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P R O C E E D I N G S

DR. BLACKWELL: Good morning. I would like to introduce our committee here today and invited guests, and I am going to have them do that honor basically, and if you would say who you are and who you are with would be great. We will start at the edge here. Go ahead.

DR. FLETCHER: I am Oscar Fletcher, College of Veterinary Medicine, NC State University, and I am representing poultry or avian medicine.

DR. KOONG: Kelvin Koong, Associate Dean, College of Vet Sciences at Oregon State University.

DR. CLEVELAND: I am Janis Cleland. I am the Editor of the Journal of the American Animal Hospital Association. I am a small animal practitioner and I am representing small animal medicine.

DR. KEMP: I am Doug Kemp. I am the Director of Pharmacy at the University of Georgia, College of Veterinary Medicine. I am here as a consultant.

DR. WOLF: Alice Wolf, Professor of Small Animal Medicine and Surgery at Texas A & M University, representing companion animal medicine.

DR. KORITZ: Gary Koritz, Professor of Veterinary Pharmacology, College of Vet Medicine, University of Illinois, representing pharmacology.

DR. GERKEN: Diane Gerken, Associate Professor, Ohio State University, representing veterinary toxicology.

DR. LEIN: Don Lein, Chair of the Committee. Cornell University, Director of the Diagnostic Lab, representing microbiology.

MS. DURAN: I am Sue Duran. I am the pharmacist at Auburn University, Large Animal Clinic, and I the consumer affairs representative.

DR. POUST: Ronald Poust, Professor of Pharmaceutics, College of Pharmacy, University of Iowa, and I am a consultant.

DR. JAAX: Nancy Jaax, USAMR. I am a pathologist.

DR. RAVIS: William Ravis, representing Auburn University, Professor and Chair, Pharmaceutical Science, and consultant.

DR. FRANCIS-FLOYD: I am Ruth Francis-Floyd. I am with the University of Florida and I am representing aquatic sciences as a consultant.

DR. BARKER: Steven Barker, Professor of Toxicology, Louisiana State University, School of Veterinary Medicine, representing analytical chemistry.

DR. STERNER: I am Keith Sterner, part-time private practitioner--occasionally, I should say. I represent food animal practice on VMAC.

DR. BLACKWELL: Thank you. If we could have the head table speakers, and if we could start over on my far left, please?

MS. DUNNAVAN: I am Gloria Dunnavan. I am Director of Compliance, FDA Center for Veterinary Medicine.

MR. GARZA: Manuel Garza, Investigator with the Kansas City District Office and I am the pre-approval inspection program manager.

DR. BATALLER: Neal Bataller. I am a veterinarian with the adverse drug experience reporting system at the Center for Veterinary Medicine.

DR. GLOYD: I am Joe Gloyd. I work for AVMA.

MS. HARRIS: I am Mary Harris, with Animal Health Division, representing the Animal Health Institute.

MR. STRIBLING: I am Jess Stribling, from the law firm of King and Spalding, here representing the Animal Drug Alliance.

DR. BLACKWELL: Michael Blackwell. I am the Deputy Director of the Center for Veterinary Medicine.

MR. MARNANE: Bill Marnane, Acting Director of the Division of Manufacturing Technologies.

DR. LEINBACH: Patricia Leinbach, the Acting Team Leader for the Chemotherapeutics Team in the Division of Manufacturing Technologies.

DR. BENSLEY: I am Dennis Bensley. I am a chemist for the Division of Manufacturing Technologies in CVM.

DR. BERTONE: Joe Bertone, reviewer, CVM.

DR. LEIN: Thank you, everyone. Before our introductory remarks from Dr. Blackwell I would like to introduce Dick Geyer, who is our administrative director for the committee, and he has a few housekeeping announcements.

MR. GEYER: Good morning. I would like to welcome all the members of the committee. We have an excellent turnout today. We are almost at 100 percent attendance and those of us in CVM really appreciate the attendance and participation of all of you.

There are a couple of things that I need to do. First of all, I need to read into the record a statement on conflict of interest waivers:

Federal conflict of interest laws preclude the participation of committee members and consultants in advisory committee meetings if they have a conflict of interest, unless a waiver from exclusion is granted by the Agency. Based on the submitted agenda for this meeting and a review of all financial interests reported by the committee participants, it has been determined that all interests in the firms regulated by the Center for Veterinary Medicine which have been reported by the

1 participants present no potential for a conflict of interest
2 at this meeting, with the following exceptions, and in
3 accordance with 18 USC Section 208 a waiver has been granted
4 to Dr. Gary Koritz, Dr. Diane Gerken, Dr. Keith Sterner, Dr.
5 Alice Wolf, Dr. Janis Cleland, Dr. Francis-Floyd, Dr. Vernon
6 Langston and Dr. William Ravis. Dr. Lein, you would have a
7 small committee but for the waivers that we have here.
8 Under these terms of this waiver, Drs. Koritz,
9 Gerken, Sterner, Wolf, Cleland, Francis-Floyd, Langston and
10 Ravis will be permitted to participate fully in discussions
11 and deliberations relating to quality standards for the
12 manufacture of animal drugs, and how clinical
13 ineffectiveness is determined under the Animal Drug
14 Medicinal Drug Use Clarification Act. A copy of this waiver
15 statement may be obtained through the Agency's freedom of
16 information procedures.
17 Then just a couple of more administrative matters.
18 I would like to introduce Jackie Pace, who is standing at
19 the back of the room. She is the administrative officer for
20 VMAC, and I would like to ask all of you who are speakers,
21 or who will be making any kind of presentation today, if you
22 have copies of written materials, will you please see that
23 Jackie gets a copy of your presentation? Also, if you would
24 give a copy to our reporter over here, Alice Toigo, she

needs a copy as well.

For the committee members, several of you I think did not get all of the materials in your notebooks. If you have anything missing, could you please let Jackie or me know and we will try to get you copies by the end of the day? I know it was a formidable amount of material. Some of you may not want any more--

[Laughter]

--but if there is a divider in there and nothing behind it, then it is probably missing. We did give you, at your table, a copy of the Current Good Manufacturing Proposal from May 3, 1996. This goes in Tab 7 in your notebook to replace what was there.

We have given you, on your tables, this morning a new agenda and a corrected list of all the committee members and consultants. So please be sure that you have those so that you are particularly following the correct agenda. Anything else that the committee members need, just see Jackie or me.

Just one last thing, a reminder to all the committee members and all of the speakers, please be sure to speak into the microphone so that you will be recorded. Thank you.

DR. LIEN: Thank you very much, Dick. And now for

some introductory remarks, Dr. Michael Blackwell.

Introductory Comments, Dr. Michael Blackwell

DR. BLACKWELL: Dr. Lien, members of the Veterinary Medicine Advisory Committee and consultants, I want to welcome you on behalf of the Center for Veterinary Medicine here today, and again thank you for giving your time and talent to a process that we regard as extremely important as we seek to carry out mission at the FDA Center for Veterinary Medicine.

Today we believe that the subject will stimulate, puzzle, amaze, and I probably could go on trying to characterize what this day may be like, and I think at the end of the day we are going to probably be a bit numb. I just ask that you hang in there with us. We apologize if it looks a bit aggressive but, again, the subject is a big one and a very important one as we seek to try and make appropriate decisions today regarding the manufacturing of animal drugs.

(Slide)

An important step toward additional flexibility in the drug approval process is to determine if current good manufacturing practices, or GMP, regulations are an obstacle to animal drug availability. And if so, to seek ways seek ways to reduce the impact. An appropriate means to begin

this assessment is to bring this important issue to the Veterinary Medicine Activity Committee for your input and recommendations. CVM is requesting at this meeting that the VMAC consider all information and data that is presented, and provide specific comment on whether the GMP requirements are an obstacle to animal drug availability.

Last year discussions were held with the Animal Drug Alliance, the Animal Health Institute and the American Veterinary Medical Association with a focus toward holding a one- or two-day workshop to better seek insights into the issues of GMPs for animal drugs. These plans evolved into CVM considering instead a Federal Register Notice inviting comments on the regulations. However, we eventually concluded that discussing this important issue in this forum, before the VMAC, was the better way to proceed. So we are extremely pleased to have you engage on the subject of GMPs for animal drugs with a particular focus on whether they are, in fact, a barrier to drug availability.

In November of 1990, the FDA Kansas City District made a proactive outreach to the animal drug industry by holding a workshop that was intended, in large part, to avoid problems for both the Agency and the industry by seeking a common understanding regarding good manufacturing practices. Note that this meeting occurred right on the

heels of the generic human drug scandal and just prior to the January 1, 1991 implementation of the generic drug legislation for animal drugs.

It was the intent of the Kansas City District that the animal drug industry not fail in implementing the generic animal drug legislation. That workshop, and a second one which occurred a year later, have significantly contributed to, and stimulated dialogue on this subject, resulting in some agreements about what is important but also helping to highlight some of the lingering questions which we hope will be aired before this committee today.

Only by inviting the participation of different portions of the veterinary industry, individuals representing the interests of practicing veterinarians and other interested parties can CVM appropriately assess the issues. The VMAC provides the Center with an excellent mechanism for comments to be made, issues to be identified and collated, and an advisory opinion to be authored by a group of experts. Without this process any changes, including legislative, would fail to achieve the objective of addressing possible obstacles to animal drug availability, except that a similar open discussion first be held.

(Slide)

There are a number of questions that have been placed before you, as a committee. In particular, we are asking whether any changes in quality standards for the manufacture of animal drugs or the administrative or inspectional procedures need to be made. If the answer to that question is yes, then we very much need to have information on what specific aspects ought to be changed and in what manner.

Of course, we are asking you today to indicate to us what other information you will need, after the end of this day, which will assist you with the first two questions.

What are some of the specific areas that we ask that you consider? They would include sterility issues; process validation; clinical studies; facilities, utilities and equipment; components; analytical testing; and, of course, other issues which will be raised by speakers today.

(Slide)

In your considerations then, we ask that you keep in mind that the scope of the questions reach to the manufacture of commercial products and clinical supplies but does not include compounding by pharmacists and veterinarians.

You will hear about sensitivity issues regarding

various animal species, and we think that these are important considerations.

And you will hear about standards and procedures that are currently being applied in both the pre-approval and post-approval context.

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Of course, the question follows what will be the implications of this kind of information, especially with respect to animal safety--this would be target animal safety--efficacy, human food safety, environmental safety and drug availability? Of course, our focus is on dosage form pharmaceuticals .

(Slide)

Today you will hear in more detail information regarding CVM's current policy in the area of manufacturing quality standards. I would like to emphasize that it is CVM's policy to establish what we would believe and hope that you would think to be appropriate identity, strength, quality and purity attributes. The operative term here clearly is appropriate.

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Also, in looking at what is appropriate we ask that you understand that within our policy we believe that our mission requires that we preserve conditions of use, the

labeling safety effectiveness, identity and strength, quality and purity of a drug product throughout its marketed life.

In reality, once a drug product is approved and enters the market things can change. They change as far as conditions of use or they may change within the manufacturing process itself. Any time these changes occur companies are required to engage with us to revisit the decision that has been made about the product in order to determine that we have, in fact, preserved its quality standard.

(Slide)

A particular challenge for the committee will be then to look at what drug quality means, and there is no one answer. Where the two extremes of the quality continuum represent total control at one extreme or total lack of control at the other extreme, CVM seeks appropriate standards to achieve safe, effective and quality animal health products that are somewhere in between these two extremes. We believe drug quality is based on a number of factors.

This meeting will help us to determine what those factors are. We need to understand what quality means and what standards are important to obtain adequate quality. We

are here to revisit formally whether the current standards of manufacturing are adequate to assure a quality product. For certain conditions of use are the requirements beyond what is needed? We need a proper balance for assuring quality while still working within the requirements of the Act and the regulations.

There are those that may believe that it is our intent to allow finance and technology to drive this process to whatever extremes technology can take us. Again, I want to reemphasize that it is the Center's position that there is an appropriate level or an appropriate standard which will apply and that may, in fact, shift under different conditions of use, actual conditions of use.

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So then our challenge is to seek an appropriate balance between quality and practicality. There are limits beyond which we believe there is a point of diminishing returns or at least there is not value added to this process, and we believe through today's discussions we will be better able to understand what those are and seek this balance.

(Slide)

So we need your advice. This meeting will provide an opportunity for the FDA and industry speakers and the

public to present information and views to you, the committee, and for the committee to continue its deliberations and provide recommendations at the fall meeting. We understand that, given our limited time at this meeting today, you are simply being asked to gather information and go away from this meeting with the intent of returning in the fall with specific recommendations based on what has been learned.

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There are many stakeholders in this, and we believe that each stakeholder may have a different perception as to what is important or what is not as important. Again, in trying to achieve the balance we hope that CVM will be making decisions in this area which will satisfy the needs of all of our stakeholders and certainly not place requirements where they are not, in fact, needed. But this is a partnering effort and I think in true collaboration, such as in today's setting, we will, in fact, achieve that.

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So to begin an open dialogue, we again have a lot of pleasure in having you here today in this public setting, and I ask that you engage in whatever deliberations will enable you to come back in the fall with specific

recommendations.

I would like to mention, as a way of introduction, the people who will follow on today, our FDA individuals at least, and we are very happy to have them present because these are our experts; these are the people that we rely on in helping us to make the decisions which will achieve our mission. You will be hearing from three people who are in the area of chemistry, manufacturing and controls, starting with Dr. William Marnane. He is currently our Acting Director of the Division of Manufacturing Technologies. Dr. Marnane is a chemist by training and has many years of experience with the FDA, both as a reviewer and in management roles. But we certainly look forward to Bill's comments.

