

from three Asian countries because of chloramphenicol residues. Has this affected your operations for those three countries on monitoring shrimp?

DR. YOUNG: We are, let's say, we do monitor. We have increased our monitoring for shrimp for chloramphenicol in shrimp. We can always do it more. But, as of yet, to my knowledge, I have not heard that we have any positives for the chloramphenicol in shrimp.

DR. MACDONALD: Excuse me. To put that, the importation of seafood into perspective, I was told that the importation of seafood, both aquaculture and wild caught, currently in dollar volume ranks number three on the importation into the United States with oil first, cars second, and seafood third, is that right?

DR. YOUNG: Correct, that is what I have heard also. But the United States is also one of the -- we fluctuate between first and second for the main importer of seafood into the United States, but that can also include your fish meals for fish for non-human consumption.

DR. PARKHURST: As a point of clarification, when you are doing, who does the inspections, like the foreign inspections, and the drug testing?

DR. YOUNG: The foreign inspections, we have a cadre of investigators that do go overseas for

inspection. The drug testing, we test that -- we collect the samples at our borders, and it is done by FDA.

DR. PARKHURST: Would it be reasonable to have the importer be responsible for some of that?

DR. YOUNG: Under the HACCP regulation, the importer needs to verify that the product is safe that is coming into the United States. They can do the testing themselves. We will look at what they -- they have paper work to see how they are ensuring safe food.

The product is under import alert that it is covered by the import to do the testing. But what we are doing, FDA verifies that the HACCP is being implemented correctly. So we are testing to -- for means of verification.

DR. MACDONALD: On the HACCP, does the HACCP business go all the way back to the pond, or does it start at the port?

DR. YOUNG: Okay. The HACCP regulation has written stops at the processor. In other words, it starts at the processor by the regulation at receiving. However, it indirectly affects the aquaculture in that the processor has to ensure that the drugs used on the farm are to be used correctly.

DR. GLENN: So could you clarify that? The

HACCP, seafood HACCP is on farm HACCP, is that what you said?

DR. YOUNG: Well, the regulation starts at the processor. It starts at the processor. However, the processor has to address any hazards that are reasonably likely to occur, and having drug residues is a reasonably likely to occur hazard. So they, at receiving, they have to make sure that any product that they take through their doors has not had any unapproved drugs or misuse of approved drugs.

So, even though our regulation does not go back to the farm, the farm is affected by the processor itself whether they want to do business with them or not.

DR. LANGSTON: As clarification, I know many of the industries in the United States have voluntary online inspection. When you say inspection of the plant, it is really their HACCP cooperation and testing of tissues? It is not an online inspection as APHIS would perform here?

DR. YOUNG: Okay. For HACCP, it is regulation. They must -- it is not voluntary. You have two programs out there. You have the National Marine Fishery Service, which has a voluntary HACCP program, which deals in some other aspects of HACCP, and also for

firms that want -- this is the domestic side of things that want to go with food lunches, they have to be in the voluntary.

FDA, it is mandatory, and we do spot inspections. This is where HACCP has helped us, and where before when we did inspections, it was just a -- what was the firm doing at that time we were there,

Now, with HACCP the firm needs to have records. We looked through the records to ensure that they have been following good manufacturing practices or good procedures 365 days a year.

DR. WOOD: But, again, those HACCP programs are only in domestically produced?

DR. YOUNG: It is required both domestically and foreign -- for foreign. The way we verify is a little bit different where domestically we can go to the domestic firm processing facility at any time. Foreign is a little bit different where we need to go through foreign governments before doing inspections.

With this seafood HACCP regulation, we are going to the importers. This is the first time we go to the importers and look at their records, where mostly the importer will have the foreign firm's HACCP plan on site. We would look at the HACCP plan to ensure that they are looking at the hazards that we feel are

reasonably likely to occur. If their HACCP plan is not in compliance, then we will put them on an import -- import alert which I referred to.

DR. LANGSTON: I wan to make sure I am clear on this. So both domestic and foreign have FSIS inspectors?

DR. YOUNG: Okay. This is not an FSIS. This is food and drug. They are not there all of the time, we do have a cadre of inspectors -- cadre of inspectors that do foreign inspection. So we will go over there and look at their HACCP plans in the firms to ensure that they are in compliance with FDA's regulations.

DR. LANGSTON: And domestically?

DR. YOUNG: And, domestically, the same thing. We have our inspectors that go to the firms ensuring that needing our regulations.

DR. LANGSTON: Okay. When I said online, I was referring to FSIS. That was the confusion.

DR. YOUNG: Okay.

DR. WADDELL: Which agency is looking at bacterial contamination of imported fish?

DR. YOUNG: Okay. The FDA is at acrobic. You are looking -- referring to salmonella listeria, et cetera, FDA does.

DR. KOCHEVAR: Are there any microbial

resistances used with fish?

DR. YOUNG: That is getting in an area that -- I mean, those are problems. So when you start to ask specific questions on that, I am not up on all of the issues to be able to fully address you there. But there are problems, yes, or concerns, I should say.

DR. LANGSTON: Any other questions?

(No response)

DR. LANGSTON: Thank you.

DR. YOUNG: Thank you.

(Applause)

MS. SINDELAR: Thank you, everyone, and the hotel's restaurant is located on the lower level. If you walk around to the right, there are stairwells, as well as an elevator, to go down. And it is called Papa John's Restaurant. And there is, for the VMAC members, a room called the Hideaway. So it is recessed in the back for the VMAC members. Thank you.

(Whereupon, the meeting was adjourned for lunch.)

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

(1:07 p.m.)

MS. SINDELAR: We are going to get restarted. And I would like to introduce to you, John Prucha from FSIS, USDA. It is a real pleasure to have him here with us this afternoon.

**Compliance with Tolerances for Imported Meats****by Dr. John C. Prucha**

DR. PRUCHA: Okay. Thank you. Good morning -- good afternoon. My name is John Prucha. I am the assistant deputy administrator for Program Coordination and Evaluation, Food Safety and Inspection Service, U.S. Department of Agriculture.

With me today, are two of my colleagues from FSIS who I would like to introduce to you:

Mr. Clark Danford, who is sitting back there. Clark, raise your hand. Right. Clark is the executive assistant to my office, and he developed and organized my presentation today.

And Rita Kishore. Rita is the principal scientist in FSIS, who plays a key role in designing the National Residue Program, which I am going to mention to you today.

(Slide)

As I think you know, the Food Safety and

Inspection Service is the agency in the federal government responsible for meat and poultry inspection. The purpose of my presentation today is to briefly explain how USDA enforces animal drug tolerances in meat and poultry products that are presented at U.S. ports of entry for import into the United States.

Specifically, I will explain how USDA's Food Safety and Inspection Service enforces U.S. import requirements through the reinspection of imported meat and poultry products.

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First, I would like to call your attention to the word "reinspection." It is important for you to understand that all meat and poultry products that enter the United States originate from countries with meat and/or food regulatory systems that have been determined by FSIS to be equivalent to the U.S. system.

Thus, every pound of imported meat and poultry product has been inspected and passed by a foreign food inspection service before it is shipped to the this country. In addition, the competent of the foreign government issues a certificate that accompanies the product.

This certificate guarantees in writing that the product has been produced in full compliance with

all U.S. import requirement. At the U.S. port of entry, FSIS conducts a reinspection of this product as part of its ongoing verification of continuing foreign country equivalence. After the product passes reinspection, it is then released into U.S. commercial channels, and, in essence, becomes domestic product.

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During calendar year 2000, a total of 30 countries exported meat or poultry products to the United States. Most of these countries are relative low volume exporters.

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The overwhelming majority of meat and poultry products, a little bit more than 85 percent, comes from just three countries: Canada, Australia, and New Zealand, three highly developed countries with equivalent meat and poultry inspection systems that are very similar to the U.S. domestic system.

In fact, the United States, Canada, Australia, and New Zealand, hold periodic quadrilateral meetings to coordinate joint positions on food safety issues, and discuss equivalent measures to address public health concerns. FSIS plays key role, a key and important role in these equivalence discussions.

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I think it is important for you to understand how FSIS makes equivalence decisions concerning foreign food regulatory systems including programs for monitoring and controlling chemical and drug residues in meat and poultry.

Currently, FSIS recognizes 34 countries as having equivalent systems for regulating meat and poultry products. As I said earlier, 30 of them are current exporters. We do not certify individual foreign slaughter or processing establishments for export to the United States.

Rather, FSIS requires the foreign competent authority, generally, the chief veterinary officer, to certify which establishments meet all U.S. import requirements.

FSIS can trust the foreign competent authorities establishment certifications, and the health certificates that accompany each shipment of product exported to the United States because we have previously evaluated their foreign meat and/or poultry inspection system, and found it to be equivalent. In matters of equivalence, I must hasten to note, FSIS policy can be summarized as "trust but verify."

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An equivalent foreign food regulatory system

is one that provides the same level of public health protection achieved under our domestic system of meat and poultry regulation. The system's approach to equivalence holds foreign governments accountable for their food regulatory program and provides a basis for FSIS to trust the health certifications that provide us.

Foreign inspection system equivalence is initially determined and periodically verified through an evaluation process. Central to that process are what we call the triad components of equivalence.

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They are document analysis, which is an examination of the official issuances of a foreign food regulatory system. And, in particular, the documents have set forth its sanitary measures.

Another component of the triad is on-site audit, in which FSIS visits the foreign country and verifies that it is delivering the program described in its official issuances.

A third leg of the triad, port of entry reinspection during which FSIS reexamines meat and poultry products from each country that exports to the United States.

The first two components, document analysis, and on-site audit, are used to determine the equivalence

of a country when it initially applies for eligibility to export meat or poultry products to the United States.

Thereafter, FSIS adds the port of entry reinspection component to complete its equivalence triad. It is interesting to note the recurrence of these three components.

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A major document analysis is performed when a country first applies for an equivalence determination. The documentation submitted by a foreign country for an initial equivalence evaluation includes a full description of its food animal husbandry practices to include veterinary drug usage, the National Residue Control Program in place to ensure compliance with government standards, and laboratory results of samples tested.

Thereafter, document analyses occur as necessary when new sanitary measures are applied to their inspection system either on initiative of the foreign country, or in response to a new FSIS import requirement. In other words, it is an as-needed event.

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Similarly, an extensive on-site team audit performed before a determination of initial equivalence is made. The purpose of an initial equivalence audit is

to verify that the foreign government is delivering the program it described in its inspection system documentation.

Initial equivalence audits include visits to farms and feedlots, a discussion of veterinary drug practices, and an on-site review of laboratory practices and competencies. Thereafter, system audits are conducted at least annually in each country that exports meat or poultry products to the United States; thus, audit are, for the most part annual, events.

