not know that it would be an effective use of our resources.

It is going to be difficult just dealing with import tolerances that come down the pipe to -- obviously, we will consider the existence of Codex standards. But if we had to explain why our standard was more stringent, that would involve a lot of resources.

I do not know if I can talk to the center with regard to whether we are going to have resources to do that kind of work. But I think I can say that if there were a judgment from you folks that we needed to be doing something like EPA has to do, which I do not think they would do unless Congress had required them to do

it, essentially, in legislation.

I think if we had to embark down that path, we would be relying on the private sector to do a lot of the work obviously. But just to check and make sure that if they claim that what tolerance they want is the same as the Codex tolerance, there is a lot more effort in pesticide residues.

Codex does not have that many animal drug tolerances set, not as many as pesticide tolerances, but it would still be a significant burden. And I suspect to have resources dedicated just to responding to trade disputes mediated by Commerce and USTR, that is going to take a lot of effort by CVM. Thank you.

Seafood: Safety & HACCP

by Dr. Kim Young

DR. YOUNG: Thank you, Aleta. I will do my best to get us back on time, because I know the lunch time is coming up and people are starting to get hungry.

Chairperson Langston, CVM members, guests, my name is Kim Young. I just recently became the deputy director for the Division of Compliance with the Center of Veterinary Medicine.

And, before that, before I came to CVM, which was last October, I was the aquaculture specialist within FDA's Center for Food Safety and Applied

Nutrition Bulks of Seafood. I also did a lot of work with the Seafood HACCP with that position.

(Slide)

One important commodity that will be affected by import tolerance is agriculture. Aquaculture is different than your meat and poultry, being that aquaculture is regulated by Food and Drug Administration, on the farm by CVM in regards to the drugs used, and also by the feed that is fed to the fish; and then, from the farm, to the consumer, to the Center for Food Safety and Applied Nutrition overseas, the food processing.

So, to give you some background on aquaculture, my presentation today will view first an overview of the global aquaculture production. I will get into the countries which export aquaculture products to the United States; and I will touch bases into what the FDA's concern of global veterinary drugs used in aquaculture.

(Slide)

To begin with, what I would like to do is give you the definition of aquaculture, as defined by the Food and Aquaculture Organization of the United Nations. The definition is: The farming of aquatic organisms including fish, mollusks; mollusks being your oysters,

clams, mussels, scallops; crustaceans, that would be your shrimp, crayfish, lobsters; and aquatic plants.

Farming implies some form of intervention in the rearing process to enhance production, such as regular, stocking, feeding, protection from predators. And then, it goes on from there basically explaining that it does not matter whether the aquatic organisms are commercially or privately owned.

(Slide)

On the global side of things, in 1999, which is the most recent figures I have, 32.9 million metric tons of aquaculture products were destined for direct human consumption. In other words, this figure does not include the ornamental fish that are grown, nor does it include the aquatic plants that are grown in aquaculture.

In recent years on a global basis, the aquatic industry has been growing by approximately 9.2 percent per year. If you look at that today, one in every four finfish that you consume is from aquaculture; and every one in three shrimp that is consumed -- this is on a global view of things -- are from aquaculture; and that in the year 2007, FAO predicts that 50 percent, over 50 percent of food fish that we will be consuming will be from aquaculture.

(Slide)

This slide will give you a better perspective. This graph shows how the aquatic industry (in green), how it has been growing during this past decade, and how the commercial, or the wild card industry has been pretty much flat for the past decade. Again, go along with what FAO predicts, that in the year 2007, if the green and the blue columns will be equal.

(Slide)

Now, most of the farm seafood comes from Asia, which produces about 90 percent of the global volume, and approximately 82 percent of the value of aquaculture products. This continent's main finfish production is carp, which has not developed a market here in the United States as of yet.

One concern FDA has is with a large majority of the aquacultural production, representing the last two bullets, that most of the production is in developing countries, which do not have the elaborate drug approval process that we have here in the United States, if they have any approval process at all.

(Slide)

The top 12 countries that produce aquaculture, the principal producers, this is 1998, again, with the FAO was the source of the information, the top 10

actually are from Asia.

As you can see, China is number one with 68.7 percent of the aquaculture grown in that country, because it is followed by India, Japan, Philippines, Indonesia, South Korea, followed by Bangladesh, Thailand, Vietnam, North Korea. United States is 11, and then followed by Norway, being 12.

Again, I want to emphasize we are looking at the countries that produce most of the aquaculture in the world.

Now, here in the United States, the per capita consumption of aquaculture products is 15.6 percent. This is based on the National Fisheries Institute, which is an association in the United States that tracks the consumption of the seafood.

And, based on the data from NFI, and also other reports that are published, along with conservative estimates on my part, I figure that approximately five pounds or 32 percent of the total seafood consumed is from aquaculture.