Bill will be followed by the industry and association presentations but later in the day, in the afternoon, he will be followed by Dr. Patricia Leinbach who is our Acting Team Leader for sterile drug--Acting Team Leader for chemotherapeutics area. She is a sterile drugs specialist and will provide her own perspective on this very important topic.

She will be followed by Dr. Dennis Bensley. He is a review chemist with the Chemotherapeutics Branch, again in the Division of Manufacturing Technologies. Dennis is a

manufacturing process specialist. Again, we rely very heavily on his expertise as we work through the questions that are posed to us.

Then we will get out of that area of focus and have Dr. Joe Bertone come before us. He is a veterinarian, a diplomat of the American College of Veterinary Internal Medicine, and he will be speaking with us about quality animal drugs, a veterinarian's perspective.

Joel will be followed by Dr. Neal Bataller, also a D.V.M., and he is going to talk about adverse reactions and medically necessary veterinary products. He is our adverse drugs experience program coordinator at CVM.

Then we will hear from Manuel Garza. He is one of our very experienced investigators with the Kansas City District, and you will be able to get a perspective from that part of the FDA. Their work is a bit different from what we do at CVM. Then, of course, Miss Gloria Dunnavan, who is our Director of the Division of Compliance.

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In conclusion, the Center for Veterinary Medicine requests that the Veterinary Medicine Advisory Committee consider all data, information and comments from all interested parties that have already, or will today, contribute to the question of whether the current good

manufacturing practices regulations are an obstacle to animal drug availability. We see this as an important step at this time in our resolving the question of what are appropriate standards. And I thank you for your attention.

DR. LEIN: Thank you, Dr. Blackwell. Are there any questions at this time for Dr. Blackwell? We will try to take questions with each presentation because it is going to be a long day here. Seeing no response to that, we will move on--thank you very much, Dr. Blackwell--to Mr. Bill Marnane, who will talk about the regulatory scheme.

Regulatory Scheme, Mr. William Marnane

MR. MARNANE: While we are waiting for Joe to take care of the situation with the slides, I might want to mention to the Veterinary Medical Advisory Committee that the narrative that I have provided you contains reference to a variety of information that has been provided to you in what I may refer to as "the big book." There is a specific tab reference for those. Not that I would expect that you would be able to consume that during this presentation, but I think afterwards, when you go over the dialogue that you have been provided, you may want to refer to those specific items.

MR. GEYER: For the committee, you should have in front of you a copy of a presentation titled "Veterinary

Drug Product Quality, the Regulatory Scheme," and then a copy of Mr. Marnane's slides as well. If you don't have them, let us know.

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MR. MARNANE: Essentially, what I will be doing first is trying to provide the VMAC committee an understanding of the regulatory scheme that is used within the FDA. I would like to share with you some of the comments regarding the regulatory process to support animal drug product quality. Specifically, my presentation will cover the meaning of the term "quality" as applied to veterinary drug products. Also it will cover the functions of FDA headquarters review staff and field investigators in determining and maintaining the quality attributes for veterinary drug products: The importance of the pre-approval compliance program; the applicable CGMP regulations that ensure quality veterinary drug products;

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The flexibility that currently exists in the CGMP regulations for veterinary drug products; the flexibility that CVM has to set quality standards for veterinary drug products that are different from the quality standards for human drug products; the role of the Center's veterinarians in establishing quality standards and, finally, the Center's

position on the need for additional flexibility for animal drug products.

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The Center for Veterinary Medicine is that part of the FDA that approves the marketing of quality animal drug products. Quality may generally be defined as processing, or I should say possessing a distinguishing attribute or essential characteristic. For our purposes, the term "quality" means the drug has attributes that are the same or similar to the product demonstrated to be safe and effective in the clinical target animal safety and efficacy studies and that any copies of these products possess the same attributes. The drug product does not contain microbiological or other extraneous contaminants. The drug product does not contain impurities, degradants, manufacturing byproducts or solvents in excess of levels demonstrated to be safe in the clinical target animal safety studies. The drug product is formulated and manufactured by a process that consistently provides a product meeting predetermined quality attributes, and the drug product will maintain all necessary attributes throughout its marketed life.

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The regulatory scheme that is in place at the

Center for Veterinary Medicine is the process by which appropriate quality is built into the drug product and maintained through the coordinated activities of CVM headquarters review staff and FDA field investigators. As part of this process, CVM review staff evaluate the chemistry, manufacturing and control, or CMC, information contained in pioneer and generic animal drug applications, and requests the inspection of all facilities involved in the manufacture of a drug product by FDA field investigators.

CVM recommends that the CMC component of an application be approved when the information contained in the application is complete, and the facilities involved in the manufacture of the drug product have been determined to be in compliance with CGMPs.

The review of the drug product application and evaluation of the manufacturing facilities are generally performed separately by CVM headquarters review staff and FDA field investigators respectively.

The regulations that address the information necessary in a veterinary drug application to support approval are filing requirements, and are not the same as CGMP regulations used by the FDA field investigator.

CVM staff perform a scientific evaluation of the

information contained in an application that supports the quality of the drug product. The CVM review and evaluation of chemistry, manufacturing and control information is performed as part of the filing requirements under 21 CFR, Part 514. FDA investigators perform an on-site data audit and verification of the information contained in the application, as well as an assessment of the adherence of the facility to current good manufacturing practice requirements under 21, Part 211 of the Code of Federal Regulations. The CGMPs are the basis for regulatory action when appropriate practices for quality assurance, as defined in the CGMPs, are not being followed.

After a drug product has been approved and there is a change in the manufacturing process, methods or controls beyond the variations provided for in the approved application, a supplemental application must be submitted. The supplemental application will be scientifically evaluated by CVM review staff to determine the impact of the changes on the quality of the drug product and, in most cases, trigger a request for an inspection by the FDA field.

So far we have discussed the different functions of the CVM headquarters review staff and FDA field investigators. The question should be raised as to how CVM and FDA field communicate and resolve differences in

interpretation of what are appropriate quality standards for animal drug products.

The single most important FDA program that fosters communication between CVM review staff and FDA field investigators in their cooperative assessment of appropriate quality standards for veterinary drug products is the pre-approval compliance program. This program was designed to ensure that attention is focused on all aspects of the manufacturing and control procedures listed in the application, on product formulations proposed in the application and any unapproved changes in formulating and manufacturing procedures.

Such coverage is necessary to assure that the processes and procedures identified in the application have been followed for the products used in the clinical studies to generate the data in support of the application, and to ensure that any modifications required for full-scale production have been validated.

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Having said that, I will focus on the application of current good manufacturing practice requirements to animal drug products. Some parts of the CGMP regulations are similar for human and animal drug products. For example, those animal drug products that fall into the same

finished dosage form class as human drug products, such as tablets, ointments, parenterals, etc., are subject to similar finished pharmaceutical CGMPs as provided in 21 Code of Federal Regulations, Part 211.

Today's discussions and comments are focused at the Part 211 CGMP regulations for finished pharmaceutical dosage forms that are similar for both human and animal drug products.

Current law requires that drugs, whether for human or animal used, be manufactured in conformity with CGMPs. This requirement was added to the Federal Food, Drug and Cosmetic Act as part of the drug amendments of 1962.

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These amendments declare a drug to be adulterated and subject to regulatory action if the methods used in, or the facilities or controls used for its manufacture, processing, packing or holding do not conform to, or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of the Act as to safety, and has the identity and strength, and meets the quality and purity characteristics which it purports or is represented to possess.

In other words, the drug sponsor must demonstrate

that their manufacturing process is under control and that they can reproducibly manufacture their product to defined standards of purity, strength and quality, similar to the drug product used to demonstrate product safety.

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CGMP regulations for finished human and veterinary pharmaceuticals were promulgated on September 29, 1978, defining the meaning of the term "current good manufacturing practice." These CGMP regulations are similar for human and animal drug products. The CGMP regulations are based on fundamental concepts of quality assurance that are recognized by most industries. These concepts are that quality, safety and effectiveness must be designed and built into a product. Quality cannot be inspected or tested into a finished product and each step of the manufacturing process must be controlled to provide assurance that the finished product will be acceptable.

The CGMP regulations are directed at preventing problems by identifying for the manufacturer those controls necessary to ensure that the resulting product has, and maintains, the identity, quality, purity and safety that its manufacturer claims.

The CGMP regulations permit the manufacturer to exercise discretion in determining the means to achieve an

acceptable level of control, but the Agency has final approval of whether or not an acceptable level of control has been met.

Since these guidelines require conformity with current good manufacturing practice, the expected level of manufacturing control required under the CGMP regulations has changed. In fact, regulations would not achieve their statutorily mandated purpose if they were not periodically reassessed to identify and eliminate obsolete provisions, or to modify provisions that no longer reflect the level of quality control that current technology dictates.

Recent proposed amendments to the CGMP regulations include clarification of current manufacturing quality control in the areas of contamination, testing and validation of the manufacturing process.

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Put another way, the CGMP regulations applied to human and animal finished pharmaceutical dosage forms describe minimal acceptable quality control for the manufacture of finished pharmaceutical drug products; generally describe what is to be accomplished and allow some latitude in how a requirement is to be achieved;

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Are used by FDA field investigators during their

inspection of finished pharmaceutical manufacturing facilities; form the basis for enforcement when appropriate CGMP practices are not being followed and, lastly, are periodically revised to keep them current.

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Having stated that the CGMPs are similar for human and animal drug products rather than the same, it is important to point out some specific examples of where the CGMP regulations provide for differences between human and veterinary drug products.

These differences are summarized in comment 42(d) of the preamble to the September 29th, 1978 CGMP regulations, which identify specific exemptions for veterinary drug products. This comment specifically states that veterinary drug products shall continue to be subject to the general CGMP regulations for all drug products, with certain specific exceptions for penicillin operations and fiber-releasing filters.

Comments regarding the appropriateness of individual provisions of these regulations to veterinary drug products have been considered and responded to under the sections involved. When the provisions of a section in the regulations do not apply to veterinary drug products exemptions of such products are stated in that section.

Thus, the concept that there is flexibility in the CGMP regulations for certain specific exemptions for veterinary drug products is not new.

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At this time it is important to understand that the level of quality for an animal drug product is not set by the FDA field or predetermined by CGMP requirements provided in 21 CFR, Part 211. Rather, the level of quality that an animal drug needs to possess is determined by the Center through a scientific review of a sponsor's application for a specific animal drug product. This evaluation and establishment of quality standards occurs during the CVM review of chemistry, manufacturing and control information provided as part of the Center's filing requirements.

These filing requirements are described in 21 CFR, Part 514 and establish the basis for the scientific evaluation performed by CVM. For example, while all human injectable drug products are required to be sterile, the Center's policy and procedures manual guide, entitled, "Sterility and Pyrogen Requirements for Injectable Drug Products," provides for some injectable animal drug products to be non-sterile when labeled appropriately. These non-sterile drug products include injectable euthanasia products

1 and hormonal ear implants for cattle and sheep.
2 Furthermore, this policy has been interpreted by the Center
3 to allow some flexibility in our requirements for intra-
4 mammary infusion drug products.
5 CVM's veterinarians are in many ways the driving
6 force behind the revision of the Center's policy, entitled,
7 "Sterility and Pyrogen Requirements for Injectable Drug
8 Products." The veterinarians recommended that injectable
9 drug products not manufactured by a process that assures
10 microbiological quality should be labeled as manufactured by
11 a non-sterilizing process.
12 I point out the active involvement of the Center's
13 veterinarians to further the understanding that policies
14 impacting on the quality of veterinary drug products are not
15 an ivory-tower approach taken by the Division of
16 Manufacturing Technologies to arbitrarily change the
17 expected quality attributes for animal drug products.
18 Rather, these policies are largely driven by clinical
19 experience, safety issues and the belief by veterinarians
20 that injectable drug products are presumed sterile unless
21 labeled otherwise.
22 Truth in labeling is one of FDA's most basic
23 criteria for marketed drug products and one of the Center's
24 highest priorities. The point is that the Center determines

the level of safety and quality that a product must possess. The FDA field would then determine the appropriate CGMP requirements to assure that the animal drug product has, and will continue to have, these quality attributes.

The Center does agree that in some instances there could be different CGMP standards for animal and human drug products, and that the CGMPs contain the necessary flexibility to allow for different means to fulfill a CGMP requirement when appropriate.

Perhaps it would be useful if I provided an example of the type of flexibility that the CVM has to determine that a different means to fulfill a CGMP requirement may be appropriate for an animal drug. The CGMPs require that procedures be in place to prevent microbial contamination and that there be adequate control of containers and closures for sterile finished pharmaceutical drug products to ensure that they are sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

However, within its framework there is flexibility for the Center to determine through its filing requirements the appropriate microbial quality for the specific animal drug product. The sensitivity of humans to endotoxin is well-known and allows for a single standard to be set for

human drug products. Contrary to this, sensitivity of various animal species to endotoxin varies markedly. If endotoxin sensitivity information were provided for different animal species, the CVM would perform a scientific evaluation of the information and set an appropriate quality standard for specific animal drug products. The FDA field would then assess the means used by the animal drug manufacturer to assure that this quality standard was met.

A different endotoxin quality standard established by the Center during its scientific review of information, provided as part of the filing requirements, would provide for flexibility for an alternative means to fulfill the CGMP requirement for sterile drug products intended for administration to certain animal species. While the animal drug product, like all sterile veterinary drug products, would still require a product specification for endotoxin, the specification would be set at a higher level, depending on the sensitivity of the species, and an alternative means to fulfill the intent of the CGMPs would be appropriate for the animal drug product.