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Port of entry reinspection by comparison of frequency is conducted each and every day on each and every shipment of imported meat and poultry at dozens of foreign entry points all along the parameter of the United States. So reinspection, you see, is a continuous daily activity.

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Today, as this meeting is being conducted, FSIS import inspectors are conducting verification reinspections on some part of the nearly four billion pounds of meat and poultry products that are imported annually.

Another point I would like to make concerns a manner in which reinspection is conducted.

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Presently, every imported meat or poultry shipment is checked by FSIS at a U.S. port of entry to ensure that the paper work is complete including the health certificate which is essentially a government-to-government letter of guarantee that the product has been produced in full compliance with all U.S. import requirements.

Every shipment is also examined for obvious transportation damage, or overt signs of spoilage. Under our current system, certain shipments are randomly selected for additional reinspections as directed by our automated import information system, which is a computer system that generates import reinspection tasks for our inspectors and records their findings.

For example, one shipment of boneless beef might be selected to be thawed out and examined for blood clots; another shipment may be sampled for analysis of certain chemical residues; while still another shipment might be examined to make sure the listed net weight is accurate.

When a shipment is selected for chemical residue reinspection, FSIS takes a sample of the product and conducts laboratory analyses for violative levels of certain veterinary drugs or pesticides.

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While FSIS does not set the tolerances for these residues, we do enforce them to the best of our ability.

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For example, in the case of veterinary drugs, FSIS commonly draws samples of animal muscle tissue during port of entry reinspection, analyzes those samples for residues using tolerances determined by the Food and Drug Administration, and takes regulatory action against violative product.

The basic criteria for FSIS regulatory action is stated in our code of federal regulations as follows:

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"Animal drug residues are permitted in meat and meat products if such residues are from drugs which have been approved by the Food and Drug Administration, and any such drug residues are within tolerance levels approved by FDA unless otherwise determined by the FSIS administrator and listed herein."

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In cases where FSIS finds the residue of a veterinary drug, which has not been approved by FDA, and thus has no established tolerance, our long established policy is that the meat or poultry tolerance is zero.

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When a violative veterinary drug residue is found by FSIS during port of entry reinspection, several things might occur. If the product sample was taken and analyzed by FSIS before the shipment is formally presented for reinspection, as if often the case when an importer wants to hold the product until it clears residue analysis, we would mark the violative product as "'refused entry,'" and cause it to be removed from the United States under the control of the competent authority of the exporting country.

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If the product had not been held pending laboratory results, again, this is the importers choice, it would subject to recall and destruction or diversion into non-human food, into non-human food use, just as if it had been produced domestically.

The violative product could not be returned to the country of origin or shipped to any other country because it is adulterated under U.S. law and FSIS would not certify it for export.

So you can see that import tolerances for animal drugs are taken very seriously by FSIS, and our enforcement activities can have a substantial impact on U.S. meat and poultry importers, as well as on foreign

exporters.

It would, however, be disingenuous of me not to mention some constraints on our ability to monitor for veterinary drug residues in imported meat. One limitation is the fact that some drug tolerances are set only for organ tissue. Most of what FSIS seize at port of entry is muscle meat.

As I stated earlier, FSIS policy is that the residue tolerance in meat is zero if no acceptable level has been determined. Practically speaking, if we did find the residue of an approved drug in muscle meat, we would consult on a case-by-case basis with FDA to determine whether the level detected should be considered violative.

Another very significant constraint on FSIS import residue monitoring is the fact that we have finite chemical laboratory resources measured both in capacity and capability.

And, as managers, we must apportion those resources appropriately to both domestic and imported products. The tool we use for making those resource decisions is our National Residue Program.

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The FSIS National Residue Program is the principal mechanism for monitoring and controlling the

presence of violative residues in meat and poultry products.

The National Residue Program has several goals. It is a tool to enforce U.S. law and the residue control regulations issued by the U.S. Department of Agriculture, FDA, and the EPA. As such, it seeks to build and maintain consumer confidence in the safety of our nation's meat and poultry food supply.

By its existence as a national monitoring tool, it serves as a deterrent to drug abuse in food animal production. It is a mechanism for the assessment and communication of human exposure to chemical residues. And, in the domestic arena, it provides FSIS a means to verify residue control measures in the production of U.S. meat and poultry products.

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National Residue Program resources are distributed across several different analytical components. The monitoring, special projects, surveillance, and enforcement components are part of the Domestic Residue Control Program. We can set those aside today except to note that most National Residue Program resources are devoted to domestic purposes.

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For example, in the year 2000 National Residue

Program, FSIS apportioned 84 percent of its laboratory samples to domestic components, and 16 percent to the import component, which is what FSIS implements during port of entry reinspection. By way of comparison, it is interesting to note that imports make up less than 5 percent of the total U.S. meat and poultry consumption.

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Planning for the import residue plan begins concurrently with domestic planning and is carried out in four phases. They are: Phase I, during which compounds of public health interests are identified and ranked; Phase II, where compounds are selected for inclusion in the program; Phase III, in which compounds are paired with product classes; for example, certain antibiotic residues in a certain species of food animal; and Phase IV, when the samples are allocated.

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Phase I in National Residue Program planning is an annual meeting of the Surveillance Advisory Team, an interagency committee composed of members from USDA, FDA, EPA, and CDC, Center for Disease Control and Prevention.

The Surveillance Advisory Team generates a comprehensive list of chemical residues of public health

concern in meat and poultry and egg products. The compounds are then ranked for relative public health concern using techniques and principles from the field of risk assessment.

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In Phase II, compounds and compound classes are chosen from the ranked list for inclusion in the annual National Residue Program. The selection line is drawn at a percentile in the Phase I ranking list, based upon public health concerns.

However, some of the selected substances might not be included in the final National Residue Program, due to nonavailability of laboratory resources. In other words, FSIS must apply non-public health criteria at this point to select compounds and compound classes for the final National Residue Program, based upon laboratory capacity and capability.

A further cut is made between domestic and import sampling with a substantial majority of sampling allocated to the domestic program. This is entirely logical and appropriate.

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Keep in mind that all imported products have already been inspected and passed under an equivalent foreign inspection system that has implemented an

equivalent National Residue Program. Thus, a National Residue Program Import/Residue Program of the United States is a secondary verification constructed for inclusion in the FSIS port of entry reinspection system.

As such, it is part of our larger equivalence verification process that I discussed earlier, which includes document analysis, specifically, a review of each exporting country's annual residue program plan, and annual on-site audits to verify implementation of the plan. The National Residue Program annual planning process continues in Phase III with identification of compound and product class pairs.

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What actually happens is a matrix of product and compounds is constructed. Products such as fresh beef, processed beef, fresh pork, et cetera, are listed on one axis, while drugs or drug classes are on the other.

At each intersecting product drug class square, a mark is placed to indicate its status in the current National Residue Program. This is simply an exercise to match up drugs with the animal species they can be used in, and display the sampling status of that pair in the current National Residue Program.

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Finally, National Residue Program planning is completed in Phase IV, where sampling resources are allocated. For the import residue plan, this involves some calculations. You may be pleased to hear that I will not go into all of these calculations here today.

In essence, a formula has been developed to allocate samples. The formula incorporates product class as a percentile of total imports, and the drug ranking scores developed in Phase I. Resulting scores determine the number of import samples per year by product class and substance.

These samples are then allocated on a country-by-country basis depending on their level of imports in each product class. The results of National Residue Program import residue planning is a four column table, and example of which, from the 2000 National Residue Program, has been included in your handout.

You might want to refer to it at this point. It is in the back of the handout that you all have. You should have a list of tables back there. No, it is not in there. It is the handout that was in the back of the room. Do you all have one of those? You will see some tables.

You do not have one? Clark, could you grab? Yes, they were in the back there. It is not that

difficult to follow along. But if you have one, it makes it a little bit easier.

(Distributing handout)

DR. PRUCHA: Okay. This is pretty simple. But you will see that the columns are titled, "country, product, compound, and number of samples." It should be in the back pages of that handout.

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The country column is a list of countries that are active exporters of meat and/or poultry products to the United States. The year 2000 import residue plan listed 30 countries.

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The product column lists product classes. In the 2000 plan, they ranged from as few as one product class per country to as many as 17.

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Most of the meat and poultry product imported into the United States is fresh meat, and that of course is mostly what we sample for residue levels. Thus, tolerances for fresh muscle tissue are important to our import reinspection program.

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The compound column lists the drugs or drug classes selected for import residue testing. In 2000,

they were the same as those selected for the domestic program, but FSIS could select different compounds for sampling during import reinspection.

An interesting point that I would like to make is that FSIS presently does not test imported meat or poultry products for animal drugs that are used in foreign countries, but are neither approved nor banned in the United States.

We simply do not have the resources, nor, in many cases, the methodology to so. But, keep in mind, as I discussed earlier, that we have previously determined that the foreign country's National Residue Program is equivalent. We do conduct annual on-site audits to verify that the annual residue plan is being carried out as described in the foreign country.

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The number of samples column is really the bottom line. In year 2000, FSIS sampling ranged from a minimum of eight annual samples per compound, per product class, per country, to a maximum of 220. Most samples were at the eight per year level.

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In closing, you have heard today how FSIS enforces animal drug residue tolerances in imported meat and poultry products through random sample monitoring of

products during port of entry reinspection.

The sampling program we administer during import reinspection is one part of our equivalence triad, with additional verification provided through review of each country's annual residue plan, and annual on-site audits to observe foreign residue control programs in operation.

The goal of FSIS is to verify that every country exporting meat or poultry products to the United States has an equivalent residue control program. While exporting countries are not required to have a residue control program identical to ours, they must demonstrate that the program they have provides the same level of public health protection achieved domestically.

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(Phone rings)

Okay. With that ring, that concludes my presentation. That was perfect timing wasn't it? Thank you very much. And I would be happy to answer any questions that you might have.

#### **Questions and Answers**

DR. PRUCHA: Yes, sir?

DR. WAGES: Question. If a country is importing beef, or, let's say, any product --

DR. PRUCHA: Any meat product?

DR. WAGES: Any meat product, yes. And they are using something like chloramphenicol, which is illegal in this country.

DR. PRUCHA: Correct.

DR. WAGES: We will have the potential to check for chloramphenicol prior to it coming into the country, in the U.S.?

DR. PRUCHA: Well, actually, that drug -- our laboratories do have the competency.

DR. WAGES: To do that?

DR. PRUCHA: To do that. But we have not included, as an example, specific example, we have not included that drug in our import reinspection sampling. The point I was making is that there is a number of reasons why we do not do that, and I touched on a number of those reasons.

We put our emphasis on the country's monitoring program, the exporting country's monitoring program. And, as evidenced by the documents that they submit to use annually, which are verified by our auditors when we send them to the foreign country.

DR. WAGES: Could you explain the slide, the not equal to/equivalent? What did you mean by that slide again, a couple of slides back?