And based again on data taken conservative estimates, I figure that 3.8 pounds of the 15.6 pounds is actually imported from other countries, and which it represents about 24 percent of the seafood that we consume here in the United States is aquaculture that is

imported.

(Slide)

Going over the top 10 products consumed in seafood, see what I have outlined in yellow, shrimp, salmon, and catfish are aquaculture products, principal aquaculture products, where figuring that shrimp and salmon both are approximately 75 percent aquaculturally grown of what we consume here in the United States; and catfish, which approximately 100 percent of what we consume of catfish is aquaculturally grown.

So what I did was base my figures on -- or my consumption of what is aquaculture and what is imported based on those three commodities, or those three species. I did not include other products that we import, such as tilapia, trout, striped bass, what we import, or what we consume.

(Slide)

The major aquaculture products that are exported to the United States will be salmon and shrimp, which is actually 90 percent of the over 44,000 aquaculture shipments sent to the United States in one year representing salmon and shrimp.

And, as the previous speaker had on the graph, the number of imports are growing quite fast. Other products that import, the mollusks, tilapia, and trout,

striped bass, frogs, catfish, and crayfish.

(Slide)

What I want to do on this slide and the next slide is just to show you where we are importing our products from, our aquaculture products. This is over a period of one year. We have 62 countries exported aquaculture products to the United States.

As you can see, they -- wide -- it was a quite range in there infrastructure, government infrastructure, and their abilities to determine the drug approvals.

What I have outlined in yellow are the countries that have exported over 500 shipments to the United States during a one year period. Bangladesh is a low income country, as described by FAO, and it exports shrimp, trout, and striped bass to us.

Canada, their main product that they export to the United States is salmon; Chile is salmon; Honduras, principal product they send to us would be shrimp; India, shrimp; Indonesia, shrimp.

(Slide)

Mexico, shrimp; Norway, big exporter of salmon to us; Philippines, shrimp; Thailand, shrimp; and United Kingdom, which is salmon from Scotland. Again, I just wanted to emphasize the wide range of countries with

wide range of government infrastructure.

(Slide)

One benefit of import tolerance is that will allow approval of tolerances for drugs in seafood species that are currently not raised here in the United States, at least, of any significance.

Since these species are not being raised here in the United States, the drug companies have no economic incentive to pursue FDA approval for a drug being dispensed in these species.

Examples of major farm species that are not commonly marketed in the United States are your carp, which is widely grown in China; your grouper, which is grown in Hong Kong; and cod, which is in major development right now in Norway.

(Slide)

Examples of drugs being used in farm aquaculture. On this slide and the next slide, I have listed the name of 33 drugs that one Asian country has approved for use in aquaculture. For those of you that are knowledgeable in pharmacology, you may question how a country can allow some of these drugs to be used.

I have highlighted five drugs that are based on CVM's present knowledge will not be given import tolerance. These drugs are chloramphenicol, flumequine,

furazolidone, your oxolinic acid, and malachite green.

The good news is this country current exports only a few aquaculture products here to the United States. And also, in the United States, we have a hazard analysis and critical control point regulation for seafood, which I will touch bases with later.

And, as a result, any drugs that have been used in this foreign country, Asian country, they make sure that none of that product is being exported here to the United States.

(Slide)

The drugs that are currently approved for aquaculture -- as you can see, there are only six. You have your chorionic gonadotropin; your formalin solution; you have your tricaine methanesulfonate, also known as MS-222; oxytetracycline; sulfamerazine, which is approved, however, is presently not marketed by the drug company; so you have your sulfadimethoxine/ormetroprim combination.

So those are the only drugs currently approved here in the United States.

(Slide)

With Seafood HACCP, this is an area that is being overseen by the Center for Food Safety Applied Nutrition, part of FDA, and in here the misuse of

veterinary drugs in aquaculture is a concern through the agency, and is reflected in this Seafood HACCP regulation.

In 1997, the agency implemented the Seafood HACCP regulation. It requires all processors -- these are processors domestically and foreign -- that they must develop a HACCP plan for those drugs or those hazards which are reasonably likely to occur. We have identified that drugs used in aquaculture are a reasonably likely to occur hazard.

The HACCP program consists of seven principles which I have listed here. First is the hazard, where a firm must identify the hazard, and the hazard being unapproved veterinary drugs in aquaculture. These could also be mentioned unapproved. It could also be misused of approved drugs.

Where would a firm determine or control this hazard is at, for example, receiving to ensure that the farm that they are receiving their products from are using drugs correctly, that they have records.

Critical limits would be no drugs above tolerances, tolerance levels; and you get into monitoring procedures, corrective actions, verification procedures, and where records have to be kept by the processing facility.

(Slide)

How do we current enforce this, the HACCP regulation?

Well, under the regulation, all importers have to ensure that the seafood products that they import have been processed under the same standards as required domestically.

This includes the foreign processor being required to document that the raw fish that they have received has not been treated with an FDA unapproved drug, and that an FDA approved drug has been used properly.