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The determination that there may be an alternative means to fulfill the CGMP requirement would be based on a scientific evaluation of the safety of the drug product,

1 based on the sensitivity of the species for which the
2 product is intended to be administered; documentation at the
3 source of containers and closures are not contaminated with
4 excessive endotoxin and, thirdly, that documentation that
5 there is a well-controlled washing, rinsing and drying
6 process that does not introduce endotoxin through microbial
7 contamination.
8 The Center does not have this information.
9 However, the example generally contains the necessary
10 elements that the CVM would use to determine that there
11 should be a different quality standard and means to fulfill
12 a CGMP requirement than that generally accepted to fulfill
13 the same requirement for a human drug product.
14 I should also point out that the example I just
15 presented would provide an alternative for specific animal
16 drug products rather than a broad exemption for veterinary
17 drug products.
18 (Slide)
19 Having stated that the Center has some flexibility
20 in the application of alternate quality standards and CGMPs
21 to animal drug products, including the flexibility to
22 determine a level of quality that an animal drug product
23 must meet, and also interpret the means to fulfill CGMP
24 requirements for veterinary drug products based on

scientific evaluation differently than the means to fulfill the same requirement for a human drug, it is important to make it clear that the Center is considering the possible need for additional flexibility within the regulatory scheme that may be appropriate for animal drugs.

(Slide)

The additional flexibility that the Center is considering includes the flexibility to exempt specific classes of veterinary drug products from specific CGMP requirements when supported by a scientific rationale. Secondly, the flexibility to evaluate proposed changes to the CGMP regulations that may not be appropriate for veterinary drug products and, if necessary, exemption from the proposed requirements. The CVM believes this flexibility could be built into the existing CGMP regulations.

In conclusion, I have attempted to lay out the basic regulatory scheme by which the FDA determines the quality attributes that a veterinary drug product should possess, and assure that these quality attributes are maintained throughout the marketed life of the drug product.

This regulatory process has for many years provided the means by which the Center for Veterinary Medicine has successfully evaluated and approved veterinary

drug products that are recognized throughout the world as safe and effective for their intended use and possessing their purported characteristics of strength, purity, quality and identity. Thank you.

DR. LEIN: Thank you, Mr. Marnane. Are there any questions at this time? Yes?

MS. DURAN: Sue Duran, Auburn University. I have one question. I know in human drug standards if I ask a pharmaceutical company to send me a bioequivalency sheet, they are required to do that which states, say, for example a drug that is supposed to be 100 mg/ml according to human standards, they have to have from 90-110 mg/ml, and all the information on how that was manufactured, where it was sterile, the pyrogen testing. Do you have that type of information available? If we asked a veterinary drug company, do you require them to furnish us with that information?

MR. MARNANE: Yes, if we have evaluated and approved a new animal drug application, certainly we have all of the information regarding the specifications, you know, for that particular product. But what you are referring to appears to be release specifications largely, and many veterinary products are compendial products and, of course, they would have to meet the compendial standards.

In most cases for finished pharmaceutical dosage forms, the range for assay is usually 90-110. There are some exceptions to that, however, you know, with microbiological testing where there is more variation. But, yes, we do have that information available.

MS. DURAN: Okay, thank you.

DR. KOONG: You made a statement earlier that the single most important FDA program that fosters communication between CVM review staff and the FDA field investigators-- with reference to that, could you give us the current state of health with regard to the communication between the CVM staff and the field people?

MR. MARNANE: Yes, certainly. I would love to do that. You know, essentially prior to the pre-approval compliance program, I mean, the reality of it was that the field did their job and we pretty much did ours. I think the pre-approval program was really very beneficial to helping us interact with the field. Why? Because it didn't only contain the component of evaluation of CGMPs and the opinion of the field, it also contained a component that the field would, in fact, get into the ANDA information, the information within the application, and do a data audit and verification of that specific information.

As such, since the review chemist at the FDA does

most of that, it kind of forced this type of interaction, you know, to occur. So over the years, you know, I think we have established a much closer working relationship with the FDA field than we had prior to the pre-approval compliance program. So the current state of the pre-approval compliance program, I think, is good and, as part of the process, particularly in human drugs, they have established a matrix approach. In other words, what they have done is sorted out the different activities that the field is responsible for and also the headquarters review staff are responsible for, because when they first initiated the pre-approval compliance program there were some redundancies because, you know, the field was essentially told you can look at the application and we were essentially told as part of this program that maybe we could do more evaluation of the opinions of the field. But that has pretty much all been sorted out so, you know, I think we have made a great deal of progress and, as I said, the program continues to evolve and I understand, at least in the case of human drugs, that there is some consideration of revising that program. CVM certainly needs to do that as well.

DR. BARKER: Bill, you said that the sensitivity of various animal species to endotoxin varies markedly, and that a specification could be set at a higher level,

depending on the sensitivity of the species. The rules for off-label use of drug will allow some of these drugs to be used in a variety of species. How would the FDA address that?

MR. MARNANE: Well, we have a lot of people who are going to be presenting from FDA today, who have a great deal of interest, particularly in the endotoxin issue, and since I know that that topic is specifically coming up later on today and will be addressed particularly by Dr. Joe Bertone, you know, I think we might want to wait, you know, until he does that, that portion of the FDA perspective.

DR. BARKER: Is he going to address the regulatory aspects?

DR. BLACKWELL: I would like to comment on this. I think it is an excellent question. I don't envision that the regulatory process will shift so that we try to anticipate any extra-label use that may occur and, therefore, require companies to go through the testing to assure that under those extra-label uses the product will be safe and effective.

It is an excellent question, and a challenge from a regulatory standpoint, but therein probably will lie some of the barrier to extra-label use. I think some products will be attempted under those conditions and found to not

work well because, probably in part, of these concerns. Now, that is assuming there is something about the product itself that carries this risk. But I don't see the process changing to try to predict and allow for all of those potential uses.

MR. MARNANE: Thank you, Mike. I mean, that is clearly a question I really didn't want to answer.

DR. STERNER: Your introductory remarks referred to the need for periodic review of the regulations and an update of them as standards change. I am curious to know about the human side of that and what programs are in place to ensure that your staff also keeps current with continuing education requirements to fulfill their job since they have to interpret and enforce the regulations.

MR. MARNANE: Okay, well, when I referred to current regulations also periodically being reassessed, I mean the reality is that, you know, the majority of the burden for a periodic reassessment of the current good manufacturing practice requirements lies with human drugs. Essentially, when there are activities at FDA where we are enjoined to, in fact, assess the need such as in the case of the Barr decision which clearly indicated that we needed to further define certain areas of the CGMP regulations, the Center for Veterinary Medicine is generally invited to

1 participate in that so that it can provide its perspective
2 of the proposed changes to the GMP regulations.
3 DR. STERNER: And with regard to your own staff
4 training and updating their educational efforts, is there a
5 program in place?
6 MR. MARNANE: There are. You know, I think the
7 most appropriate program that I think is available within
8 FDA is for field investigators and, unfortunately, the
9 reality is that very few slots are provided for headquarters
10 staff, period. I think the Center for Veterinary Medicine
11 usually has maybe only one or two provided. So, in all
12 honesty, I would have to say I think we could use a little
13 bit more contact with that type of very recent training
14 than, in fact, we are getting.
15 MS. DURAN: One more question. As a buyer, when I
16 look at a product how do I know that that product has been
17 through FDA approval? Is there any nomenclature or anything
18 that says that you have approved that product?
19 MR. MARNANE: Basically we encourage, as part of
20 our labeling, that there be a statement on the labeling that
21 says "FDA approved."
22 MS. DURAN: But it's not required? I just went
23 through a lot of products before I came here and I couldn't
24 tell what was approved--

1 MR. MARNANE: Yes, I don't think it is required
2 but generally we encourage it. I mean, most sponsors want
3 to put that on. I mean, it obviously says something to the
4 end product user. It says that this has been looked at by
5 FDA and contains the characteristics of quality, strength
6 and purity. So most sponsors like to put that on.
7 DR. FLETCHER: I have a couple of questions. On
8 page five of your talk, following the broad concepts of the
9 CGMP regulations there is a statement that the regulations
10 are directed at preventing problems by identifying for the
11 manufacturer those controls necessary to ensure, etc., etc.
12 What kind of input does the manufacture have in declaring
13 what controls they believe would be appropriate to assure
14 those broad concepts?
15 MR. MARNANE: Well, essentially the control--I
16 mean, this gets into the "what" and "how" issues associated
17 with GMPs and I think we will hear quite a bit from other
18 speakers about that today but, you know, certainly the
19 manufacturer--the onus is upon them to have in place what
20 they believe are adequate controls for that process and to
21 validate those controls adequately to assure that the end
22 product will have the expected quality attributes. Then, of
23 course, the field investigator will arrive on site and
24 either agree or disagree that those controls are, in fact,

adequate. If they don't agree, then the field investigator may, in fact, make some recommendations as to what additional control may be appropriate for that particular process.

DR. FLETCHER: Okay. Then on page eight of your talk there is the question of the Center--this relates to the flexibility that might be present in the regulations relative to animal and human drug products. My question is does the FDA field staff, in fact, allow that flexibility?

MR. MARNANE: Well, once again, I don't think I can hit on this point enough, we set the quality standards--

DR. FLETCHER: Right.

MR. MARNANE: --headquarters does. And I think that is the beauty of the pre-approval compliance program. I mean, for a number of years we have had a very close interaction over the phone, and a lot of that interaction was, in some cases, disagreement in terms of the quality standards maybe that we had set and the appropriate assurance levels to see to it that that quality standard is met. So generally there have been some contentious issues. We have been able to resolve those through working individually with the field investigators. So, yes, there is that flexibility.

DR. FLETCHER: Okay.

DR. LEIN: In that same vein, is there a review back at headquarters again when there is at least disparity, or so-called by industry, that a field investigation is over-burdened possibly of what they think the regulations are?

MR. MARNANE: We have received requests at headquarters and have contacted the district for a series of discussions regarding their expectations. I have to point out up front though that, in fact, many times the headquarters does agree with the field. I mean, the field is on-site and they may have a lot of very valid observations. It is very difficult for us, sitting in an office somewhere in Rockville, to second guess what they are seeing. So it is sometimes very difficult for us to sort through what a firm will tell us versus what we will find out when we, in fact, deal with the investigator. But in probably 98 percent of the cases we have always been able to come to a reasonable resolution. Sometimes that resolution was merely explaining the basis of our conclusion and why we agreed with the investigator to the drug sponsor who thought that perhaps the expectations of the field investigator were excessive. So it has worked, yes.

DR. LEIN: Other questions? Yes?

MS. DUNNAVAN: I am Gloria Dunnavan, the Director

of Compliance. I would just like to comment. From a compliance point of view, whenever we are looking at a GMP problem there is always open dialogue between the Center and the field and possibly with our attorneys as well. There is always that dialogue going on, and there is always an opportunity for a firm that is having a problem to be involved in the dialogue with us. Now, that can go beyond just pre-approval issues; it can be a compliance issue dealing with a marketed product.

DR. CLELAND: I am Janis Cleland. Is there means for any kind of mediation? I mean, you mentioned that if the investigators and the Center, here in Rockville, that they would come to some sort of agreement, but what if there is a real discrepancy or a real feeling on the part of the manufacturer that the requirements are not what they feel they should be? Is there some means of mediation that doesn't involve just going to CVM?

MR. MARNANE: Well, I mean, the only other avenue I can think of, if you are not coming to CVM to assist in the mediation of an issue, then that would mean to me that you are probably choosing to deal directly with that issue with the district or regional office and the investigator who made the observations. I mean, I don't think we have ever seen anything go beyond either dealing with the field

or dealing with headquarters or headquarters dealing with the field. We have always been able to resolve issues. So if there is a higher level for mediation, I don't know what it is.

DR. LEIN: Other questions? Well, it was a good discussion. Thank you very much, Mr. Marnane. We are five minutes early and we should take a break. Let's all be back here promptly at 10:00 and we will try to stay on schedule. Thank you.

[Brief recess]

MR. GEYER: For the committee members and consultants, first of all, we have placed in front of you a pink sheet with some attachments. That is your travel voucher information. So please be sure to sort that out and keep it with you, you will need it.

The other announcement has to do with a request that some of you made for some additional copies of material that was not in your book. A number of you said you didn't get what was supposed to be in Tab 5. Well, that is all right because there wasn't supposed to be anything in Tab 5.

That will not be covered in the quiz! That is the Animal Health Institute presentation, and you should have had a copy placed on your table this morning. So if you don't have one on the table as opposed to the notebook, let

us know and we will get you copies. The other copies that several of you asked for, we are getting them made for you.

DR. LEIN: You notice how tricky they are with the committee, trying to see if we really looked at this notebook!

[Laughter]

We will start in with the industry and veterinary presentations. Mr. Jess Stribling first, from the Animal Drug Alliance. And what is the first acronym, the GPIA?

MR. STRIBLING: That no longer pertains. The Animal Drug Alliance was begin by the Generic Pharmaceutical Industry Association, which is the largest trade association of the human generic industry. Then some years ago we broke off from GPIA. So the GPIA is a misnomer at this point.

DR. LEIN: I am just so happy to hear that we can drop an acronym! Thank you.

Presentation by Jess Stribling, Esq.

MR. STRIBLING: Good morning, ladies and gentlemen. My name is Jess Stribling. I am attorney in the Washington office of King & Spalding, which is an Atlanta-based law firm. During my years in the Chief Counsel's Office of the Food and Drug Administration, I was counsel for a time to the then Bureau of Veterinary Medicine, which was headed by Don VanHouweling.