DR. PRUCHA: That was the whole gist of what I

was trying to explain to you all, is that --

DR. WAGES: I understand but --

DR. PRUCHA: That we do not require a foreign country to have a mirror image, exactly the same so-called sanitary measures. All of the laws, regulations, et cetera, et cetera, they can have in place alternative but equivalent control programs for assuring us that the product coming into the United States has the same level of public health protection.

When it comes to, for example, a drug like chloramphenicol, the tolerance is zero. So we look in their in their programs, and we look in their inspection system for all of the things that they are doing to assure us that the meat in the box that is coming to the United States contains no residue levels of a disallowed drug.

So that is what I meant by that slide, that -- let's see if I can back this up. That is the one you are talking about?

DR. WAGES: Yes, you have got to remember I played so much football without a helmet.

DR. PRUCHA: Right. So the point is that the foreign -- we look to the foreign country to have equivalent controls. "Equivalent sanitary measures," that is the jargon, but we do not expect them

necessarily to have the same exact controls, or sample exact measures. But the outcome, the output needs to be the same.

DR. WAGES: And you clearly do not check every lot of meat coming in?

DR. PRUCHA: No.

DR. WAGES: So, let's say, a drug is banned in the United States; the tolerance in that country is a tenth of a part familiar.

DR. PRUCHA: Correct.

DR. WAGES: They have verified that in their own testing?

DR. PRUCHA: Yes.

DR. WAGES: But, at the United States level, with that banned drug, the tolerance is zero.

DR. PRUCHA: Correct.

DR. WAGES: You would have to check that product to ensure that it was zero tolerance wouldn't you, or would you not?

DR. PRUCHA: Well, keep in mind that there is four billion pounds of product coming in. So we are not going to be able to sample every one of those pounds. So our emphasis is on looking to see that there is appropriate preventative measures and control measures in the exporting country.

We do that through looking very closely at the exporting country's annual National Residue Control Program, and how they are executing that program. And so, once every year we get submitted to us, is the plan for the upcoming year, and the results from the previous year.

We look very carefully at what that data shows us. And, in addition, we go on-site with our auditors to verify that how they are carrying out that program, and they are just not graphiting in the results. That is essentially our program.

DR. HOLLAND: I would assume that the exporting country has responsibility for trace backs, if there are positives, and things of that sort.

DR. PRUCHA: Correct, that would be part of their National Residue Program. So if there ever is an indication that there is a positive, for example, we would look very closely to see what that country is doing in response to that finding.

DR. HOLLAND: So you do have a mechanism in place in that a habitual abuser is not getting more product into the country?

DR. PRUCHA: We would look to see how the foreign country deals with that sort of a situation. Again, that is the information that we look for in their

plan when they submit it to us every year. And that is the kind of information that our auditors are charged with verifying when they go to a foreign country to conduct their audits.

DR. HASCHEK-HOCK: I have two questions. One is a follow up to what was asked previously. Foreign countries are expected though to certify that the products are in compliance with USDA tolerances?

DR. PRUCHA: Correct, with every shipment, there is a health certificate which is, like I said, essentially, a government-to-government letter of guarantee that the product has been produced in full compliance with all of our requirements.

You see, just to comment on that, I think there is basically only two countries in the world, the United States and Canada, that have simply one system of meat and poultry inspection.

Most of the countries of the world have a system in place to meet the requirements of their trading partners, and then they have a domestic system, and some countries even have two or three systems.

That is why it is very important to us to be sure that those particular plants that are, in fact, exporting product to the United States are in fact operating in full compliance with all of our

requirements, so we look for that guarantee from the competent authority.

DR. HASCHEK-HOCK: My second question is: When you talk about the types of inspection or reinspection, you mentioned formulation sampling. Can you expand on that a little bit? What do you look for in that?

DR. PRUCHA: I am not sure I am following you. Did I use the word "formulation?" I just gave a number of examples. And what I intended to do was give you just a number of examples of what might go on at import reinspection, and, in addition to collecting samples for residue analyses, but there are a number of other activities going on.

DR. HASCHEK-HOCK: Okay.

DR. PRUCHA: And that is probably what I saying I think.

DR. HASCHEK-HOCK: I guess I was looking at it from drug formulation. But do you mean like --

DR. PRUCHA: Labeling of the product.

DR. HASCHEK-HOCK: Labeling?

DR. PRUCHA: Correct, I was just using that as some examples of everything that we spot check the product for.

DR. LANGSTON: In part, one of the questions

we have asked us to address whether or not certain good agricultural practices may result in a different safety factor, one of those being route administration.

We know that IM repository injections tend to give longer residue profiles at the injection site. How do you presently handle a situation where you may take one sample from a box of meat and it very high in that one sample, but not in the others, say, that one sample that was very high was likely an injection site?

DR. PRUCHA: Well, the truth is that we hardly ever find positive on imported residue analyses. If, and when we do find a positive, we take that very seriously, so immediately we would consult with our colleagues in the Food and Drug Administration, as well as get on the phone with the competent authorities in the exporting country. And, essentially, we would take that on a case-by-case basis.

One of the things that we do do, if we do find, if we ever do find a positive, that any -- the next 15, we just -- that is just an arbitrary number, but the next 15 shipments are held and tested for -- and not allowed to enter the country until the analyses are completed.

So we would not expect to see a scenario as you just described. If we did find any positive, we

would be very concerned, especially for a drug that had zero tolerance.

I do not know. Rita or Clark, if you ever want to add anything to my comments, just grab the microphone. Yes, sir?

DR. MACDONALD: I was looking at your plan in Denmark. For this 2000 plan, there were 220 samples either taken or scheduled for arsenicals. That seems like a big number for a compound that is not approved in Denmark for swine. That was for a cause obviously. It was a reason for that.

DR. PRUCHA: I am not sure why that number is. Help. Do you have a comment on that number, Rita?

DR. KISHORE: No, I do not know. I am looking at the number and it looks like a misprint on there.

DR. PRUCHA: I could only speculate why that number is that high, and I can research that and give you a specific answer to your question. I do not know. We may have found a positive, and that would trigger extensive follow up sampling.

DR. MACDONALD: Okay, thank you.

DR. PRUCHA: I will get back to you on that, with a specific response.

DR. KISHORE: It looks like a misprint to me when I look at that.

DR. PRUCHA: That would be a good answer.

DR. WADDELL: You list on the chart, on the table, on most countries just antibiotics. What test or analysis is done on the sample for antibiotics?

DR. PRUCHA: Grab the microphone, Rita.

DR. KISHORE: Okay. For antibiotics, we do antibiotics by bioassay. It is a seven plate assay, and the same assay is used for domestic sampling also, and it tests for a wide variety of antibiotics in there.

DR. PRUCHA: Did that answer your question?

DR. WADDELL: Yes.

DR. PRUCHA: Thanks.

DR. WAGES: And the exporting company when they certify a shipment of meat to the United States, do their residue tolerance -- do they certify that their residue tolerances meets our standards or theirs, meaning that if they had -- if we had a product -- again, I am back to if they had a product used in their country that is banned in the U.S., but their residues were a tenth of a part per billion in meat, would they certify that it is lower than that, or would they lower -- would they certify that it is zero for us?

DR. PRUCHA: Well, the health certificate is filled out for every shipment. And so, they are essentially guaranteeing to us on a shipment-by-shipment

basis that everything that underpins that production of that product is in place and operational.

And so, when it comes to a specific issue of residues, the reality is that we are relying more extensively on the annual submission of the residue program, and on the annual submission of the results from the previous year. That is really where our emphasis is on.

So they are not certifying that every -- I mean, in reality, they are not certifying that a particular shipment that samples have been taken from that from every box, for example, to be an extreme.

They are not really certifying that every box -- that a sample has been taken from every box and the sample has been analyzed, and the finding has been in compliance with FSIS requirements.

They are essentially certifying to us that all of the programs that we are expecting to be place and operational are, in fact, continuing to be carried out during the course of the year when we are not there to physically review and examine exactly what is going on.

That comes back to the point I tried to make earlier in the presentation, that we do operate in in a trust but verify mode, that we go through an extensive evaluation exercise up front to develop a level of

confidence that the export -- that the responsible officials and competent authorities in the exporting country are reliable.

And so, we do operate in that mode; trust but verify. But we do conduct these various verification exercises that I attempted to describe to you.

DR. KOCHEVAR: So does that imply that you would never approve a plan from a country that had an allowable level of, say, chloramphenicol, but if that was part of their meat inspection system to allow some level of a banned substance in this country, in their plan?

DR. PRUCHA: We would allow them to use that drug with the understanding and the full expectation that the measures that they have in place, underpinning the production of meat for export to the United States, are designed to assure zero tolerance.

DR. WADDELL: Could you back up two slides, the 33 -- and on the second bullet point?

On the second bullet point, can you think of some specific examples of drugs that would fit that, those description, or that description?

DR. PRUCHA: I had a list of these in my brief case.

(Away from mike) If I anticipated this

question, and probably not, but I have a table with animal drugs approved in other countries, but not approved for use in the United States. And if I could just name off a few, and then I will let you see this.

For example, Australia -- I do not even know how to say all of these. But, Closantel, which is an antiparasiticide; Triclabendazole, which is an anthelmintic; Atramectin, which is anthelmintic. Canada, we have got Dimitridazole; Denmark, Carazolol, Ciprofloxacin, et cetera, et cetera. So there is a number of these.

(Away from mike) And then I have another table ---. But I have another table of these countries that are giving compounds that are prohibited. ---.

You can see that the animal husbandry practices in the urine chart, wherever the spots came from -- oh, just call whenever you want to.

As I am sure you know that there is a lot in tropical countries and other parts of the world, there is a number of different environmental conditions and animal husbandry conditions that are a lot different than the United States.

And so, drugs are used in those countries which there is no need to even to use those drugs in this country. So there has been no -- my understanding

is because of that -- principally, because of that reason, the drug companies have not petitioned FDA for the use of those drugs in this country.

MS. SINDELAR: Excuse me. Because all of this information is publicly available, I will need the original two pieces, and I will make copies for all of the VMAC members, as well as for public display. Thank you.

DR. WOOD: You stated that one of the constraints you are dealing with is that some tolerances are set for organ tissues, but when you look at a muscle tissue, muscle meat, are there particular compounds where that is more true than others, or is that a general rule of thumb?

DR. PRUCHA: Rita, do you want to address that one? I think that is a general rule of thumb. I think most of the tolerances are set for organ tissues, and not from muscle meat.

DR. WOOD: And so, the tolerance levels then that you established for the muscle tissues are tolerance levels that are set by USDA then, or are they set by FDA?

DR. PRUCHA: FDA. Do you have any comment on that, Rita?