The FDA does perform verification of foreign compliance with these regulations. For one, we do -- FDA does do foreign inspection of the foreign processors, and also of the producers.

We review the HACCP plans at the importer, where the importer must keep records of what is happening overseas to ensure the food safety. We also have a drug testing program going on.

We do have import alerts. An import alert is where, if we find that a foreign processor is not in compliance with our regulations, or we do some drug testing and we find that their residues will put the product from that firm on an import alert, whereby, that

product is not allowed into the United States until that foreign entity can show that drug residues are not there, or that their HACCP plan or their implementation of HACCP is fully in place. With the drug residues, we have the import alert 16124; and for the HACCP plan implementation, we had 16120.

(Slide)

So what are we doing for drug testing?

Currently, we have few drugs that we are testing for. We were testing for chloramphenicol in shrimp; flumequine in catfish and shrimp; malachite green in catfish; piromidic acid in shrimp; oxolinic acid in catfish, salmon, and shrimp; and oxytetracycline in shrimp.

The Center for Veterinary Medicine currently has approximately 20 drugs that is in -- that they are determining methods, some stages of development. So we are working on having more methods for testing in seafood. And as they are determined, they will be put into the program for testing of foreign products.

(Slide)

We also have a database for drugs and chemicals used in aquaculture. Right now, we are gathering information on that. The Center for Veterinary Medicine has engaged the services of a

contractor to collect drug usage data from foreign countries that export to the United States.

The data includes information such as the types, amounts, and use patterns of drugs and chemicals used in the countries, in a foreign country's aquaculture industry. As the information is gathered, a human food safety risk assessment will be conducted.

(Slide)

The FDA used the results of this project basically to prioritize the monitoring of the drugs and chemical residues in the edible tissue of imported aquaculture products. When I say edible tissues, that would be the flesh and the skin of the finfish.

We will use the information to prioritize the development of methods to be used in monitoring programs. I would say we have approximately 20 methods that we are developing now.

If we find that there is a drug that is being used that we do not have queue, we will change our priority to get a method for determining residues of that drug in the flesh; and provide a basis for promoting discussions with foreign countries regarding the hazard concerns identified by the risk assessment.

(Slide)

So how do we encourage the import tolerances

for these countries?

The driving force, basically, would be the enforcement of our current regulations. Actually, this year we have increased foreign inspections. We have increased drug residue testing with additional drug methods in place.

And also, not allowing current or future shipments from firms not complying with the regulations to be imported into the United States will create the need for foreign countries to send us data for developing import tolerances.

(Slide)

In summation, the demand for seafood in the United States and the world cannot be sustained right now by the wild catch alone. Aquaculture is becoming more and more important. Aquaculture must now and even more in the future provide a significant portion of the fish consumed in the United States given that:

(1) FDA unapproved drugs are used in foreign countries. We have established that.

(2) The U.S. is importing more and more aquaculture products.

(3) That FDA's role is to protect human health. The agency needs a regulatory means of assuring that possible drug residues in aquaculture are safe.

Mr. Chairman, and VMAC members, we look forward to hearing your thoughts on how the FDA might best regulate import tolerances. Thank you for listening. Any questions? Yes?

Questions and Answers

DR. WAGES: Do we currently export any fish to any other countries? And, if so, who to?

DR. YOUNG: We are major importers; we are also major exporters of seafood. With regards to aquaculture products, what we are exporting -- it is not -- I am trying to think myself what are our aquaculture products -- not that much at this time that I can think of right now. We were exporting some catfish. However, the market for -- the dollar exchange, et cetera, has dried up that market for the catfish industry.

DR. WAGES: The reason I ask is if we have three listed drugs that we use --- to the United States, it was not listed on your international use of drugs.

I was wondering if we exported fish, how do they view, or what tolerances are set, or how do they set their tolerances on importing drugs that are not used in their country?

DR. YOUNG: We are working with them trying to develop equivalencies with the foreign governments where they will go along with what, how we are enforcing our

regulations.

For seafood, the biggest one right now is the seafood HACCP regulation, in which we send the certificates saying that the firms here in the United States are following the compliance.

We only send those certificates when we know we have been to the firm, their HACCP paper work, et cetera, that they are in full compliance. This also, the domestic process in their HACCP verification, goes to the farmer to ensure that drugs are not being misused.

DR. GLENN: I have a question regarding the -- let's see, the drugs for which you said we will not receive U.S. import tolerances. I assume those are the ones that are not approved for use in the United States?

DR. YOUNG: Correct. They are not approved here in the United States, correct.

DR. GLENN: And you are testing for drugs in muscle tissue of various aquaculture species that are being imported. What level is acceptable in that testing process?

DR. YOUNG: Okay. Those drugs that we are testing for, no residue is acceptable, zero tolerance.

DR. MACDONALD: Recently, in the last couple of months, the EU has banned the importation of shrimp