1 I am here this morning in my capacity as the
2 Executive Director of the Animal Drug Alliance, an
3 association of companies that make animal health products,
4 including generic animal drugs. The Alliance is grateful to
5 the Center for Veterinary Medicine for providing this public
6 forum on the critically important issue of appropriate
7 manufacturing requirements for animal drugs and for the
8 opportunity for me to address you on behalf of the Alliance.
9 And I should say also that we are particularly grateful to
10 Dick Geyer for the very careful, thoughtful, fair way he
11 went about organizing this meeting.
12 The Alliance's position is fully stated in the
13 fifteen-page April 8, 1997 letter to Dr. Sundlof that is at
14 Tab 3 of your materials. This morning I want to briefly
15 address three points: first, the background and context out
16 of which this issue has arisen; second, the issue itself,
17 the determination of appropriate manufacturing standards for
18 animal drug products; and third, a response to the issue,
19 our suggestions as to what should be done.
20 Under background two points must be made: The
21 first is that there is a distinction between the CGMP
22 regulations on the one hand, and a company's procedures,
23 processes and methods used to fulfill the requirements of
24 the regulations on the other hand. The regulations

establish the quality standards for the manufacture of human and animal drugs. Company practices concern those procedures, processes, methods, assays that are used to meet the requirements of the regulations. In FDA's terminology, the CGMP regulations prescribe what must be done to manufacture a quality product. A company's procedures, processes and methods are how the company goes about fulfilling the "what" requirements of the regulations.

Let me give you an example. There is a CGMP regulation that requires that companies making sterile drug products establish appropriate written procedures to prevent microbiological contamination and validate their sterilization processes. This regulation states what must be accomplished--prevention of microbiological contamination by written procedures and by validated sterilization processes. But the regulation, at least to this date, doesn't tell a company how to do that. A company is free to use terminal sterilization, aseptic processing, ethylene oxide, or irradiation, and it is not told how to go about validating the processes. Those decisions are left up to the company.

That is the distinction between the "what" of the regulations and the "how" a company goes about fulfilling the requirements, and that distinction is critically

1 important because, to my knowledge, there is no controversy
2 in the animal health industry over the regulations. Let me
3 say that again. There is no controversy in the animal
4 health industry over the existing CGMP regulations. They
5 are fine just as they are. They are, as one of my partners
6 puts it, "immutable principles" for the manufacture of
7 quality drug products. The controversy is not with the
8 quality standards in the regulations but, rather, with FDA
9 investigators and CVM reviewers determining how companies
10 must go about fulfilling the requirements of the
11 regulations. That is where the issue is.
12 The second background point is that for years FDA
13 investigators and reviewers made a common sense distinction
14 between the manufacture of animal drugs and human drugs.
15 FDA investigators and CVM reviewers required animal drugs to
16 meet the quality manufacturing standards with whatever
17 procedures, processes and methods were appropriate and
18 necessary for animal drugs without regard to what was
19 required for human drugs.
20 Then in 1990 that all changed. FDA investigators
21 and CVM manufacturing reviewers began requiring animal drug
22 companies to use the same procedures, processes, methods,
23 assays as are used by human drug manufacturers to fulfill
24 the requirements of the regulations. And it is that that

1 brings us all here today. It is not the quality of the
2 manufacturing standards of the CGMP regulations. Rather, it
3 is the FDA's and the CVM's unceasing imposition of human
4 drug requirements for how animal drug companies must meet
5 the what requirements of the CGMP regulations. And the
6 essence of the concern is whether these human drug
7 requirements are always necessary to make a quality animal
8 drug product.
9 Now, I said with regard to the regulations that I
10 knew of no controversy in the animal drug industry about the
11 regulations. They are fine. I would say that with regard
12 to the second level, the "how" companies are to go about
13 fulfilling the requirements of the regulations, that
14 probably there would be no controversy in the industry about
15 95 percent of those requirements. Probably 95 percent are
16 appropriate and necessary. We are not talking about
17 throwing out all manufacturing quality requirements. We are
18 not talking about a complete overhaul in manufacturing
19 requirements. What we are talking about is the imposition
20 of human drug manufacturing requirements on animal
21 manufacturing just because they are required for human
22 drugs.
23 If we are to pick up Mr. Marnane's terminology,
24 our concern is that CVM and the FDA investigators have not

1 been flexible enough, but we agree with them that this is an
2 area where CVM and FDA have flexibility. Unfortunately, the
3 flexibility, so far as we can tell, is always to adopt
4 whatever human drugs adopts.
5 So much then for the background and context. Let
6 me describe the issue as clearly as I can. Clifford Stanley
7 was professor of theology at the Episcopalian seminary in
8 Alexandria, Virginia, for decades. Dr. Stanley punctuated
9 his lectures on the various doctrines of Christian theology
10 with the question, "if it doesn't make any difference, what
11 difference does it make?" "If it doesn't make any
12 difference, what difference does it make?" In so doing, he
13 tried to mold the Episcopalian clergy into preachers and
14 teachers who would not simply mouth pious platitudes, but
15 constantly focus on how the Christian faith influences and
16 changes, hopefully for the better, the way people live. Dr.
17 Stanley know that pious platitudes that make no difference
18 in the real world are useless.
19 For the past six years the Animal Drug Alliance
20 has been asking a similar question about FDA's and CVM's
21 imposition of human drug manufacturing requirements on
22 animal drugs. Do these additional requirements, just
23 because they may be appropriate and necessary for human
24 drugs, make any difference in the real world where animals

live?

The late Atlanta comedian, Louis Grizzard, loved to tell the story of a Georgia, Alabama football game in which a bulldog named Uga, the University of Georgia's mascot, led the Georgia team out onto the field and then, standing in the middle of the field before the thousands of fans in the stands and nationwide television, commenced to groom himself in very private places. A Georgian fan, caught up in the enthusiasm of the big game, exclaimed, "I wish I could do that!" To which his companion said, "That dog will bite you!"

[Laughter]

Animals groom themselves in ways that we would consider unsanitary for human beings. They eat, drink, and inhabit areas that are higher in gram-negative bacteria states than ours. As a result, they carry a certain level of natural resistance to endotoxins that humans do not have. In light of this real-world distinction between the way animals live, and eat, and drink, and humans live, and eat, and drink, is it necessary to require that animal drugs be manufactured so as to achieve the same statistical levels of assurance of sterility as drugs for human use or, if there has not been any problem, to require companies to present data showing the level of endotoxin that may be present?

1 That is one way to describe the issue as the Alliance has
2 raised it.
3 Let me try another way. There are basic tests,
4 procedures, processes and methods that must be required to
5 build a safe, effective and quality drug product, whether
6 for human or animal use. After that basic work has been
7 done, additional requirements may not enhance the real-world
8 safety, effectiveness and quality of the product, but only
9 add a statistical level of assurance of safety,
10 effectiveness or quality. Query whether the same level of
11 assurance--we are not talking about real-world safety,
12 effectiveness and quality but whether the real-world
13 statistical assurance needs to be the same for animal drugs
14 as for human drugs given a safe, effective, quality product?
15 In the early 1970s, FDA was working on helping and
16 making the industry make products that were safe, effective
17 and had quality. By the end of the 1980s, compliance with
18 FDA's basic requirements resulted in a safe, effective
19 quality product. Today, in the later 1990s, additional
20 requirements tend to add a statistical level of assurance
21 but few of these changes would make any real-world
22 difference in the life of the animal.
23 Clearly then, where once basic safety,
24 effectiveness and quality have been established by

1 requirements, should not additional requirements that only
2 add statistical levels of assurance of something at least
3 undergo a thorough cost-effectiveness examination before
4 being imposed on animal drug products because those are the
5 requirements for human drug products? We are not asking for
6 much. We are just asking for some process to look at the
7 issue and to ask questions. That has not been done.
8 Let me try to state the issue one more way, just
9 to make sure that it is clear. Prior to June, 1995, intra-
10 mammary products were not required to be sterile, nor was
11 any labeling so stating required. The lack of sterility was
12 an exception to the general rule that injectable drug
13 products must be sterile and pyrogen free. In June, 1195,
14 without any notice or discussion, CVM changed the rule and
15 required that new intra-mammary products would have to be
16 sterile or labeled as non-sterile. However, the older
17 products could continue to be non-sterile and didn't need to
18 be labeled as non-sterile. Now you figure that out; I
19 can't.
20 If there was a real-world need for intra-mammary
21 products to be sterile, why were the older products not
22 required either to be sterile or to include the labeling of
23 not sterile? And the fact of the matter is, if it is okay
24 either to be sterile or non-sterile what difference does

1 sterility make? Of if there was no real-world need for the
2 older products to be labeled as non-sterile, why impose such
3 a requirement on new intra-mammary products? The answer, I
4 assume, is that sterility makes them better in terms of an
5 increase in statistical assurance of quality. But that, you
6 see, capturers the question that the Alliance is asking: Is
7 a requirement that makes a statistical increase in assurance
8 of quality but no real-world difference, as is evidenced by
9 the fact that pre-June '95 products can continue to be
10 marketed non-sterile without any labeling, make any sense as
11 necessary for animal drugs? My guess is that the right
12 answer is sometimes it does make sense and sometimes it
13 doesn't make sense. But the practice of the Agency and the
14 Center, at least viewed from outside, is that every single
15 new requirement for human drugs is imposed on animal drugs,
16 totally apart from whether it makes any sense in the real
17 world.
18 The policy letter goes on, it states that the
19 reason for the new requirement is that--and I am quoting--
20 any viable organism, in addition to pathogens, when place in
21 an advantageous medium can cause problems, end quote. I
22 agree with that. I assume do agree with that. But that
23 begs the question: So what? Does the fact that something
24 can happen mean that we need to add requirements to make

sure that it never happens? Or, is the likelihood of it can happen so remote that it is simply unnecessary to add a requirement over that particular event that can happen but probably won't?

Normally a regulatory agency will promulgate rules to protect against problems that have arisen in the past. In that case there are hard data of experience on which to justify the requirement. Furthermore, a regulatory agency may promulgate rules to protect against problems that are likely to occur in the absence of the rule, even if those problems have not yet occurred. The FDA, after all, is a public health agency and has an obligation to all the American people to do that. I would go on and say that I believe, perhaps because I spent so many years at FDA, that a regulatory agency may even do so for problems that are only reasonably likely to occur. But there is some point when we leave the real world of what might occur and enter into the dream world of fantasy and nightmare. "It can cause problems" is not enough, by itself, to justify imposition on animal drug manufacturing requirements.

This is especially true for animal drugs because animal drugs are price sensitive. There is third-party reimbursement for human drugs. I do far more human drug work than I do animal drug work, and I have never had a

1 client complain about a new requirement that is very
2 expensive that would show manufacturing quality for human
3 drugs because they simply pass the cost of that requirement
4 off onto the drug product. It is picked up by the third-
5 party reimburser and the patient doesn't pay anything more,
6 at least directly. He has no idea how many costs he is
7 paying indirectly. But there is no third-party
8 reimbursement for animal drugs. Food producers and pet
9 owners pay the full freight. As a result, there is a limit
10 to what they will pay. If FDA-approved drugs are too
11 expensive, they will not be used. Instead of approved
12 drugs, food producers and pet owners may choose to use no
13 drugs, or illegally imported unapproved drugs, or drugs
14 compounded in a bathtub, or approved and unapproved drugs
15 extra-labelly. Dr. Sundlof has eloquently redefined the
16 meaning of safety to take into consideration the real-world
17 effect of not having an available supply of approved animal
18 drugs, saying you can't just look at the product in itself
19 but have to look at the world in which it is used and
20 realize that the safety of the food supply is enhanced if
21 FDA-approved drugs are being used, and it is not enhanced
22 and may be detrimentally harmed if counterfeit drugs,
23 illegally imported drugs, bathtub-compounded drugs, or drugs
24 used extra-labelly are used in food animals. In other

1 words, imposing manufacturing requirements that only
2 statistically enhance drug quality, without making a real-
3 world difference, may result in a less safe food supply.
4 What, then, should be done? Let me make four
5 suggestions:
6 First, and this may be most important, the
7 appropriateness of manufacturing requirements needs to be
8 addressed on a requirement by requirement basis. What is
9 the specific requirement that FDA or CVM believes is
10 necessary? We can have a great time talking philosophically
11 today about what standards should be applied in the
12 justification and imposition of new requirements but that
13 will get us nowhere.
14 I listened to Bill Marnane's speech and I thought
15 right on; there is nothing in there that I disagree with. I
16 can't go so far as to say that Bill has agreed with
17 everything that I have said but I wouldn't be surprised if
18 he has agreed with the thrust of what I have said because
19 when we talk philosophically, up there in the air, either
20 there is no disagreement or it is a disagreement that
21 doesn't have any practical effect in the real world. And
22 looking at the issues involving animal drug manufacturing
23 requirements, we are dealing with what is more akin to
24 Justice Brennan's comment about pornography, "I know it when

1 I see it." We need to look at each specific requirement one
2 by one. And I am confident that for most of them we will
3 know when we see them whether they are really necessary and
4 appropriate or whether they go beyond the pale.
5 It is interesting that the industry has been
6 championing this kind of specific review. The Animal Health
7 Institute, i its paper that you have received, has specific
8 requirements that it believes are unnecessary and should be
9 reviewed. The Animal Drug Alliance's April 8 letter to Dr.
10 Sundlof lists 31 specific requirements that it believes are
11 unnecessary. This list provides a good place to start in
12 looking one by one at what industry, at least, believes may
13 not be appropriate requirements, remembering that 95 percent
14 of the requirements are perfectly appropriate. We are
15 looking at a very small number, relatively speaking, but a
16 critical number and numbers and kinds of tests that can be
17 very expensive.
18 Second, there needs to be a process for examining
19 specific CGMP requirements one by one. The Animal Health
20 Institute suggests that this committee recommend the
21 formation of a working group comprised of representatives
22 from the animal health industry and its regulators. The
23 Animal Drug Alliance concurs with that recommendation and
24 hopes that the Advisory Committee Act will permit such a

thing.