DR. KISHORE: From what I have seen, most of

the tolerances are set for muscle and liver or kidney or muscle. One of the drugs that comes to mind that no tolerance has been set for muscle is telmicocin in cattle, though the telmicocin in pork has a tolerance for muscle and liver. So there are very few of those that the tolerance is not set for muscle. I think about 17 or 18 of those.

DR. PRUCHA: I do not know what kind of a time schedule you are on. I am happy to answer questions or attempt to.

MS. SINDELAR: Thank you, Dr. Prucha.

DR. PRUCHA: All right. Thank you very much.

(Applause)

MS. SINDELAR: This is just for your information. Some of the questions that might arise following these discussions for which you would like answers to, we have asked the speakers to please stay, whenever possible, to answer any questions. So thank you.

DR. ROBINSON: I have a couple of other comments. One is generic for the rest of the advisory committee meeting tomorrow and the day after. If you have a phone or a pager with an audible alert, please change it to vibratory or turn it off. We would appreciate it if they were not going off in the

sessions.

The second comment is that we really appreciate Dr. Prucha and his colleagues coming here to provide the FSIS perspective on import tolerances. I would like to make a point or draw a distinction for the committee. Many of the questions that you have been asking, particularly with respect to Dr. Prucha's talk, are germane to the issue before the committee.

**Public Disclosure and Environment Assessment**

**by Dr. Mark Robinson**

DR. ROBINSON: There really are two distinct issues here; the first being the process by which import tolerances are established; the second being the implementation of the surveillance in enforcement of those tolerances. The questions to the committee really have to do more with the former than the latter.

(Slide)

The last comment I would like to make is that the agenda does not list the entire subject to which I am going to deal, which is actually public disclosure and environmental assessment.

I note that there is a bit of fear in the face of the committee members that we are going to go back over ADIs, and safe concentrations, and tolerances, which is not the case. Hopefully, this presentation

will be mercifully short.

There are two questions before you. I am ahead of the game here, because the questions will be formally introduced to you at a later time. But we need to pose the questions in a shorthand in order to cover this area.

We have no truly formal expanded presentation. But we felt that in order to deal with these questions, we needed to tell you what is the status quo with respect to drug approvals in the United States, so that you might have some basis on which to frame the questions, with respect to import tolerances.

(Slide)

The first has to do with public disclosure, and the question I believe is question number three, reads something along the lines of: Should we disclose to the public that we are considering an import tolerance for a new animal drug? If so, when, how, and in how much detail?

(Slide)

In the code of federal regulations, with respect to both NADA's and INAD's, it states that, "The existence of this file will not be disclosed by the Food and Drug Administration before an approval has been published in the federal register unless it has been

previously publicly disclosed or acknowledged."

So why would we ask this question in the first place?

The FDA has been asked to provide a greater degree of transparency with regards to its decisionmaking. In the area of a new animal drug application or an investigational new animal drug application, we have yet to find information that would cause us to believe that disclosure of information prior to an approval would in any way be protective of the public health.

In other words, if the drug does not get an approval, it is not going to be used in the United States. And so, we keep confidence with respect to the information of that submission until an approval is made.

Now there may be other issues at hand, which is a subject for the committee to consider, as to whether or not we should keep with the status quo applied to NADAs and INADs for import tolerances, or whether we should go in another direction.

(Slide)

Similarly, the fourth question to the committee reads, in part, that: "We are considering modifying the regulations such that an environmental

assessment will not be required in conjunction with an import tolerance, or the establishment of an import tolerance.

(Slide)

The status quo, with respect to NADAs and INADs in this country, is that actions requiring preparation of an environmental assessment include approval of NADAs, abbreviate an application, supplements and actions on INABs, unless excluded under 2533(a), (c), (d), and (e).

So what are (a), (c), (d), and (e), you ask?

(Slide)

First, if the action does not increase the use of the drug, meaning, the use of the drug in this country, (c), for substances that occur naturally in the environment, (d) for low environmental exposure, and this in part would relate to minor use, minor species, consideration, where an additional approval just is not going to up the ante, (e) action on an INAD.

You can get a categorical exclusion during the investigational phase of the new animal drug application. So, again, the question to the committee is: Should we handle this with the same ground rules as we do an INAD, or an NADA, or should we go in a different direction? And that is it.

Are there any questions on those two subjects?

Yes?

### **Questions and Answers**

DR. HASCHEK-HOCK: My question is: You have indicated some reasons for not disclosing prior to approval. Do you have some reasons or potential considerations why disclosure should be made earlier than approval?

DR. ROBINSON: Me, personally, no. That is the question to the committee. Are there reasons? I have no compelling reasons from a professional perspective. Again, it is slightly different for INADs and NADAs.

We are talking about drug use occurring in this country, and the central focus is protection of the public health. I do not know a specific argument that would propel me to consider public disclosure.

But we felt that in the interest of what the FDA is being asked to provide, in terms of transparency, that we should at least consider this question and solicit input.

DR. KOCHEVAR: Do you have any sense of how industry feels about that, whether they think it would be important not to have disclosure until a tolerance was set?

DR. ROBINSON: We have at least one industry spokesperson in the public session. I will let them address that specifically. My feeling is that they probably do not care one way or the other, but they would prefer that we maintain nondisclosure for U.S. drug approvals. But I will let them speak to that.

Any other questions?

(No response)

DR. ROBINSON: If not, it is my pleasure to introduce Mr. Jim Heslin, who will moderate the open public discussion.

### **Open Public Session**

**by Dr. Jim Heslin, Moderator**

DR. HESLIN: Hi, my name is Jim Heslin. I am the agency training officer. And, occasionally, I get asked to help facilitate meetings and discussion sessions including several that have occurred sponsored by the Center for Veterinary Medicine.

I just wanted to say that the role of the facilitator is generally getting people to share their comments and perspectives. It has been my experience, particularly, here at CVM, that that is not a particularly difficult thing for folks to do. If they have a perspective, they are not shy about introducing it.

One of the other things is I try to keep people to the ground rules for discussion purposes. I have had pretty good luck with that. There was one occasion, I think at a prior meeting -- and I do not see the person here, so I will say this -- where this gentleman was going over his allotted time and I had to sort of intervene and say, "If you would please conclude your remarks."

Well, over the next several minutes, he used more variations of inconclusion and insummary than I have ever heard in my life, but I do not expect that to be an issue here.

Basically, the ground rules are these: If you have a comment, come forward to one of the microphones, identify yourself and your organization. If you have a lot of information you want to enter into the docket, something that is printed, or extensive comments that you can submit later, you are free to do that.

I have to be aware of the time, though I think we probably do have ample time here this afternoon for public comments. And, with that, I wanted to move to a scheduled presenter, Bob Livingston.

**Presentation by Dr. Bob Livingston**

DR. LIVINGSTON: Hi, my name is Bob Livingston. I am an employee of the Animal Health

Institute. I will try not to be repetitive because we had a very thorough introduction of the human food safety procedures for a new animal drug application.

(Slide)

Let me just highlight some of the points that were mentioned this morning and are of particular concern to the animal drug industry, at least the pioneer animal drug industry.

Let me start out by saying that the primary concern for the animal drug industry is the approval of new animal drugs for use in the United States. Import tolerances are only of secondary concern.

The first item here is that legislation specifically states that the Food and Drug Administration is supposed to use similar food safety criteria, as required for domestic tolerances.

The comments that I would like to make on this, that the criteria used by the Center for Veterinary Medicine is very similar to that used by the Codex Alimentarius, and also to the European Union and Japan.

There are minor, minor differences, and right now the European Union, Japan, and the U.S. are participating in a process called VICH, where they are trying to even further harmonize the preapproval

requirements for new animal drugs.

(Slide)

The legislation also states that there may be several sources of safety data. There was no indication or guidance given on the confidentiality of data. The drug industry would encourage the center to take into account the confidentiality of the human food safety for animal drugs.

This is an issue that is before the Codex Committee on residues of veterinary drugs right now, and we had encouraged the center to follow -- or, actually, encourage this discussion within Codex in the resolution of this problem.

Also, very much of a concern to the animal drug industry is the setting of harmonized tolerances will promote further international harmonization of regulatory requirements for veterinary drugs.

(Slide)

Human food safety requirements. As pointed out earlier, obviously, you will need toxicological studies and residue studies. But we feel that it is very important to also take into account the manufacturing information, and the example was pointed out this morning by looking at different isomers within an animal drug.

But in the consideration of the residue studies, it is critical that you have knowledge of the conditions of use of that drug. In fact, in your evaluation the human food safety of a particular animal drug, you should have access to the label as to how that drug is regulated.

(Slide)

Let me see if I can explain some reasoning why you need to know the conditions of use. As was pointed out earlier by Dr. Friedlander, that radiolabeled studies are required to determine the total residues of the animal drug in all of the edible tissues; from these radiolabeled studies, that you determine a marker residue, at least in one tissue, and probably more than that.

But what is of critical importance is the ratio of that marker residue to total residue, and that ratio is dependent on the conditions of use of the drug. This ratio provides the linkage between all of your toxicology studies and the tolerance, and that ratio is dependent on how that drug was used, the dose level, the route of administration, the length of administration, et cetera.

Another point that I would like to stress on the residue data is that Codex has recognized that for

international trade, you need more than one target tissue. Typically, you have an organ tissue, but for international trade you also need a tolerance in muscle tissue.

AHI would like to encourage that in the evaluation of import tolerances that you not only focus on muscle tissue, but you use the same procedures as if that drug was going to be approved in the United States to avoid causing problems later if some company wants to get that drug approved in the United States.

(Slide)

As was mentioned earlier, and in your handout material, that a withdrawal study is not required. You may not require a withdrawal study to determine a withdrawal period, but you need some idea of the depletion of that marker residue in order to establish a tolerance.

If that depletion is not rapid enough, it may make it very difficult to establish a tolerance. And you have to remember that that exporting country, if they are going to export meat products with that drug, they have got to establish a withdrawal period.

So I would not out and out say that no withdrawal study is required. Although you have not been presented the four questions, I -- well, two of the

four you have.

(Slide)

I would like to provide my comments on the questions. And the first question was whether you can set a food safety tolerance based just on toxicity and residue data versus obtaining a residue data under conditions of use. It is very difficult to consider residue data without knowing the conditions of use.

I am not clear on exactly what that question was getting to, but you cannot just take residue data out of the air and apply it to setting a tolerance. I would like to also emphasize that the Codex procedures use essentially the same criteria that are used in the United States for domestic tolerance.

I have here that Codex uses what they call good agricultural practices or you might be more refined to say good veterinary practices. I say good agricultural practices here because some of the animal drugs are not used under veterinary control.

The last thing that I will mention on question 1 is that you need to use the manufacturing information on the animal drug.

(Slide)

Question number 2 addresses one of the issues today, or later this morning we were talking about

whether different formulation would lead to different domestic tolerances. And the question 2 was whether there were analytical methods that you would be able to tell whether a residue was due to the use of the drug product for which the tolerance is approved.