Third, FDA and CVM need to establish an agency process and a CVM process for examining new requirements before they are imposed. Understand that most new requirements do not go through any kind of public process that allows the industry to comment and have input. Rather, they are imposed by FDA investigators in form 483, that list of violations that an inspector leaves at the end of an inspection, or CVM reviewers in incomplete letters on pending applications, or maybe in the policy letters, such as the one I discussed which was issued without prior comment from industry. And I tell you, in those forms FDA and CVM reign supreme. You want to know what hopelessness is? You join the animal drug industry at that point.

The Alliance suggested such a process to CVM several years ago. We suggested that the Center Director hold a weekly "incomplete letter" day analogous to the NADA review day. At that meeting he would review all the outgoing incomplete letters with the reviewers who wrote them, asking of each requirement stated in a letter has this requirement ever been imposed before on other companies? If so, when was the first time it was imposed? How many times has it been imposed since then? What was the basis for the requirement? What was the need that this requirement sought

to address? And if a requirement were being imposed for the first time, he would ask what is the basis for this requirement? What are the data that suggest that such a requirement is necessary? Do you have any adverse event data? And if you do, is this event likely to occur again or was it atypical, some kind of aberration? Does the requirement even relate to the event that it is attempting to prevent in the future? What will it cost? If there is a problem that requires attention, is there a less expensive way to meet it? In this kind of procedure necessary new requirements would still be imposed, as they should be, but unnecessary ones could be deleted. We still think this is a good idea, and we still think that Dr. Sundlof should do it.

Finally, the Alliance's letter to Dr. Sundlof notes that many years ago products were released on the basis of finished product testing. Then in-process controls were required. Now prospective validation of the entire process, including initial validation of equipment installation, process performance qualification and product performance qualification is required. FDA's May, 1987 guideline on general principles of process validation, which really initiated the intensive drive toward prospective validation, states that, and I am quoting, successfully validating an entire process may reduce the dependence upon

intensive in-process and finished product testing, end quote.

The Alliance agrees with that but it notes that even though companies are validating the entire process prospectively, in-process controls and finished product testing requirements remain and from time to time are increased. The Alliance proposed, in its letter to Dr. Sundlof, that FDA conduct a complete review of each and every required in-process control and each and every required finished product test, with the assistance of non-governmental consultants expert in CGMP and in dialogue with the regulated industry, since I am not sure the Advisory Committee Act will really allow a working group, to determine whether each is necessary in the manufacture of drugs for animals or whether it can be deleted.

Note that in so suggesting, we are not proposing the abolition of in-process controls or finished product testing requirements. Nor are we proposing a decrease in both the in-process controls and the finished product testing requirements.

We are proposing that, in light of full initial equipment, process, and product validation, either some of the in-process controls or some of the finished product testing requirements may no longer be necessary to assure

animal drug product quality.

Our assumption is that once the requirements have been established and met to assure the manufacture of a quality product for animals in fact, increased requirements to provide additional theoretical and statistical assurance of quality may not be as necessary for animals, like Uga, as they may be for people. Thank you very much for your attention.

DR. LEIN: Questions for Mr. Stribling? Yes?

DR. LEINBACH: First of all, I would like to make a comment on the labeling issue for intra-mammary products, and I think if you will examine the policy a little more closely you will find that all intra-mammary products that are not sterile are required to be labeled as being non-sterile even though they were approved long ago, before this policy letter was written.

I wanted to make another comment about attachment B on your letter. You actually didn't discuss this, but since it is a handout, I just want to point out--

MR. STRIBLING: Dr. Leinbach, it was one that the Alliance has presented to you in the past--

DR. LEINBACH: Right.

MR. STRIBLING: I hope you recognize that.

DR. LEINBACH: I do. I do recognize this--

MR. STRIBLING: Okay.

DR. LEINBACH: --and I just want to make the comment that the basic assumption on which you base these calculations is not scientifically valid because it assumes that all endotoxin derives from viable microorganisms, and this is not true. It also derives from non-viable microorganisms and I know of no way to estimate what those numbers or quantity might be. So, therefore, I really don't believe there is a way that you can theoretically calculate what endotoxin levels may be in any drug product, be it human or animal.

MR. STRIBLING: May I comment?

DR. LEIN: Yes.

MR. STRIBLING: First of all, with regard to the policy letter, if I misstated it, I am sorry but the issue is still there. If products can be marketed that are non-sterile and have to say non-sterile, why is it necessary to have products that are sterile? Is there a real-world difference that sterility adds? If there is, then I would be the first in the world to say get those non-sterile products off the market. But if there isn't, there isn't.

With regard to the attachment--I get out of a lot of things this way, I am a lawyer and not a scientist. The author of that form is sitting behind me at the table, Kevin

Schinze, from Phoenix Scientific, and may I ask if he would like to respond to Dr. Leinbach's comment about the chart?

DR. LEIN: Please.

MR. SCHINZE: My response to that attachment, it is indeed hypothetical and theoretical. It is a fact that endotoxin is not derived strictly from viable microorganisms. I would say, however, that in the newer and up to date CGMP facilities and veterinary medicine today that manufacture finished sterile dosage forms for pharmaceutical use the environmental controls are such that gram-negative organisms simply are not present, if at all, certainly to any extent where endotoxin levels are going to reach pyrogenic activity. The industry has made it a practice in the last six years that I am aware of, at least within our facility, to do bulk viable assays on all solutions, whether they be sterile injectable or oral for whatever purpose, and more often than not the microbial count in those solutions is virtually none. And, to a fault, we do not find gram-negative organisms within our facility and I don't believe most people do either with appropriate process controls in our systems.

So the issue about massive quantities of endotoxin being found in components, for example, extruded polyethylene bottles that come out of the mold in excess of

130 degrees centigrade, or stoppers, or being included in raw material levels that are USP or NF in nature or come from quality manufacturers is virtually nil. So if you exclude the possibility of spontaneous generation, then it gets real difficult to get levels of endotoxin, and if you look at that again, it is hypothetical, but I think the point is well made that it takes a tremendous number of colony-forming units or non-viable activity to produce levels of lipopolysaccharide that are going to, from a dilution effect standpoint, affect the finished dosage for deleteriously.

MR. STRIBLING: Dr. Lein, may I bring that back to my presentation?

DR. LEIN: Yes.

MR. STRIBLING: This is an excellent example of the fact that individual requirements need to be discussed with specificity because you heard an issue raised by Mr. Schinze that I doubt was considered by the Center, namely, hey, what is the state of the industry and its manufacturing processes, and do we have an industry that by and large is free of gram-positive bacteria so we don't need to worry about it? Those are the real-world differences that need to be considered in assessing whether a requirement is necessary, and then there follows a compliance issue to be

sure, namely, okay, what do we do about those that do have those problems? My answer is criminally prosecute them but don't impose an unnecessary requirement on the industry as a whole that is designed only to take care of a handful of malefactors.

MS. DURAN: Well, I have been practicing pharmacy for a long time. When I first started practicing pharmacy we compounded human IV fluids and the water table went down and we started getting pyrogens and we were no longer able to manufacture a pyrogen-free fluid. So major companies bought very expensive ultrafiltration systems to make the water in the front good quality. I don't so much have problems with pyrogen testing as I have problems with what I want to know what you started with to begin with. If I have a product that started with distilled water, there are two problems that you have. You have flavobacteria and you have Pseudomonas cepacia, and that is very hard to culture. The only way you can pick that up is if you put a filter and you run large amounts of fluid through that filter and you culture that. Both of those produce massive endotoxins and even in dairy cows they cause DIC and death.

So number one, endotoxins are a problem in a sick animal. Second, yes, dogs don't have a problem with endotoxins but horses do. And I am sitting here, thinking

as a consumer and a pharmacist, okay, now I have veterinarians coming to me and they are going to use this off-label drug for dogs and now I have to say, okay, is this drug made from distilled water or was it made from sterile water for injection? Does it have pyrogens in it? Because I guarantee you, if you give a lot of pyrogens to a horse you are going to kill him.

So you are really making it very complicated for the practitioner and you are going to have to be an educated chemist to know what products you need to use.

Again, back to the label, I can deal with cheaper products and I can deal with the label, but I have to know what is in that product and I have to know somewhere down the line what standards you used, and I do not have the time to be checking and I think that is the role of the Center of Veterinary Medicine, to say these are the standards. I can adapt plus/minus 20 percent if the veterinary field feels that that is adequate but I still need to know up front what I have as a product. There are good companies out there but there are also bad companies, and if you look at the recalls every day, somebody has to be making some standards and we have to know where the endpoint is.

MR. SCHINZE: I think it is a fair statement to make, not necessarily from the companies that belong to the

1 Animal Drug Alliance but from the industry, the major
2 players use USP water for injection. We use it in our oral
3 solutions. We use it in our topicals. We use it in
4 everything we produce. It is the result of a five effect
5 distillation process. That water system moves out of a 316
6 low carbon stainless steel storage vessel through a 316 low
7 carbon stainless steel loop at 11.5 feet/second in excess of
8 90 degrees centigrade, 24 hours a day, 365 days a year. We
9 have never, ever isolated a bacterial isolate or fungal,
10 microbial, whatever out of that system in the six years of
11 our facility. And I don't think most others, and I have
12 been in other facilities, worked in other PMA firms in the
13 animal health industry in my life, and they too have only
14 water systems that use USP water for injection.
15 That gentleman down there, Mr. Garza from the
16 Kansas City District, I can tell you, would not allow
17 injectable products to be made with microbial burdened water
18 in the Kansas City District. It just doesn't happen. We
19 start with good materials, the best that can be made. I
20 certainly can speak for no one but ourselves but I believe
21 that is a standard that is fairly common across the board of
22 the major players in this business.
23 MS. DURAN: Well, that is what worries me.
24 Everybody is not the same, and somewhere we have to have

standards. And do you culture your filters? Do you change filters really often?

MS. SCHINZE: I can tell you about three facilities in the United States that if they go out and take evasive action against them right now that you will clean up the entire United States veterinarian industry in the pharmaceutical field.

MS. DURAN: Well, every major fluid company over the years I have practiced has had a recall, all the four human major fluid companies have had a total recall because they had gram-negative bacteria and endotoxins in their fluids. And so you have to really keep up with that and somebody needs to be watching that. My point is the consumer can't do that. The practitioner can't do that.

MS. SCHINZE: I don't think that is their responsibility. I think part of the issue, and I mentioned this last fall at an FDA seminar, there has to be communication, a trust factor between the CVM and industry. We are the experts. We have to be charged with the liability and the responsibility for maintaining that our products are quality products and that they probably meet or exceed anything that is necessary for veterinary health. And I don't know that that trust has always been there but I know that there has been a steady course on behalf of CVM,

1 Bill Marnane and his people, the Kansas City District
2 certainly, to establish that sort of communication and
3 trust. But I think the bottom line is as an industry we
4 have to have the respect and the obligation and liabilities
5 that go along with that respect for seeing that we do give
6 you and the consumer a quality product. But the water
7 systems in the major facilities that play the game in this
8 business today really aren't an issue. And if you look at
9 recalls on the veterinary side, we certainly, I think, have
10 done a better job historically on the animal health side.
11 DR. BERTONE: I have two comments. One is on the
12 issue of Uga. An animal's environment has nothing to do
13 with its sensitivity to endotoxins. So, I am sorry, that
14 was essentially insulting to me to make that comment.
15 On the second note, what I think it is really
16 important that we have to understand that endotoxin is given
17 a lot of--we focus on endotoxin and basically the reality is
18 that is because that was the easiest toxin to isolate; that
19 is where most of the research has occurred but in my office
20 right now I have a book with 280 bacterial toxins that you
21 can buy for research studies. So even though we are
22 focusing on endotoxin and gram-negative organisms, there is
23 also gram-positive endotoxin, there are bacterial toxins,
24 from fungi and from multiple organisms. So to focus on that

issue I think is inappropriate or incorrect. Again, I think Uga is a great dog.

MR. GARZA: A comment on use of USWFI for production. Generally it is not a problem with the use of WFI because, once you have WFI within a closed system, it remains essentially sterile and endotoxin-free. That problem, if it occurs based upon the controls at the facility, is that once it is drawn from the system, how it is handled, and it is the post-depyrogenation contamination issue; it is not the issue of generating WFI.

DR. LEIN: Other questions? Dr. Barker?

DR. BARKER: Either Mr. Stribling or Mr. Schinze could answer this for me. What I heard described was that certain members of the industry are already meeting all of the requirements in terms of monitoring for endotoxins and trying to eliminate those from the product. Have the costs that seem to be a concern of the industry already been covered in meeting the regulations?

MR. SCHINZE: I would think to a large extent yes.

DR. BARKER: So the argument that this is a cost impact concern is moot?

MR. SCHINZE: No, sir.

DR. BARKER: Why not?

MS. SCHINZE: Because what it has done, it has

lowered the operating profit margin, if you will, of the players that have complied with this level of regulatory impact.

DR. BARKER: And we are trying to get everyone to meet those levels. So there would be additional cost to the people who are not complying to bring it up to the standard but the major industry, 95 percent, have already met the regulations and are meeting the regulations?

MR. SCHINZE: I think that is fair. The people that are producing licensed drugs that are subject to routine inspections by the district offices of the FDA are meeting those requirements, yes. It is the firms out there today that do not produce licensed products or the pharmacists who are compounding, under the protection of a law which is not fair and equitable to the industry, that have the potential to cause problems. There are about three firms in the veterinary industry today that produce fluid expansion type products sterilely that do not own an ANADA or an NDA and are not inspected on a routine basis as are some of the licensed players. I think if you look at the EIRs historically it would show you there is a trend and repetitive action of non-compliance. The fact also is that it is very difficult in the veterinary industry to take the price of a drug up. We produce USP lidocaine 2 percent 100

1 ml. We are the largest producer. We produced over three-
2 quarters of a million bottles of that product last year. I
3 sell it for 95 cents. It meets all the sterility and
4 endotoxin requirements of a 2 cc carpel that you get at your
5 dentist's office for about $4.00 that is produced by Astra,
6 on the East Coast. I would venture to say it would be hard
7 for us to buy 100 cc bottle of USP product that is sterility
8 and endotoxin free for 95 cents with a human label on it.
9 MR. STRIBLING: May I add something to that?
10 DR. LEIN: Yes.
11 MR. STRIBLING: Dr. Barker, you raise a good
12 point. The fact of the matter is that most of the industry
13 is here. The question, quite frankly, and the fear that the
14 industry has, and the reason we have been screaming like
15 John the Baptist in the wilderness trying to get attention
16 is that there appears to be no stop to this. When I hear
17 Dr. Bertone say that he has 281 additional toxins my hair
18 stands on end as I think, my gosh, we can add tests till the
19 cows come home on each of those 281 toxins.
20 Dr. Duran, please, let's all understand the
21 industry has no objection to the CGMP manufacturing
22 requirements. We agree on probably 95 percent of the
23 requirements. Believe you me, as an ex-FDA-er, I believe
24 that FDA is absolutely essential for the well-being of the

American people and their animals. I am committed to that. No one wants no standards. The issue that we are raising, and the only issue that we are raising is that given the fact that in the 1990s we now have throughout the industry, with maybe one or two exceptions, a solid, safe, effective, quality product. Do we not owe it to ourselves to at least ask questions about any further requirements to say is this really necessary? And as I said in my talk, on some of them we are going to say yes but on some of them we are going to say no, and that will be amazing.

DR. BARKER: Mr. Stribling, you quoted Rev. Stanley, whether things matter or not, unfortunately, he didn't know a lot about microbiology.

MR. STRIBLING: That is exactly right, and neither do I, as you can tell.

[Laughter]

DR. BARKER: Perhaps lawyers shouldn't talk about science and scientists shouldn't talk about law, but Rev. Stanley didn't know about certain things that could have an effect and things that we know today do have an effect. Does it matter is part of the question in building quality into a product.

MR. STRIBLING: Uh-huh.

DR. BARKER: The CGMPs are intended to do what the

1 regulations require, that quality be built into the product,
2 be defined, be documented, be reconstructible so that both
3 industry and the regulatory agencies can understand what has
4 been going on, what has changed, and where a problem may be.
5 You have talked a lot about the negative aspects of CGMPs.
6 Surely the industry sees some positive aspects in this as
7 well in being able to protect itself from accusations from
8 the outside. Could you address that for me?
9 MR. STRIBLING: Dr. Barker, I thought that I had
10 addressed that on two or three occasions, both in my
11 prepared remarks and in my comments--
12 DR. BARKER: Okay.
13 MR. STRIBLING: Yes, the industry would create the
14 manufacturing quality standards if FDA didn't impose them.
15 There is no way for this industry to function without the
16 highest quality necessary. We are not debating that. We
17 are not questioning that. We are not criticizing that.
18 DR. BARKER: Yes, sir, but I am a little confused.
19 MR. STRIBLING: Let's look at specific recent
20 requirements and new requirements and ask, okay, it could
21 happen: a) what would happen if it did happen, because it
22 might not be so bad--
23 DR. BARKER: Yes, sir--
24 MR. STRIBLING: --and b) is it even likely to

1 happen or is it remote? I think that is just a way of doing
2 good business--
3 DR. BARKER: Yes, sir--
4 MR. STRIBLING: --that I think people do in every
5 area. But I agree with you, sir. I am not disagreeing, nor
6 is my Alliance disagreeing with you, nor is the animal
7 health industry disagreeing with you. There have got to be
8 standards.
9 DR. BARKER: Well, many of the specific examples
10 you listed in the letter to Dr. Sundlof, April 8, 1997, are
11 arguments against specific regulatory--
12 MR. STRIBLING: Yes, they are.
13 DR. BARKER: --requirements.
14 MR. STRIBLING: Yes, they are.
15 DR. BARKER: Not about them telling you how but
16 what.
17 MR. STRIBLING: I don't believe there is a single
18 regulation that is challenged in there, is there? I think
19 it is all how to fulfill the regulations.
20 DR. BARKER: No, there are certain things that you
21 would request basically to opt out of having to do, which is
22 not how you should do it but whether you should do it.
23 MR. STRIBLING: Right.
24 DR. BARKER: What should be done, not how it

1 should be done.

2 MR. STRIBLING: Whether you should do it the way

3 FDA has been asking it be done, yes.

4 DR. BARKER: Well, that wasn't clear in your

5 letter. But many of these things are clearly quality

6 control issues.

7 MR. STRIBLING: They are all quality control

8 issues.

9 DR. BARKER: Yes.

10 MR. STRIBLING: Of course.

11 DR. BARKER: And I am a little confused, in having

12 heard your argument, why these particular things would be

13 issues that you would take up, given the discussion of being

14 told how to do it when what is represented here is what is

15 being done.

16 MR. STRIBLING: But what is being required to

17 fulfill the requirements of the regulation is what these

18 pertain to. They pertain to what I call third-level GMPs

19 which is what does the company do in its processes,

20 procedures, methods to fulfill the requirement of the

21 regulation.

22 DR. BARKER: Right.

23 MR. STRIBLING: The issues that are in the letter

24 are issues that we believe raise legitimate questions in the

1 context that I spoke this morning, are these really
2 necessary? The question is not do they add to quality. I
3 would suggest that any test and every test and every assay
4 you could do would arguably add to the quality, but does it
5 make any difference to the quality in the real world? That
6 is what I am getting at.
7 You would be interested in knowing that before
8 sending this letter in to the Center for Veterinary Medicine
9 I had it quality controlled by sending it to the Parenteral
10 Drug Association and to a number of consultants for the
11 human pharmaceutical industry, and my question was is there
12 anything in here that doesn't pass the red-face test because
13 I sure don't want to be signing my name to it. As a result
14 of that, we have 31 items instead of more items than that.
15 I did strike some. But what I heard from PDA, and that is
16 important because the president of the PDA is the former
17 head of drug manufacturing quality at the Food and Drug
18 Administration, was all of these issues are legitimate but
19 not everybody is going to agree with you. All of them pose
20 issues that pass the red-face test. They ought to be asked
21 and, secondly, many of them are being asked in the human
22 pharmaceutical industry as well as the veterinary industry.
23 But there is not unanimity on whether an individual one
24 should be discontinued or should be continued. They are

debatable and we offer them for that. And, quite frankly, we hope that maybe as a result--if this goes anywhere with animal drugs maybe the Center for Drug Evaluation and Safety, for Drugs, whatever it is called, will wind up following suit and exercising some of the same processes and procedures.

DR. FLETCHER: Mr. Stribling, first, I appreciate your points about Uga. I have to say to you, as a University of Georgia graduate, most of us want to hold Uga to a much higher standard than just about any other dog--

[Laughter]

--my question is, I would like to have you summarize for us either the who or the process, maybe both, but the who or the process should determine what makes sense in the real world.

MR. STRIBLING: I don't believe that any one group or any one individual alone can make that decision, Dr. Fletcher. I believe that is--look, I was an FDA lawyer for ten years. I counseled vet medicine for three of those years. I drove Dr. VanHouweling nuts, telling him he couldn't do this, and the law didn't allow that, and he couldn't do this, that and the other thing. I came into private practice in 1984 and a few years ago called him and apologized for the grief I gave him because, looking at

1 things now from the other side, my background was broadened;
2 I had learned so much more; I a still an advocate for FDA
3 and for quality requirements. But I also understand that
4 there is a real world out there where you can't have
5 everything you want. So I don't believe that anyone can do
6 it. I believe, just out of my own experience, it takes the
7 requirements of people in academia. It takes the
8 participation of the regulators and the compliance folks who
9 have to work it out. It takes the industry that knows how
10 drugs are made and what is necessary. It takes the
11 veterinary profession to talk about what drugs are needed
12 and how they are to be used and where they are likely to be
13 used in accordance with the label and practice, or how they
14 are to be labeled extra-labeling. That, to me, is the fun
15 of working at FDA because no issue is single. It takes many
16 disciplines to enable the Agency to function and to do its
17 public health mandate in a way that is appropriate in the
18 real world. It is a challenging issue. It is tough to do.
19 I don't think anyone can do it alone but I think together we
20 can.
21 DR. LEIN: I think at this point, we are at eleven
22 o'clock, we have had a good discussion here, but there may
23 be some other questions but we are going to move on to the
24 other speakers in trying to stick to a time situation.

Thank you very much, Mr. Stribling, and the people that have asked questions here today. The next presentation is by the Animal Health Industry by Miss Mary Harris.

Presentation by Ms. Mary Harris

MS. HARRIS: Good morning, ladies and gentlemen. Thanks for the opportunity to appear before you today. My name is Mary Harris. I am the Director of Manufacturing Regulatory Affairs for AlPharma, Inc., Animal Health Division.

I am speaking today on behalf of the Animal Health Institute. AHI is the national association representing research-based manufacturers of animal health products. For more than fifty years AHI members have developed and manufactured pharmaceuticals, vaccines and feed additives used in modern food production and the medicines that keep pets healthy.

Through adherence to established standards, our membership builds quality into each step of the manufacturing process, producing consistent quality products. Our products support a large, diverse customer base of veterinarians, producers, consumers and pet owners. Our industry is regulated by multiple agencies, including FDA's Center for Veterinary Medicine.

Over the years we have worked with CVM to develop

a relationship of mutual respect and open communication. We believe that through dialogue the various sides of an issue can be clarified and discussed, with the ultimate goal of reaching a consensus which is in the best interests of all parties involved.

AHI conducts its deliberations and arrives at its recommendations through the use of task-oriented working groups. These working groups are formed for a specific purpose, such as to provide comments on a proposed regulation. The groups are composed of individuals from our member companies who have expertise in the particular area under consideration. They are dedicated to completing their task efficiently, using a process which provides for comprehensive input and consensus building.

To this end, AHI has found that these goals are most effectively and efficiently achieved by working with the Center for Veterinary Medicine, as well as other affected trade association groups, in a cooperative manner that ensures that the end product will meet the quality standards of all interested parties and will not result in long, contentious and unproductive standoffs.

After ten years of collaborating on manufacturing change issues, in 1995 a working group from AHI and representatives from the Center for Veterinary Medicine, as

1 well as the Animal Drug Alliance, successfully worked
2 together to reform the process for reporting post-approval
3 changes to chemistry, manufacturing and control procedures.
4 Once the new program, known as the alternative
5 administrative procedure, AAP, was finalized, a joint
6 workshop was held to educate the industry and to address
7 questions. This pilot program will enable industry to
8 implement minor changes in their facilities, manufacturing
9 and control procedures without compromising product quality.
10 At the same time, the Center for Veterinary Medicine is
11 likely to realize a more efficient utilization of its
12 resources since the number of submissions to the Agency
13 should be dramatically reduced. All of this was done within
14 the existing framework of the current good manufacturing
15 practice regulations, and it is now part of the AHI's
16 proposed regulations to implement the Animal Drug
17 availability Act which the President signed last October.
18 There have been numerous other examples of this
19 kind of partnering between industry and the Center,
20 including a pilot program to submit electronically notices
21 of claimed investigational exemptions, two flexible labeling
22 workshops, and we are currently working together to
23 standardize NADA technical section formats. Indeed, even
24 the Animal Drug Availability Act, which aims to increase

1 product availability, was the product of a coalition between
2 animal drug manufacturers, consumers and the Center for
3 Veterinary Medicine working together toward a common goal.
4 Now, we believe that it is necessary to consider
5 the impact of economics of manufacturing compliance and
6 international harmonization, the impact that these have on
7 the animal health industry. To present a single economic
8 perspective on the manufacture of animal drugs for AHI
9 member companies would be misleading. Each member company
10 has its own philosophy of what practices provide them a
11 competitive advantage. For example, most AHI animal drug
12 section member companies are a division of a larger human
13 pharmaceutical company. When both human and animal drugs
14 are manufactured in a facility synergies are experienced in
15 GMP compliance for organization and personnel, buildings and
16 facilities, equipment, laboratories, and controls for raw
17 materials, finished products, labels and distribution.
18 Such facilities cannot easily accommodate
19 differences in GMP practices for veterinary versus human
20 drugs. Implementing separate practices for animal drugs may
21 not lead to reduced product-related manufacturing cost
22 reduction. Additionally, the risk of confusion over when to
23 apply which practices would not be acceptable.
24 Now, other AHI member companies specialize in

1 veterinary drug development and manufacture. Such companies
2 may benefit from redirecting regulatory compliance costs of
3 manufacture towards development of additional indications
4 for use for existing products or for research in additional
5 species. It is important to recognize the financial burden
6 to animal drug sponsors for proving safety and effectiveness
7 of an animal drug for multiple species as distinct from
8 human pharmaceuticals.
9 The total cumulative research and development
10 expenses for discovery, development and registration of a
11 new chemical entity, including all related applications for
12 multiple species and education, is estimated at more than 15
13 million dollars.
14 AHI member companies may not clearly fall into
15 only one of these categories. Recently there has been
16 significant consolidation in our industry. Currently, an
17 AHI member may sponsor ANDAs for new chemical entities
18 requiring significant research investment, as well as
19 supplemental ANDAs to add claims, species or manufacturing
20 sites for products originally approved decades ago, and also
21 manufacture and market generic copies of pioneer products.
22 It is also important to recognize that animal drug
23 manufacturers market a variety of dosage forms which are
24 unique to veterinary medicine. With such complexity

inherent in our business, it is clear that good manufacturing practice is considered fundamental good business practice.