And, to my knowledge, there are no practicable analytical methods to determine whether that animal drug was -- animal drug residue was due to one formulation over another.

However, if you were concerned about the formulation, the USDA residue monitoring program will allow you to put any controls you would like on that particular drug. You could control it by limiting it to that country, and to the use of that drug in that country.

However, you cannot get too specific, because if you want to abide by Codex tolerances, you have to recognize that Codex tolerances are not restricted to any individual formulation. They are determined based on specific formulations, but there is no restriction.

(Slide)

Question number 3, just addressed by Dr. Robinson, as to whether this information for a request for an import tolerance should be released to the public prior to actually setting an import

tolerance.

And, as was pointed out, there is no public release for a new animal drug approved in the United States prior to issuing it in the federal register, and there is no reason to treat an import tolerance any differently.

In fact, you can make an argument that because a new animal drug in the investigational stage is widely used that there is more of a reason to divulge that than there is an import tolerance.

(Slide)

Question number 4 is concerning the environmental impact. AHI is not aware of any information that establishment of an import tolerance would have any impact on the environment in the U.S.

And a further statement, which I will follow up, the U.S. has no obligation to control the use of animal drugs in a foreign country other than to inform the country of any specific concerns that the U.S. has.

(Slide)

The EPA has issued in the federal register a guideline for the establishment of import tolerances for pesticides, even though that guideline is out for comment, but that guideline is being used by EPA today. And it is interesting what is in that guideline, because

I think it almost parallels the process that could be used for animal drugs.

But, EPA, they use existing data to the greatest extent appropriate. They make a statement in the guideline that they will use Codex tolerance or publish a notice for public comment explaining the reasons for the deviation. This is actually in the Food and Drug Act, as a result of the Food Quality Protection Act.

(Slide)

Some more comments on the EPA guideline. The EPA specifically requests residue data representative of the pesticide use in other countries that export food to the U.S.

Repeating what was already said, and this is verbatim out of their guideline, "The agency had no authority to regulate pesticide use in other countries. It is the EPA's policy to harmonize as tolerances with the levels established by Codex if protective of public health."

(Slide)

The last, in addition to ensuring public health, EPA emphasizes that their setting of import tolerances are in compliance with all of the international obligations that the United States has

such as the WTO agreement, the so-called SPS agreement.

I think it would be very instructive for CVM to thoroughly consider the EPA guideline, and it was encouraging that in the advance notice of proposed rulemaking that they said that they would consult with USDA and EPA in developing these regulations.

I do not know if you have time for questions or?

DR. HESLIN: I think we probably have a couple of minutes.

DR. LIVINGSTON: Any questions?

#### **Questions and Answers**

DR. LANGSTON: I have one relative to confidentiality. I suppose when I looked at this from the viewpoint of establishing import tolerance, let's say, if a country put forth as the sponsor to get this drug tolerance set. And, obviously, if they generate the data, they can do what they want to with it.

But I had kind of presumed that they would go to the drug company and request information, and that that company would probably provide it so that it would promote the use of their product more perhaps by being allowed to export more.

Where do you foresee an instance where the company would resist that? Could they be coerced to

give information they did not want to give? In other words, when would it be an issue of confidentiality?

DR. LIVINGSTON: I think, in general, the company would be more than cooperative in trying to get an import tolerance because you are promoting the use of their product.

One of the areas that they have run into problems where that is not true in Codex is that when a company starts developing a new animal drug product, they have an idea of how extensive of a market they want for that drug, in terms of what are the conditions of use that they want to get approved?

One of the problems you run into is that once an ADI is established, it is kind of like a bank account. And so, when you get an approval, you use a certain amount of that ADI. And a company that owns the data, they should have control about where that drug is being used so that there is some ADI left over for them for further development.

The case and point here is a drug company may want to develop a drug for many species. However, if a third party came in and said, "I want to develop that drug for a dairy application, just by the fact that you are setting a tolerance in milk, you may use up all of the ADI to the point that that would limit the

development of that drug by the company that owned it."

So, in general, I do not think you are going to have much of a problem. But when you are talking about confidentiality, you should go to the company that owns that data and inquire if there are any problems, and whether they would support use of that import tolerance.

DR. HESLIN: Okay, thank you.

DR. LIVINGSTON: Thank you.

DR. HESLIN: Okay. The floor is now open for additional comments.

(No response)

DR. HESLIN: Okay. No one at this point has any comments they wanted to enter? Yes?

MR. HATHAWAY: My name is Mike Hathaway, and I represent the Catfish Farmers of America. I would like to raise a couple of questions: One is I have not noticed any particular logic for having an approval for a drug for an imported product, or for residues of it, that is not also approved for use by a domestic industry.

An example might be an antibacterial, which may have therapeutic uses in the U.S., it may be used abroad, but I fail to see the health difference in having a residue of a product in a food product that is

all right for an imported product, that is not all right for a domestic product. From a food safety issue, it does not seem to make sense.

The other issue is that, with respect to the additional approval process, this additional approval process of drugs that are not or could not be approved in the United States. I have not seen the logic in not subjecting an imported product containing a residue to the same kind of requirements that are used for approval for a product in the United States.

Simply saying, that the U.S. government or FDA may have requirements that are difficult for the imported product to meet, if they are not a worthwhile requirement for the U.S. product, they should not be imposed; if they are, then they should be imposed on imports as well.

A few questions on resources. (1) I think we have had information from Dr. Young and probably it is common knowledge to many that imported seafood is, based on the year 2000 numbers that I have available, would indicate that about 68 percent of what the U.S. consumes is -- seafood that is consumed is imported.

If we can also assume that the greatest risk of exposure to U.S. consumers is from the countries that have the largest number of importations. And I would

say first that the data I have got is that there are several countries that have more than a thousand shipments per year, Chile, Ecuador, India, Indonesia, and Thailand; 500 to 1,000 includes Bangladesh, Honduras, Mexico, and the Philippines; and 100 to 499 include China, Taiwan, and Vietnam.

If these are the countries of greatest potential risk, why aren't the resources for equivalency agreements being dedicated to those countries so that we have not simply a question of the U.S. taxpayers and industries having the burden of paying for inspection here, which we all know was inadequate, when we could be, and should be imposing a burden of equivalent inspection in food safety on the countries that cause the greatest potential risk to the U.S. consumers.

I am not aware of any WTO requirement or NAFTA requirement that makes us absorb that cost on the import side. And the difference between what is done in the meat and poultry issue and the seafood issue is really very startling.

It appears that we devote 14 percent of our resources for inspection of meat, if I am correct, to 5 percent of consumption. I am not sure what the numbers are for seafood, but I suspect it is vastly different.

And, in fact, I would guess that we probably have far more inspection that is worthwhile inspection in the United States than we have in any foreign country. Because if you do not have the right through an equivalency agreement to do an inspection without the diplomatic permission of the country that you are going to, it does not seem to me to be likely to be worth very much.

So if we are going to have a foreign inspection, I know the Office of Seafood says we do have foreign inspectors. I have not seen data on inspections in foreign markets that would indicate that those inspections are anything close to what the U.S. -- or inspections in the United States are, particularly, in these countries that provide the largest health risk to the U.S.

So I think as a question, one, is that if we need more resources to foreign inspection, we should impose that requirement on the foreign governments and on foreign processors in the same manner it is done really indirectly I guess by the Department of Agriculture for meat and poultry.

In other words, the foreign governments have to show the United States that they have an equivalent system that protects U.S. consumers, and in the absence

of that they do not. I know this is not a forum necessarily for resources.

But if we have a problem, and we do, with respect to imports, should we not address the problem where it is most likely to occur? And should we not impose those costs on the countries that are benefitting from exports to our market in the same way that we impose those costs on U.S. producers for serving this same market?

I think that is all I had. Thank you.

DR. HESLIN: Okay, thank you. Does the committee have any questions of clarity for this speaker?

(No response)

DR. HESLIN: Okay. Anyone else have comments that would like to offer?

(No response)

DR. HESLIN: Okay. If you are waiting because the agenda says there is a session after break, if you are waiting for the break, maybe you should comment now. Because I have a feeling, absent any other comments, we are going to take a break, and then Dr. Sundlof will move forward.

(No response)

DR. HESLIN: Okay, thank you.

MS. SINDELAR: Thank you. We will take a 15 minute break, and Dr. Sundlof will then present the questions to the committee.

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

MS. SINDELAR: And I will let Dr. Sundlof present the questions to the committee. Thank you.

### **Presentation of Questions**

**by Dr. Stephen Sundlof, Moderator**

DR. SUNDLOF: All right. We are going to move into the questions that were posed to the committee on the issue of import tolerances. Let me just give some housekeeping notes here first.

It was asked if we get through the questions and the committee can reach consensus this afternoon, can we just move everything up. And part of the problem is that we have speakers that are supposed to be speaking tomorrow afternoon on the next issue.

They would not be available in the morning. Some of them are coming in tomorrow morning. And so, what I would like to suggest is that the committee get as far as they can.

But we will say any of the final answers, we will go around at least one more time tomorrow morning, make sure that everybody has had a good chance to sleep

on it and is ready to make their final discussion points tomorrow morning.

One of the other questions that I have been asked during this time is all of the presentations that were given this morning, and the Powerpoint slides, and all of that, will that information be available?

And I have talked to Aleta Sindelar and she assures me that all of the materials that were presented today will be available on CVM's homepage tomorrow; and the information that gets presented tomorrow will be available on Thursday, et cetera, so that everybody should have fairly rapid access to the information that was given out today.

What I will do then is I will read the questions, and I will take the questions one at a time. The committee will then be allowed to discuss the issues. By the way, the committee has access to anybody in the audience who they think would have information that could help them if you get stuck.

So, feel free to ask questions of the FDA or to any of the presenters that gave out information with the exception of Dr. Prucha, who I think has already left. So, with that, I will read the issue, and then the question is up here on the screen so you can also see it.

We set tolerance based on an acceptable daily, or allowable daily intake, and the relationship between the marker anilide and total residue. To establish a tolerance, we consider conditions of use including the formulation, dose, and route of administration, and manufacturing features including drug potency and purity.

Regulatory agencies outside of the United States and international organizations may use different or additional factors to establish maximum residue levels. The factors used by these regulatory agencies may include different edible tissue consumption factors or animal husbandry standards such as good agricultural practices.

The effect of considering these factors may be a different tolerance value than the value established only on the basis of human food safety data, as presented in Section 1(b) of the advance notice of proposed rulemaking.

So the first question for the committee is: There are different approaches that we could use to find a safe import tolerance. We can look at toxicity in residue data and build in a conservative safety factor alternatively.