Another synergy that AHI member companies can experience is supplying high quality animal drugs to the global marketplace. Compliance with FDA GMPs conveys to another country's regulatory agency a good understanding of those practices and, therefore, a foreign agency may act favorably on the manufacturing dossier it receives.

Our member companies' inspectional history is available to foreign reviewers under the Freedom of Information Act. Upon request, FDA provides certificates of export to foreign governments. When a manufacturer can use a single manufacturing standard to meet the requirements of many countries the cost of manufacture can be distributed across a broader market.

Changes to FDA's quality standards could jeopardize access to foreign markets, which is contrary to the FDA Export Reform and Enhancement Act, which also was passed last year.

When FDA export legislation was enacted, U.S. animal drug manufacturers immediately benefitted. Prior to reform drug product formulations and labels had to be approved by the FDA for a manufacturer to be able to legally

ship to a country where the product was registered. Sometimes this was often impossible. Manufacturers were restricted to marketing drugs labeled for domestic use to foreign purchasers or moving production and controls outside the U.S. With export reform utilization of our production facilities in the U.S. has been enhanced, and this has the potential to lower our costs.

Additionally, when products are manufactured for a foreign market in a U.S. facility, they are usually produced in compliance with U.S. FDA GMPs. This is similar to the production of human and veterinary drugs in a single facility. It is generally most practical to comply with the higher standard rather than attempt to implement changes for exceptions.

Certainly, our access to foreign markets for animal drug products is critical to our business. AHI is an active participant in the VICH, Veterinary International Cooperation on Harmonization. FDA and CVM share this common goal with us. It is our conviction that many regulatory standards can and should be harmonized between countries. Safe and effective animal drug products that meet similar quality standards must be made available globally.

Our extensive participation in VICH is important in many ways. First, human drug manufacturers and

1 regulators have been working together for several years
2 under ICH. On the positive side, FDA has published in the
3 last year numerous ICH guidelines in the Federal Register.
4 On the negative side, areas where requirements for
5 veterinary drugs may differ from human drugs have often been
6 overlooked and CVM itself has been stretched to provide
7 resources for input into the ICH guidelines. Until VICH can
8 issue its own guidance documents the gap will be filled with
9 CDER or ICH documents which may unnecessarily restrict
10 veterinary approaches.
11 Second, many of CVM's existing guidance documents
12 are undergoing revision. Changing these documents to
13 reflect CVM's current policy must incorporate international
14 harmonization. Such revisions will conserve CVM resources
15 and provide greater benefit to the regulated industry.
16 Now, AHI believes a working group should be formed
17 to address the issues that will be identified here today.
18 This group should be comprised of representatives from the
19 animal health industry and its regulators. We believe that
20 VMAC should recommend formation of a working group to
21 clarify the interpretations of GMPs in the form of
22 guidelines, policy documents and inspectional findings which
23 interpret the GMP regulations.
24 Now we would like to propose some answers to the

1 questions that are facing VMAC today. In response to
2 question one, should FDA make any changes in its quality
3 standards for the manufacture of animal drugs, or in the
4 administrative and inspectional procedures by which it
5 implements those standards?
6 We would answer no, FDA should not make any
7 changes in the quality standards for the manufacture of
8 animal drugs but, yes, changes in administrative and
9 inspectional procedures by which FDA implements those
10 standards for animal drugs are certainly warranted.
11 For question two, if yes, what changes should the
12 Agency make? Our general suggestion will follow in our AHI
13 recommendations. Specifically, we would like to present an
14 example for each of the topic areas to illustrate two
15 important points.
16 First, the need for cooperative problem solving
17 between the industry and its regulators. Second, these
18 examples illustrate some very diverse interpretations of
19 policy as it has been applied to our individual member
20 companies. These interpretations need to be clarified
21 through dialogue between industry and CVM.
22 Let me emphasize that these examples are anecdotal
23 and are not meant to represent the collective opinions of
24 all AHI member companies, nor do they represent AHI policy.

On the issue of sterility, the CDER guideline on sterile bulk drugs does not reflect real-world practice. The requirements to be able to perform media fills or process simulations in a bulk plant plan is not in line with the capability of that type of process. The difficulty in performing a simulation and in interpreting its results is far greater than the probability of non-sterility of the product itself. It adds nothing to the quality of the product, but does add greatly to its cost. It is especially difficult in existing plants that were not designed for this.

Many veterinary antibiotics, such as penicillin, are produced in existing, often older, plants and are low cost options in the veterinary market. This market is not well served by raising the sterility assurance requirement and making existing alternatives either more expensive or completely unavailable.

As another example, new animal implant products are required to be sterile, but both past experience and grandfathering indicates that the requirement is not necessary. Furthermore, intra-mammary infusion products fall into this same category.

When considering the container closure integrity of a sterile product, the nature of the product itself needs

to be considered, including its antimicrobial efficacy properties. Flexibility needs to be employed in the insistence for one standard for container closure integrity.

Regarding validation, validation is a valuable and necessary process. However, it has been applied in places where it does not contribute to end product quality. Focusing our efforts on areas where it has the most value would benefit industry. The Center should allow flexibility in evaluating a company's choice of a validation method.

In the animal health industry we have many small volume products. These are very difficult and expensive to validate according to current standards. Since the cost of validation is distributed over a very small number of units and production volumes may only be one batch per year, the high cost of developing and validating these products may be prohibitive.

Now, FDA's compliant program guidance manual pre-approval inspections contains a statement in part 5, regulatory administrative strategy, which indicates that examples of significant problems include, but are not limited to, validation of processes not completed for the drug product in the application. This is in contrast to a recent FDA guidance which indicates that process validation does not need to be completed prior to the pre-approval

1 inspections. Furthermore, the guidance document states the
2 validation data is rarely submitted in applications. Yet,
3 with more frequency we are being asked to provide such data.
4 The Center for Veterinary Medicine, in conjunction with
5 other areas of FDA need to review and, if appropriate,
6 revise the guidance documents. It also must be made clear
7 what the expectations are with regard to validation because
8 we believe that various districts interpret the guidance on
9 process validation quite differently.
10 In the area of clinical supplies, the need for
11 adherence to good clinical practice, good laboratory
12 practice and good manufacturing practice requirements for
13 the manufacture of clinical supplies used in pivotal animal
14 drug studies is clearly understood. However, if these same
15 practices are imposed on the manufacture of clinical
16 supplies for studies early in the development of a new
17 animal drug, the development of new compounds for animal
18 health will surely suffer.
19 Now, for human drugs full GMP controls, such as
20 formal analytical method validation and equipment
21 qualifications, are expected at the start of Phase III
22 clinical trials and long after the Phase I safety and Phase
23 II safety and efficacy. In animal drug development pivotal
24 target animal safety and efficacy trials commence

immediately after preclinical work and are often performed concurrently. Cooperative programs between industry and CVM in the issuance or revision of pertinent clinical manufacturing guidelines or compliance policy documents would better serve the public health than would revisions to, or additions to existing manufacturing regulations. The expectation for full GMP controls, like those for approved products, for developmental studies is unnecessary.

Regarding facilities, utilities and equipment, FDA's proposed changes to GMP regulations in 21 CFR, 211 would remove the exemption which currently exists regarding the need for dedicated facilities for penicillin-containing drugs. We are not aware that control of contaminants, particularly penicillin, has been a significant problem that would warrant removal of this exemption. A cooperative approach with CVM to retain this exemption would be preferred to a change in the regulations.

Regarding components, potable water is not needed as the minimum makeup for all fermentations. Many fermentation raw materials are complex and unrefined, such as lime salts, cotton seed protein, lard, oil, etc. The use of highly purified water with these materials does not improve the safety or efficacy of the final product.

Regarding analytical testing, the AAP program

allows for implementation of minor changes to methods which do not alter their performance. This is another area where the requirements for filing supplements for prior approval had inhibited innovation and improvement. However, the AAP program has addressed many of these concerns in a positive manner.

As to question three, what information does the committee need in order to answer the previous questions? We believe that VMAC needs a great deal of additional information. The information would be best developed in a forum different than the one we have today. GMP practices could benefit from more practical guidance from CVM which is specific to animal health products. With a comprehensive set of guidance documents, consistency by field inspectors would be more likely to occur.

The VMAC should also consider the global aspects of the business. International regulations and guidelines will undoubtedly play a major role in the future of our business. And by virtue of sheer size and economics, the animal drug industry and its regulators will be left in the dust of the human drug industry and its regulators if we don't unite together toward a common goal. Currently, we have to live with some human drug guidelines for which we had no input during their development. This is despite the

fact that our products and patients are much more diversified.

We should be trying to find a way to work for our industry concerns to be heard in early stages of human drug guideline development that may adversely affect our business. We should be in a position to negotiate regulatory concessions, for example, for medically necessary products. If we fail to work together we are all going to lose.

I would like to thank the VMAC members for your attention to our concerns and recommendations. You have a big responsibility and we look forward to you for sound guidance. I know you share our goal of providing safe quality products for pets and farm animals. Thank you.

DR. LEIN: Thank you. Are there questions for Mary Harris from the committee?

DR. GERKEN: I have a question.

DR. LEIN: Yes?

DR. GERKEN: You state in the second to the last page that this information would be best developed in a different forum, other than the one we have today. Are you making a suggestion? Do you have a suggestion what kind of forum would be the most advantageous to get additional information?

1 MS. HARRIS: Well, I don't mean to disparage the
2 supplementary information that you have. That is very
3 valuable. But we have been working with the Center in a
4 workshop. We have been exchanging paper for a long time.
5 We really feel like a workshop where the technical experts
6 exchange their anecdotal experiences and come to a common
7 understanding of the practical limits and the regulatory
8 restrains is the best forum. Did I answer your question?
9 DR. LEIN: Other questions? Do we know what is
10 happening at least globally with these regulations? Is
11 there a format that is evolving that you can see at this
12 point? Maybe, Dr. Blackwell, would you know that or would
13 someone in the audience know that?
14 DR. BLACKWELL: Dr. Sharon Thompson is our lead in
15 this area, and I will ask for her to come forward and
16 comment.
17 DR. THOMPSON: Hi. With respect to the GMPs and a
18 format, okay, well, there is not an international format for
19 GMPs at this time. What was referenced earlier by the
20 speaker from AHI was an initiative that is going on, the
21 VICH. That is to develop specific requirements for parts of
22 the GMP, like stability testing requirements. So we have a
23 group that is looking at what has been done for human
24 pharmaceuticals with respect to the ICH and seeing whether

1 those can be adopted for veterinary products with some
2 modifications. That initiative is trying to develop an
3 international standard per se for veterinary products with
4 respect to GMPs.
5 There are other exercises that are going on.
6 There is some talk about eventually looking at GMPs as a
7 whole in the ICH. That is the International Conference for
8 Human Pharmaceuticals. There has not been a decision yet
9 whether they will take on the broad issue of GMPs and try to
10 develop an international standard.
11 But right now, pretty much, my understanding is
12 that the requirements in the U.S., the FDA GMPs are very
13 compatible with those in the European Union. They are
14 pretty much identical. So any changes made to our
15 requirements would put us on a non-level playing field. I
16 don't know if that answered your question. Does that help?
17 DR. LEIN: It does. On the industry side, is
18 there anything happening? As we look--as I look at what is
19 happening with industry and mergers, some of these are
20 pretty well worldwide. I would expect they are playing a
21 role in what is being developed in several of the
22 governments. Is that true or not?
23 MS. HARRIS: Yes. I would call on Ken Stank, if
24 he is in the audience, to respond on the international

harmonization issues.

DR. STANK: My name is Ken Stank. I work with Eli Lilly and represented the Animal Health Institute in a recent VICH process, meeting in Tokyo this past March. Bill Marnane participated in that meeting as well as a representative for the CVM.

I think it is a good process. It is looking at the development of new drugs primarily, not necessarily working with the good manufacturing practices as they relate to established products. But I think we have to make a start some place. I think the end result of this whole process is that it is going to reduce the cost of drugs around the world. We won't be duplicating effort. So it is good; the whole idea is good.