We could also review conditions of use such as

good agricultural practices, route of administration, and dose, which may result in a different safety factor or factors. Additionally, we could consider manufacturing information such as that required for a domestic application which could also result in a different safety factor or factors.

Which approach is preferable? And I turn it over to the committee.

### **Committee Deliberations**

**by Dr. Cory Langston, Moderator**

DR. LANGSTON: Okay, just a comment before we begin. Everyone here was picked for their expertise, but not necessarily in the same area. In fact, some of the people are probably more attune to the second issue of pathogen load and less toward residues and vice versa.

So if any of us make any comments that someone else is unfamiliar with the term, acronym, the lingo, feel free to just chime up. No one seems particularly shy here anyway.

So, with that, I will open it up. And does anyone have any particular comments or issues they would like to see resolved?

(No response)

DR. LANGSTON: I wanted to add something

relative to clarification on the question, Steve. When you say we could look at toxicity and residue data and build in a conservative safety factor, is that more or less saying that we can do it the way we are doing our domestic application, or what is different about that particular option?

DR. SUNDLOF: It is my understanding that that pretty much mirrors the present way that we establish tolerances here in the United States. But does anybody from CVM, who may have helped craft that question, have any additional information?

Am I substantially correct or -- yes, Dr. Robinson.

DR. ROBINSON: I think that part of the intent there was to express that if we only look at the toxicology and the residue chemistry data, absent any other information, that we would tend to be a little bit more conservative actually than we would with a full package in a new animal drug approval in the United States.

So it would really be to add additional safety factors to cover any uncertainty that we might have with respect to the issues, the underlying assumptions that I illustrated of, particularly, of chemistry and manufacturing controls.

DR. KOCHEVAR: If the processes were not substantially the same for domestic and foreign, wouldn't it become sort of a back door for companies to have a product to gain access to this market in a way that would not be equitable?

In other words, I am still bothered by the GMP and GAP part of this, the fact that in the process that is envisioned there really would not be any way to safeguard the purity, identity, all of those issues about the product that is being evaluated.

So I guess the question I have, and this would be just from a public safety point of view, why wouldn't the process be pretty much exactly the same as it is for domestic?

DR. GLENN: And I had the same question.

DR. HASCHEK-HOCK: My comment was that apparently there are at least 34 countries, at least to my understanding, that where the U.S. feels fairly comfortable on equivalency, if not identical practices. I assume that they have looked at differences.

Is it correct that they have looked at how the toxicity and residue data are presented and evaluated and feel comfortable that these are equivalent to U.S.?

Should there be some difference in what is required between those countries and countries where

equivalency is not considered similar to the U.S.?

DR. SUNDLOF: Again, I am going to ask CVM folks if they can address those issues.

DR. LANGSTON: While they are considering who is going to get up and talk about that, in clarification, Debbie, are you saying that basically because of manufacturing processes, a residue is not a residue?

DR. KOCHEVAR: I guess more that you could establish a certain standard. And then, if you are going to assess a product as it came in, that you would not be sure that what you were checking in that product when that particular drug was given to the animals, yield that that made, would be the same process that you would get if the same drug was given to another animal just because of the variation in the product.

In other words, there is not an assurance that the drug was manufactured in a way that would allow you to predict residues in a standard way every time. Does that make sense at all? I may have strayed here from a logic.

DR. LANGSTON: No, I think it does, in the sense that if you have differences in formulation that result in a different absorption rate, you might have a different metabolic profile and associated different

total residue profile.

But, relative to that, this is a question for someone else though at CVM. When we are doing NOELs in the rodent and other mammalian species, in that NOEL established all the dose of the parent drug without taking into account the toxicity tolerance by the ratios of the various metabolites.

So, yes, there might be a difference, but we are already discounting that difference when we are looking at establishing NOEL. Am I incorrect about that? So if someone could answer that, and then we will answer the other question.

DR. SUNDLOF: Dr. Friedlander, I think you spoke this morning about -- I think it was you, who spoke about that we consider all of the metabolites equally toxic to the --

DR. FRIEDLANDER: We do consider all of the metabolites equally toxic to the parent, unless they are demonstrated to be otherwise. And in dosing the toxicological species, we anticipate that the drug is undergoing metabolism; that the rat or the mouse is being exposed to all of those metabolites, and that the toxicity profile we are seeing is essentially the complete picture.

When we go over to the food animal, what we

are looking to see is that we have not missed anything in terms of a metabolite that is in the cow, and maybe is not formed in the rat, in which case, we would say, well, the rat has not seen everything that cows make.

And since people eat beef, people will be seeing something that cows make that the rats did not make and we will have an incomplete picture. If this were to happen, we would be looking at sending the package back to have some additional assessment made to sort of pick up that missing metabolite and look at it to see if there were toxicological concerns there.

DR. LANGSTON: Yes, but let's say at a given dose in the rat, at a point in the study where the metabolism was such that three-fourths of the parent compounded and metabolized, one-fourth remaining drug, and this was associated with --- toxicity; and you went to the cow and you had the opposite scenario of three-fourths parent, one fourth metabolite, you really are not going to change your NOEL based on that.

It is the same metabolites. You are still drawing the toxic effect from what's occurring in the rat though, am I correct?

DR. FRIEDLANDER: Correct. And for the food safety part, we would not be particularly focused on any toxicological manifestations in the food animal. That

would be the purview of the target animal safety group. They would focus in on that component.

DR. LANGSTON: So, in light of that, that is where I have a problem with these subtle changes in absorption rates and formulations. Granted, huge effects should be taken into account for, but we are still not addressing them at the very basic level of the NOEL.

DR. KOCHEVAR: And this may be a very minor issue. But if a drug is not manufactured according to certain standards, is there anything else in there besides the active ingredient, which is what we would be looking for, that also could potentially be harmful to people when they ate the meat?

I mean, I guess, it is just a question of quality standards for the product even if it is not the actual residue for that drug. And that may be a minor point. I do not know.

DR. LANGSTON: I hate to keep having this dialogue with Debbie. But I do not know. Well, I will just close.

DR. WOOD: Just so I am curious, to Deborah. I mean, what is it then that you are arguing for? Is it something that is different in terms of --

DR. KOCHEVAR: No, I guess drugs that are

manufactured in this country have a requirement for GMP. They have had to come out of a facility. And so, when you do characterizations of those drugs downstream, then you pretty much know what you have because that is part of the approval process.

If a drug came in from another country, and what we were looking at was the marker residue, which, as Cory points out, you know, and the bottom line, it is either there or it is not. And, as long as the metabolites are all accounted for, then that probably addresses that issue.

But I guess my concern from just a public health point of view is, are there other things in that pharmaceutical that make their way into meat?

I mean, it is almost like packaging for a piece of food. I mean, you look at everything that goes into the packaging to see if it has some adverse effect on the food. So it is probably not even a drug issue anymore. It is a formulation of that drug, and the quality standards used when that occurs.

DR. LANGSTON: I think, to some degree, that overlaps into question 2 that Dr. Sundlof will be talking about, whether or not you can tell a different formulation, one from another.

And, certainly, if there is a different

vehicle or excipient that is used in a formulation, perhaps, we could follow that to tell it is product A versus product B.

Whether or not it is harmful, I would presume most are on the GRAS list, the generally recognized as safe. But if that were not the case, it would become an issue, and I am not sure how you would deal with it.

And there have been those instances, for example, I think tryptophane, there was an instance where some sort of byproduct got into tryptophane and caused eosinophilic myositis in humans, but they still do not know what that was. But I have really no way to suggest to overcome that is the problem.

DR. WOOD: I, too, I guess share the concern about purity, strength, and the active ingredient formulation, and all. Is that more an enforcement question, or is that a question that can be dealt with as -- I mean, is that a USDA question, or is that an FDA question, I guess is what I have been wondering?

DR. HASCHEK-HOCK: No, we are talking about some specific issues here. I think the general thing that we need to be concerned about is that the safety data and the tolerance that is set meets the current standards for domestic tolerances.

And whether it is up to us to determine

exactly what needs to be done to achieve that, I am not sure if we can address all of the specific issues. But my feeling is that the important thing is that we do have the same level of safety in the tolerance that is set based on the data as we have with our domestic tolerances.

DR. GLENN: I would also like to support that. It seems to me we have a very specific mechanism to establish domestic tolerances for human safety. Why would this body deviate from that and say we are going to do it differently and have a different level of safety?

I am sensitive to this issue of regulatory burden and international harmonization, however. I did hear that this morning. But when you get to the science, if we have accepted this domestic tolerance setting procedure, why do we want to deviate from that for? Could someone explain that to me?

DR. HASCHEK-HOCK: That was not exactly my point. My point is we want to reach the same endpoint. But if we have countries where we do accept their current practices, then it would seem that we do not have to go back to look at their -- how their toxicity data was arrived if the GMP are accepted by the U.S., that should be enough for us -- if it is accepted by the

U.S. in general, then that would not need to be addressed from the raw data.

But, basically, and to me, and that was my question before, you know, have all of these aspects been looked at, say, in the 30-some countries that have been determined to have equivalent practices to the U.S.?

DR. LANGSTON: Clarification on that, Steve. When you are talking about GMP, really, the company that produces the drug where we are having a residue discussion really, you do not have access to making them the GMP in their manufacturing do you, only if they are wanting to market to the U.S.?

DR. SUNDLOF: That is correct. We cannot inspect them for GMP compliance. But I think part of the question is that -- one of the parts of this question is, additionally, could we consider manufacturing information such as that required for domestic application?

And it may be we may be able to require from the importing country that they -- that we would deny an import tolerance unless we had some assurance that the drugs that we are considering were approved under the U.S. good manufacturing practices standards, or something that we consider to be equivalent.

DR. KOCHEVAR: And I think that is what I was trying to get at a little while ago, is that if you are starting with a product that you have some assurance has been made under those conditions, then you have a degree of safety that you do not have if you do not have that assurance.

DR. LANGSTON: I would tend to agree that if you can get assurances of GMP life practices, then you should be able to judge your residues relatively similarly across lines.

DR. MACDONALD: Cory, on establishing an import tolerance, it is obvious that the way to go is to go ahead with the documentation criteria that currently is in place in the United States. Somebody wants an import tolerance, the pathway is very, very clear. I disagree with that. I think that is a totally valid way to do it, and probably the only way to do it.

My only comes up is the situation where drugs that are not approved in the United States for which an import tolerance is not going to be provided, what do you do in those cases to handle the use of those products, and that tissue ending up coming into the United States?

How do you evaluate those drugs short of saying, no, we will not import tissue from creatures

that were fed the following list of drugs period?

Okay. How do we assess, or how do we evaluate the case where they were used, and how do you come up with a way to evaluate the risk to the consumer under those circumstances, i.e, a sulfonamide is used that is not approved here but is available and is used in another country?

How do you evaluate that tissue in terms of importation? Do you just flatly say you cannot import it? Do you set some sort of a value based on your knowledge of the other members of the class? How do you deal with that?

The straight import tolerances, as far as I am concerned, you deal with it the same way you deal with it on a contemporary application. In the United States, the only thing you do not do is worry about the efficacy portion of it. But the safety portion, which we are focusing on, is the same. Those are the rules.

But what do you do when you are presented with a situation, as the FDA is, USDA is, of tissue that has been fed another drug, or a drug for which this has not been done? How do you set a number?

DR. ANDERSON: I may have misunderstood this morning. But I thought they said that in that case what their criteria was, zero tolerance. So they were not

refusing to accept the meat. They would accept it, but it was a zero tolerance level. Is that your understanding?

DR. LANGSTON: Clarify me then. Because my understanding was, in that instance, where it was not approved but used elsewhere, that we would still have access to their raw data so that they would still be doing the carcinogenicity studies, the rodent toxicity studies, et cetera, and we would be looking at those. And if it was not adequate data, either in numbers or quality, we would revert back to a zero tolerance.

DR. KOCHEVAR: But isn't there another class? I mean, there was the class of banned substances like chloramphenicol, and those were zero, not getting in, no matter what. But then, like you, I thought the ones that we do not have here, but they are not the end, you had the possibility of submitting the data and trying to get a tolerance for it.

DR. MACDONALD: Well, if you are looking at -- pick a class like the sulfonamides, many members of the class, many of them are used in various states. The data that you are looking for to establish a tolerance is not available. I mean, the tox studies are not there.

If they are there, they were done in the '60s,

probably are incomplete. It is just not an adequate package. But what do you do when the situation happens? To me, that is the concern. As far as the question on how do you do an import tolerance, that is a slam dunk.

DR. WADDELL: I was under the understanding that, take a banned drug like chloramphenicol, those products can still be imported to the U.S., as long as they are zero tolerance. That is the question I have is, you know, I mean, how can we ban a drug here, and then allow it to be used even with a zero tolerance?

I mean, why don't we have the drug available here, then it would have the same zero tolerance for American animals?

DR. LANGSTON: I do not disagree with that, and that was kind of what the gentleman with the fish industry pointed out. Unfortunately, I think we are getting into an area that I do not think our committee has any prerogative over.

Debbie, I do not disagree with you, but I do not think we can address it. Did you have anything else?

Back to your question, Alexander, that is a problem. There are either one or two approaches I would view either of the -- straightforward. You just cannot approve it. You have to generate the data. I have

considered whether or not it would be possible to go back and look at regression correlation for things that did exist within a class.

For example, how does the LD50 for that compare to the NOEL for known drugs? I am using LD50. It could be certain safety factors; it could be therapeutic index; it could be anything like that.

But it is a little iffsy, and I am a little uncomfortable with it, but that is about the only thing I can think of short of requiring the studies. I probably would require the studies.

DR. MACDONALD: Well, you know, this is what I do. And, in terms of retrieving the data necessary to do these evaluations, in many cases, the data does not exist. If it did exist, it is no longer available, not because somebody wants to hit it, it is just not available anymore.

And so, contemporary drugs that were focused into the animal health industry where this information is available, that is probably drugs in the last 25 years targeted specifically for the animal health industry.

A lot of the drugs you saw listed on the fish slide were drugs of opportunity. These are drugs that you can go up and buy. They are available and people

use them. That does not particularly mean they have any blessing, or any data, or anything else to go along with it. That is just the way it is. It is not here, it is there.

DR. KOCHEVAR: I guess I had a question of the FDA folks.

Do you think the major people who would be interested in this, the countries who would be interested in these, would be for those products that are for diseases that we do not have, like you were saying with Australia, so that it is not a question of something tried to get approved here and did not get approved, was deemed unsafe, or has been banned here, like chloramphenicol, but it is just a product that just flat does not exist here because we do not need, that those would be the major people who would be interested in import tolerances, or major cases?

DR. SUNDLOF: That was the original impetus for the legislation that led to import tolerances, but I do not think that that specifically excludes us from setting import tolerances for drugs that for which there might be a market, and for whatever reasons the pharmaceutical company did not pursue an approval in the U.S. So I think you have to consider both.

DR. HASCHEK-HOCK: I would just like to make a

comment on inadequate data. I do not think that there is any way that the U.S. should go ahead and accept inadequate data. I mean, we are looking at public safety and if the data is not there, I do not see how we could approve and set tolerance levels for that.

DR. MACDONALD: No, I agree with that. I do not take issue with that. My only comment is you saw the list of drugs. Okay. I mean that did not -- you did not make it up. I mean that came from a use pattern of some sort, and they are gearing up to do a monitoring program based on what they can gather for the intelligence of usage for these drugs.

DR. LANGSTON: So, Dr. MacDonald, you obviously have considered this. So your view is that they would need to do the extra studies if it was going to be approved. Am I paraphrasing that?

DR. MACDONALD: Well, I think that to do what the U.S. requires, to do what the EU requires, to do what Japan requires, to do what Australia requires, and what is required by JECFA, the review committee for Codex, you need adequate toxicity studies, and the list that Dr. Robinson presented is the list, the studies that Dr. Friedlander presented are the list in all of those cases.

And if you do not have all of the points on

that list, you have to struggle to obtain a ADI and an MRL. I mean, there are certain experimental things that you might not be able to do in these limitations. But, fundamentally, if you do not have those studies, plus an array of genotox and microbiological profile, it is not going to fly in any of those venues.

DR. LANGSTON: I tend to agree. I do not think it should. As clarification as to what else we are discussing, the next sentence says, "Alternately, we could also review conditions of use such as a good agricultural practices, route of administration dose, which may result in a different safety factor or factors."

I am trying to remember if someone did mention that perhaps this is in there because, relative to good agricultural practices, the way a drug is used, it might actually be a lower tissue limit, which, if you applied that, would say that they are not following good agricultural practices if they are coming up higher than we want them to. Therefore, they set the residue limit based on what is a good agricultural practice rather than the food safety data.

Did I hear that correctly, Dr. Sundlof, that is why that sentence is kind of in there?

DR. SUNDLOF: I think so. I would like to get

some clarification from some of the CVM folks.

One of the issues that got discussed this morning was that certain countries establish their tolerances or MRLs based on the ADI first. It is a function of the ADI.

But if the actual use practices would result in tissue residues which are much lower than the ADI-based tolerance, than various countries will lower that tolerance to be consistent with the label indications, with the label usage directions. So that is one of the issues here.

The other may be another issue. And, again, I would defer to CVM folks, who are closer to this, would be that, do we assurance that the countries for which this drug is being use are enforcing their own good agricultural practices, such that the drug is available with certain label indications, but in practice it is being used in a way that is much different from what is actually in the label.

Is there somebody from CVM that would like to speak to either of those? Dr. Weber.

DR. WEBER: Just to reinforce what I think I have been hearing here is that, for example, the JECFA, which has MRLs that are widely adopted by Codex, and some of those even wind up in the EU. The toxin residue

packages are, in recent years, virtually identical to what we see.

We often and usually wind up with, in many instances, the same ADI. But, as Dr. Sundlof was pointing out and the chairman here also pointed out, the good agricultural practices is an issue where we differ in how we would set a tolerance here, as opposed to the MRL that they ultimately adopt.

We, as a practice, embody or use virtually, in most instances, the entire ADI, based on what the sponsor wants and wants a partition, especially if they see milk or eggs or other things, as was mentioned earlier; whereas, the EU -- and you see this coming through in JECFA quite a bit -- they take that same ADI and say, you do not need a zero day withdrawal, or one day withdrawal.

It is a therapeutic drug. A four or five day withdrawal consistent with returning to the herd or something like that is adequate. They will go out and pick the MRL, the tolerance at something beyond zero or one day withdrawal, which is the zero one day withdrawal can be totally consistent with the ADI.

It is consistent with the safety of the compound; whereas, applying what is called general good agricultural practice, they might pick a factor of two

less than we might. Again, it is within the ADI. But, again, they may not use the entire ADI.

So, starting with virtually the same ADI, while we believe that using up to and including the ADI, is consistent with public safety, they can pick under general agricultural practices something lesser saying for that therapeutic drug, two, three, four, and five days may be acceptable.

DR. LANGSTON: I know I would propose that it should be based on the food safety issue, and not on good agricultural practices. If anyone would like to change my mind on that?

DR. KOCHEVAR: Would it be the case that in considering the GAP would always make it a tougher standard?

(Nodding of heads)

DR. KOCHEVAR: Always tougher. So if we are happy that our standards are tough enough, and unless we are ready to toughen up the standard for the domestic side too it seems like that would be a hard way to go to include it.

DR. LANGSTON: I tend to agree.

DR. WOOD: Does the good agricultural practice address at all the injection site issue, and how the drug is administered?

DR. LANGSTON: Could someone comment on that, who is more familiar with foreign good agricultural practices?

I would think it would but --

DR. WOOD: That would have some impact or bearing on it, but we are not addressing or dealing with the injection sites. We are looking at the tissue or the organ itself overall, right, in terms of tolerance levels?

DR. HOLLAND: Yes.

DR. WOOD: Right.

DR. HASCHEK-HOCK: I mean, one of the things that is listed separate -- and this may be not quite relevant to this, but route of administration and dose would seem like there is two issues: One is what is done regularly in agricultural practice? But the other one related to residues would be how the compounds administered in development of the residue data?

Because the current U.S. regulations are that -- my impression is that the drug, the radiolabeled drug needs to be administered, the route of administration that it would be in practice, and also close to the actual dose level that would be used in practice.

DR. LANGSTON: That is correct, relative to determine the residue profile in a target animal, but

not for determining the toxicity in the rodent species, or mammalian species.

DR. MACDONALD: Well, all of the tox work is all oral. All the toxicity work associated with this is all oral toxicity in their lab animal species, because that is a safety evaluation because man eats the tissue. So it is an oral aspect.

DR. WOOD: One other question that may or may not be appropriate to this issue, and that has to do with having a policy that can move and be adjusted to future policies at the FDA.

For example, as the FDA CVM adopts a policy dealing with antibiotic resistant bacteria, and where that may factor in in some way in tolerance levels, is there adjustment or recognition of that at this point, or is that really not on the table?

We certainly are concerned about that question. We all are. But how does that get addressed? Or is it addressed more by looking at how the country is addressing and monitoring antibiotic resistant bacteria overall? How is that question? Where is that question on the table, if at all, in these four questions basically?

DR. LANGSTON: My view would be it would be addressed through the HACCP inspections of that country.

I do not consider it a part of this discussion, but I am willing to open it if anyone does.

DR. MACDONALD: Well, we are dealing with the impact of the residue in the tissue, its absorption in man, and its impact on man's intestinal tract. In other words, we are dealing with the residue itself. We are not dealing with the organisms in the target animal's tract. We are dealing with the residue and its impact, right? Okay.

DR. ANDERSON: I would just like to add, I agree. I mean, I do not think that. But, certainly, any residue that end up in a human intestinal tract will add to the selected pressure which could lead to resistance, but I do not think it is a driving force for antibiotic resistance.

DR. MACDONALD: See, what I would like to do -- and, of course, this is a 20 year crusade that I have -- and that is that the residue should be evaluated, not only -- well, it should be evaluated on its impact to man, on its bioavailability to systematically to man, and it should also be evaluated on its impact to the intestinal tract bacteria.

In other words, you eat meat. The meat is digested. The supernatant has an effect, or no effect. That is what we should be looking at. We should not be

looking at anything else. I will get off my soap box.

DR. KOCHEVAR: Not to beat a dead horse here, but back to that import tolerance for banned substances. Because, I mean, that does seem like an issue that has to be dealt with either -- it is clear that it has to be a zero tolerance.

But is it a zero tolerance coupled with the knowledge that a country says, yes, it is okay if you use this drug, but you just cannot have anything in the meat if you are going to sell it to the U.S.? Or would we not think that was the same standard as we hold our own producers to?

And so, would you require that their HACCP plans also had the substances listed as banned substances?

DR. SUNDLOF: Well, that is not a question that we asked the committee. But under issue number five, I think that is a good place to bring that.

DR. LANGSTON: I think that also comes up along that same line of foreign approved drugs that, is it fair to our producers to be able to import meats into the U.S. that these producers have newer drugs that are not yet approved and can optimize their production, decrease their disease? Does it give them a competitive advantage?

But, again, that is not one of the questions right now.

Well, basically, I view this as three parts, based on the three sentences of the question put to us. (1) we have the existing criteria, and I have heard most people say that what we are using right now seems to be fairly adequate, why change it, as long as the data is solid and provided that the good agricultural practices probably are not too much of an issue.

The last sentence dealing with manufacturing should be an issue, at least some sort of GMP like assurances. One thing that I have wondered about, however, before we leave this issue, and that is in policy versus implementation.

I know we were told to concentrate on policy not implementation. But do we need to be concerned about the issue of whether you can assay these compounds in muscle, as opposed to the target tissue, or is that something else somebody else will deal with?

DR. SUNDLOF: No, I think that is a fair issue to deal with.

DR. HASCHEK-HOCK: Just one comment. In the first part, where mention that the current procedures are adequate, are you implying that the whole gamut of procedures that are used currently by the U.S. would

need to be applied to other countries?

Or are some things performed by at least specific countries acceptable so that the FDA does not have to go and analyze all the data from every aspect of the drug production?

DR. LANGSTON: My view is that there ought to be some lenience in it. I do not think you need to be too dogmatic about it, as long as it is reasonable.

DR. KOCHEVAR: Yet, by the same token, we make manufacturers here if they have a different formulation go through the whole show again. So it seems like we need to be consistent in what we require producers to do.

DR. LANGSTON: I suppose my thinking was, you know, if they go 45 instead of 60 day on a trial, can you take that? I do not know. Maybe the answer is you cannot. Maybe you have to require a 60 day. I am open to others.

DR. HASCHEK-HOCK: I think the formulation comes under two, but I mean it is all interrelated. But, perhaps, that should be addressed separately.

DR. LANGSTON: Let's wait to question two for the formulation. Any other comments about question 1? We have not really talked about the issue of muscle assay, since I brought it up. Anyone have any ideas

about how to handle that?

DR. MACDONALD: Well, muscle is the tissue of trade. So, even though the target tissue might be liver and you have a method for that, what is coming into the pore is muscle. So you unequivocally have to have a method for muscle.

I do not think that is -- I mean, the system in the United States for many years did not deal with muscle. It only dealt with the target tissue. The idea was as the animal goes through slaughter, you grab delivery, you measure it. If that is clean, the whole animal is clean.

But, as everything gets separated, and what has been the item of commerce is muscle. So, therefore, there has to be a safe concentration, and there has to be a method for it.

I do not think it is ideal, by the way, to have a method. I mean, in today's world the only question is money, as to cost of the assay. I do not say we can get down to --- number yet, but we can drive it pretty low if you really want to go there.

DR. LANGSTON: So you are, more or less, saying that they should be able to develop the assay in muscle if needed to, if pressed?

DR. MACDONALD: No, I think there is no

question in today's technology. I am quite convinced that using the older concentration techniques that we used, coupled with current HBLC, triple quad MSMS machines, will give you the sensitivity and the conformitory data to prove unequivocally what you see is what you have got, and to do it, I say,  $1 \times 10^{-14}$ , if you need to, maybe a little further.

Which, you know, when you start thinking about this whole residue stuff and exposure to man and what we should be concerned about, when you get below  $1 \times 10^{-9}$ , I mean, is there really a concern?

See, as a scientist, as an analytical chemist, one of the things that I worry about is signal to noise, and that is seeing a signal about the noise. And, at some point here, we have to consider the biological noise that we are exposed to and relate a given incident to that biological noise.

At some point, it is only noise; and, at some point, it is real. But I do know the model is valid. I just do not know how to make it work. But we do not address that, and we start getting down to  $1 \times 10^{-9}$ ,  $10^{-10}$ ,  $10^{-11}$ , and  $10^{-12}$ , we can do it.

There is no sweat -- not no sweat, but we can do it. The question is, is it meaningful measurement after you do it?

DR. WOOD: Didn't we hear in the presentation and in the questions afterward from USDA that they are on a case-by-case basis already doing assays on muscle tissue, and even if the target tissue is an organ? And I was wondering, if so, how that is accomplished?

DR. LANGSTON: Someone else can respond. My view of that would be that what they are doing is they are assaying muscle, and if it is negative, great. That still does not mean that the liver would not have been above a violative residue.

It is only if the muscle tests positive would they pursue it. So, even though it is negative, it does not mean it is not a violative residue elsewhere, or it really would have been, the whole carcass would have been condemned even though the muscle tested negative.

I will play devil's advocate a little bit here just to see what sort of reaction I get. But there is another option, and that is if your muscle falls below the limit of detection of your assay as it now exists, the one that is being used to detect liver or kidney, and that would be to follow your tissue depletion curves such that you go down and at the point where you begin to find a limited detection in muscle, extrapolate that back to total residue and see how far all of you are from the NOEL.

It will be above probably your target tissue total residue. But the question then would become, perhaps, given the situation, perhaps, that safety factor was not necessary, instead 1,000 fold safety factor with 100 fold safety factor.

Do you understand what I am saying?

DR. KOCHEVAR: Lynn, what do you think of that?

DR. FRIEDLANDER: I think it is important to remember that when we start talking about muscle, we are talking about muscle relating only to muscle. And I think we also have to remember that you are not necessarily chasing a number with a method as low as you could go. You are only chasing a number as low as you need to go to establish safety.

So it is entirely possible that we could establish tolerances for muscle that would be completely consistent with the performance of the method and maintain safety without having to go to the extremes of what the method could do?

And it is important to separate those two, because the reason you do not have to keep chasing things with muscle is because you are not implying that muscle is addressing the safety of anything other than muscle; whereas, with the target tissue, the target

tissue is going to address the safety of everything.

So you could conceivably be chasing a lower number for your target tissue because it is going to speak to all of the organs, of the edible organs, liver, and kidney, and the muscle, and the fat. And you could actually pick a higher number for muscle, because all it is going to address is the safety of muscle.

DR. KOCHEVAR: But right now there is only one tolerance for a drug, right? In other words, there is no differential numbers on any domestic --

DR. FRIEDLANDER: Yes, there is. There is a target tissue tolerance, and there is a tolerance in any other tissue where we have the data to support it, and there is a historical context here that probably was not brought out in the presentations.

We have, as our definition of residue, as Dr. Robinson pointed out, we went from a no residue, zero, to a negligible tolerance of .1, to now a much more risk-based tolerance, and we have moved in terms of what tissues we have applied tolerances to, where we have put numbers.

So, in the case of negligible tolerances, we may have a tolerance of .PP1 -- .1PPM across the board for every tissue. For some of our more modern approvals, we may have only a number for the target

tissue.

For some of our most modern approvals, we may have a number for the target tissue and for muscle, and it depends on where you are in this time continuum in a regulatory sense. It also depends on what data are available in the package. If there simply are not data to do with muscle tolerance, we have probably passed on doing a muscle tolerance.

DR. KOCHEVAR: So that approach would not be inconsistent with what you already do for domestic tolerance?

DR. FRIEDLANDER: No.

DR. KOCHEVAR: Okay.

DR. LANGSTON: Well, I would propose that that is something for you to consider overnight, especially if ADI for muscle could be taken into account for that factor.

DR. HASCHEK-HOCK: Just one more comment on that. Since usually the muscle is much lower than the target organ, if data was not available on muscle tissue you can conceivably set it higher at the target organ, which would just have a higher tolerance, rather than perhaps not approving it because that data was not available. Although, I think it probably would need to be made on a case-by-case basis.

DR. MACDONALD: You could calculate a muscle based on the target, based simply on consumption. Do you know what the tolerance is in liver? Do you know how much liver you are going to eat?

Translate that to 3x, or 5x, or 6x, whatever it is, the amount you are going to eat in muscle. If the value drops that much, then that is -- you know, if push came to shove and you had to do it, that is the way to do it, because you have established it for the target tissue.

DR. LANGSTON: Good comments. Any other comments on question 1? Again, we will delay actually your final views on this particular question until tomorrow morning.

DR. HASCHEK-HOCK: I felt I did not get my question answered, and maybe it is something that could be perhaps answered tomorrow morning. And that is, again, on the countries where there appear to be equivalency standards, how comparable are the residue studies in good manufacturing practices? Have all of these been considered in the equivalency area?

DR. SUNDLOF: Let me address that. Those equivalency agreements are between FSIS and the -- however many countries that they have these equivalency agreements with. It does not involve such issues as

good manufacturing practice standards.

It is basically how they conduct their inspections in the plant, what kind of residue inspection program that they have? Is it equivalent to ours? But it does not address the finer issues of things like good manufacturing practice and quality of drugs that are administered to animals.

DR. HASCHEK-HOCK: How about in comparison to the European Union and WTO, and those organizations or agreements? Have those issues been addressed specifically?

DR. SUNDLOF: Well, I will try and answer this, and maybe other folks can help me. The European Union has fairly similar standards to what we have in the United States. They virtually require the same kinds of studies.

We are moving closer and closer towards total harmonization through the BICH process. So in the future we expect to be virtually identical in the kinds and quality of data that we require to make these kinds of decisions.

The WTO basically is a body that resolves disputes between member countries when they have disagreements. And under the SPS agreement, the Sanitary Phytosanitary Agreement of the World Trade