The problem we face, representing industry here, in the United States, the animal health industry, is that, unfortunately, the ICH guidelines are out in front and the charge to our VICH group is can you make these work? I felt extreme pressure during those meetings to adopt the ICH guidelines despite the fact that in many instances we highlighted a number of issues that we felt were not really appropriate for veterinary animal drugs. That is a difficult process. The European regulatory group seems intent on adopting human drug and animal drug standards in

1 the same manner, and part of that is driven by the fact that
2 their reviewing agency deals both with animal and human
3 drugs. So it is a lot easier for them to have one standard
4 in front of them and they don't have to distinguish them in
5 treatment for these different kinds of drugs.
6 So apart from that, I would just comment that it
7 would be nice, as Mary has indicated if we could be involved
8 in the ICH process earlier on to provide some input from the
9 animal drug perspective. I feel that would be very, very
10 helpful. That is not happening today. And I know that the
11 CVM would perhaps like to participate in that process early
12 on as well but, because of resources, they just don't have
13 the time or the resources to be able to do that. That is
14 the criticism that I would have of that process but, again,
15 we are doing the best we can and at the end of the day I
16 think we are going to end up with something that is going to
17 be acceptable for all concerned.
18 DR. LEIN: Thank you.
19 DR. THOMPSON: Can I make one comment just to
20 clarify something with respect to the comments that were
21 made? It might be helpful. With respect to the fact that
22 CVM I think wasn't interested or didn't have the resources
23 to participate in the ICH, I don't think that that is really
24 very accurate. Early on we were very interested in trying

1 to modify the ICH, the human exercise, to also include
2 veterinary products and there really wasn't interest on the
3 part of the ICH overall management in broadening that out to
4 include animal products. So we basically made the effort to
5 basically start a similar exercise for veterinary products,
6 the VICH. Part of the exercise, as Bill Marnane can attest
7 to, is to look at what is done for the human products and
8 see whether we should adopt that for veterinary products.
9 That includes trying to look at the requirements and seeing
10 if those can be eliminated or reduced for veterinary
11 products if they are not appropriate. So that is just to
12 clarify.
13 MS. DURAN: Just backing up a little bit, what
14 concerns me more than worrying so much about standards, and
15 like the gentleman over here who is trying really hard and
16 expressed with great passion that he is trying to do a
17 really good job, what concerns me is we have all these
18 products on the market that say "for veterinary use" that
19 are not approved. And I don't want to buy products that I
20 don't know what they are. Now, how is it legal that someone
21 can manufacture a drug and put it on the market and sell it
22 to veterinarians and consumers without ever going through
23 any approval system?
24 DR. LEIN: Dr. Dunnavan? I don't think it is

legal.

MS. DURAN: So I guess I had better go home and start making a list.

MS. DUNNAVAN: There are products out there that have not gone through the premarket approval process. But they are drugs under the Act that can be marketed but they are subject to the good manufacturing practices requirements. Whether they have gone through the approval process or not, they have to be manufactured in conformance with GMPs. So what CVM has not attempted to do in the pre-approval process is deal with these up front for products on the market. But whether it has gone through the approval process or not, it still should be manufactured in conformance with good GMPs.

DR. LEIN: Joe, you were going to comment?

DR. GLOYD: Yes, I think this was not a GMP issue at the time but I have to tell you that FDA's own figures a number of years ago said there were 17,000 veterinary drugs out there on the market that had not been approved by FDA. However, that only constituted something like less than one percent of the total veterinary drug market, and they were considered drugs not to be of regulatory concern. So that is certainly an issue but I don't think it is a GMP issue today.

1 DR. LEIN: Yes, Dr. Blackwell?

2 DR. BLACKWELL: I just have to add that the Center
3 believes that in an ideal world all products on the market
4 will have a legal status. We also are quite cognizant of
5 the fact that there is no one solution to what we see before
6 us today. For example, there are entire product classes
7 where unapproved products have been marketed, and if we were
8 to take actions to stop the marketing of these products it
9 would create voids, putting at risk, of course, the medical
10 care of animals. So that is clearly not an acceptable
11 approach.

12 There are products, however, on the other end of
13 that spectrum which are competing with approved products,
14 and those are a bit more of interest to us in the near term.
15 So we are currently now trying to address how to best fix
16 the problem, and that fix will not always--at least this is
17 what I anticipate, will not always occur by the traditional
18 approach. There are probably product classes that could
19 reach some kind of legal status without the very lengthy
20 regulatory process that currently is in place. That will be
21 based still on data. We need to have information before us
22 to reach a decision that the product should have
23 marketability as a legal product. But the question is will
24 this require the traditional approach of requiring certain

1 studies be done and the whole nine yards. In some cases the
2 answer would be yes. We are seeking creative ways to
3 address other instances where we might be able to find a
4 different way to approach it.
5 DR. LEIN: Other questions? Yes?
6 DR. BARKER: Miss Harris, on page 6 of your
7 handout for your talk, is it your opinion that FDA should
8 not make any changes in the quality standards for the
9 manufacture of animal drugs? Correct? But the changes
10 should come in administrative and inspectional procedures.
11 What seems to be the problem with the inspectional
12 procedures? Inconsistency in interpretation?
13 MS. HARRIS: Yes, I think it is a variation
14 between districts interpreting the GMP regulations and
15 policy documents differently so that a manufacturer in one
16 district may not have the same application of the
17 regulations as a manufacturer in a different district. That
18 is one of the areas of concern.
19 Also in the review areas. Without a written
20 guidance document, manufacturers can't be certain that their
21 applications are being reviewed to the same standards as
22 another sponsor's applications are. So what we would really
23 like to see is some written documents so that we can know
24 what to expect in these reviews and in the inspections.

1 DR. BARKER: And in inspections where, let's say,
2 a 483 is issued you have the opportunity to defend that
3 interpretation by that inspector with the FDA. Is that
4 process inadequate?
5 MS. HARRIS: No, it is not inadequate to the firm
6 that is being inspected and that inspection incident. I
7 think where the inadequacy comes in is in informing the rest
8 of the regulated industry that this is a standard that needs
9 to be met, or that this is a 483 finding that should be
10 challenged. It is a communication issue.
11 DR. BARKER: But in a society of quality assurance
12 there is a lot of argument about interpretation of a
13 regulation among the very professionals that exist in both
14 private industry and in government. So there has to be, of
15 course, some recognition that that is going to occur. I
16 guess the best process is that on that occasion, where you
17 have the opportunity to defend your interpretation of the
18 regulation, as long as it has no outcome on the quality of
19 the product that FDA would want to have mechanisms to
20 provide the flexibility needed to interpret that.
21 MS. HARRIS: I believe that exists. That
22 flexibility does exist.
23 DR. LEIN: I think we need to move on. The hour
24 is getting short and we want to give Dr. Gloyd time for his

presentation. Dr. Gloyd is fro AVMA.

Presentation by Dr. Joe Gloyd

DR. GLOYD: Yes, that is true, I am from AVMA. I am an AVMA staff member. Those of you who are veterinarians and paying your dues to AVMA are among my 59,000-plus bosses.

I have been asked today to address the issue do good manufacturing practice requirements affect animal drug availability. And there is a short answer but I am not going to give you that one--

[Laughter]

Also, I appreciate being invited here. This is my first experience of being invited as a speaker. In the past I have taken the opportunity to avail some of you with my thoughts, whether you wanted to hear them or not. But I really appreciate this.

One of the things that I am concerned about is that, in an attempt to meet the requirements of the paperwork reduction act, some of your packets may only contain every other page of my handout--

[Laughter]

--so we will try to remedy that later on. To proceed here, my friend, Dr. Joe Bertone, recently conducted a survey of practitioners across the United States, asking

1 the question should animal drugs be manufactured using the
2 same criteria that are required for human drugs? Well, I
3 saw that survey and I expected that probably the way the
4 questions were asked the answer would be yes, and it was.
5 So I will tell you about that later.
6 At first blush, it would seem that these criteria
7 should be applied across the board for animal and human
8 drugs. But when the effects of applying these criteria to
9 all animal drug manufacturers are measured, the majority of
10 veterinary practitioners would probably change their minds.
11 Although the Bureau of Veterinary Medicine, which was the
12 predecessor to the present Center for Veterinary Medicine,
13 began in the late 1970s to require injectable animal drugs
14 to be sterile and pyrogen free, the actual enforcement of
15 rigid GMP requirements did not occur until about 1990, and
16 you have heard that before.
17 Incidentally, the CVM proposal to require
18 veterinary injectable to be pyrogen free was met with strong
19 opposition by at least two well-respected veterinary medical
20 college faculty members, one at the University of Minnesota,
21 the late Larry Stowe, and one at Colorado State University,
22 Bob Phillips. Both of them sent letters of protest to FDA
23 based on their personal knowledge, research and experience.
24 In the years since FDA's field inspectors began

1 requiring animal drug manufacturers to meet GMPs that are
2 required for manufacture of human drugs, a number of animal
3 drug products have either disappeared entirely from the
4 marketplace, are in short supply, or have been temporarily
5 unavailable, only later to be back on the market at a much
6 higher price.
7 I am going to mention a few examples of products
8 that have been affected adversely in terms of availability
9 because of manufacturing requirements.
10 First, injectable iron. Prior to the enforcement
11 of GMP criteria, this inexpensive product was available from
12 a number of manufacturers. In 1991 several manufacturers
13 were forced to cease production because they did not meet
14 the GMP requirements. For nearly two years this injectable
15 product was unavailable, resulting in substantial economic
16 loss to the swine industry, not to say anything about animal
17 deaths and suffering. When the injectable iron supplies
18 were again available the price was two and a half to three
19 times the previous cost.
20 Thiamylal sodium, this anesthetic drug has been
21 unavailable since 1993. The remaining supplier of that
22 product voluntarily recalled its products effective in June
23 of that year. According to the information we have received
24 from CVM, and I am quoting, previous inspections in 1990 and

1 '91 had found GMP deviations, including deficiencies in the
2 validation of aseptic filling operations and environmental
3 testing. That same letter from CVM indicated that the
4 adverse reactions reported, and I will quote, were not of
5 magnitude and seriousness to characterize it as an unsafe
6 and ineffective product when administered per FDA-approved
7 label directions.
8 Now, obviously, there are alternative anesthetic
9 agents available and they are being used. But a product
10 that was considered by many veterinary practitioners to be
11 safe, effective, convenient and inexpensive is no longer on
12 the market.
13 Penicillin, that has been mentioned before. Once
14 again, a product previously available from a number of
15 sources is now available from only three manufacturers at a
16 cost of around five times what it sold for prior to 1990,
17 when it was available from a large number of sources.
18 PZI insulin, previously available as a human
19 product produced by Eli Lilly, the firm ceased production of
20 protamine zinc insulin in 1991. Subsequently, Eli Lilly
21 transferred its manufacturing rights to a California firm
22 which has been frustrated continuously by GMP requirements
23 for validation of pyrogenicity and sterility requirements.
24 The firm has apparently been making the product

available free of charge to some thirty-seven university research institutions. However, the supplies have run out and the product is no longer available to those institutions, and I think that happened at the end of March.

According to a representative of that California firm, data from research institutions show that the non-GMP produced product has been used for 36,000 clinical days in research animals without causing an abscess. The same individual reports that he fielded forty-seven calls from practicing veterinarians in a two-week period requesting PZI insulin. Of course, those requests were not filled.

A letter from CVM states that the majority of individuals contacted believed that PZI insulin was "a nice to have product" rather than a medically essential one, and that the product would not be missed to any degree. Ironically, one of the FDA-contacted individuals who believed insulin wasn't a medical necessity was working on a project to evaluate a non-insulin substitute for treatment of diabetic cats.

A CVM letter to AVMA also states, and I will quote again, it would be a mistake to potentially jeopardize the purity and potency of a delicate, highly bioactive compound that has such exacting production standards. If a sponsor wishes to obtain approval of an insulin product for small

1 animals, that product must be an exact copy of the Eli Lilly
2 product in potency and purity. It could be that the Center
3 for Veterinary Medicine has received some different messages
4 lately.
5 Follicle stimulating hormone, or FSH. For a few
6 years there was a labeling controversy between two
7 manufacturers of FSH. One firm had marketed the product for
8 a long time with a label stating that it was to be used for
9 FSH deficiencies in a number of species. Later on another
10 firm received approval for the same drug labeled for
11 inducing superovulation in cattle. The second firm argued
12 that it was against the law, as spelled out in AMDUCA, for
13 practitioners to use the first firm's drug for inducing
14 superovulation because that drug was not labeled for that
15 particular use. The first firm then experienced problems
16 meeting GMP requirements for producing their product and
17 subsequently ceased production.
18 That may have solved the problem between the two
19 companies but, unfortunately, for practitioners the second
20 firm's drug did not meet expectations of efficacy by
21 practitioners who were using t he drug. There are
22 anecdotes, probably are all untrue, that some individuals
23 were importing an FSH product from outside the United
24 States, and also purchasing the second firm's product. Then

when the imported product was used for embryo transfer, the records would show that the U.S. firm's product was used when it actually was dumped in the garbage can. That is probably all not true.

[Laughter]

Several other injectable animal drug products continue to be in short supply, primarily, according to veterinary product distributors that we have contacted, because that California manufacturer has been the source of their injectable animal drugs.

Some of the products that have been called to our attention include adrenocorticotropic hormone or ACTH, atropine, furosemide, amphetamine, 100 ml dexamethasone, phenylbutazone, vitamin B complex and oxytocin. These products all require sterile water in their manufacture, and the validation of sterility and non-pyrogenicity according to GMP standards is the nub of the problem.

This problem has been unresolved for at least three years. Just recently we learned that companion animal practitioners cannot obtain diethylstilbestrol pearls for use in treating urinary incontinence in spayed bitches. Apparently the source of the raw material has dried up. Whether this is related to GMPs or not is yet to be determined.

What is the net result of drug shortages due to lack of compliance with GMPs? Is the cost of compliance comparable to the benefits derived? Some drugs, such as thiamylal which was used safely and effectively in many veterinary practices, may never again return to the market. Others may be available from other sources but, because of lack of competition and increased production costs, the price of those products will rise or has already increased.

Another factor in the GMP criteria issue is that of human drug products that are no longer marketed. An April 10, 1995 notice in the Federal Register listed 107 abbreviated new human drug applications that were being withdrawn. How many of these generic products which are no longer marketed may have had applications in companion animal medicine? One might ask whether these products will be forever lost to the veterinary clinician, or if they are available will they be cost effective for use?

The Center for Veterinary Medicine has long insisted that economic factors cannot be considered in the animal drug approval or manufacturing process. If that philosophy is a legislative mandate and not just an FDA-generated policy perhaps it is time for new legislation.

In the long view it may be concluded that applying GMP criteria to all animal drugs is harmful to animal

1 populations, both in terms of lack of availability of needed
2 products and in terms of drug costs that are so expensive as
3 to preclude the proper treatment of animals.
4 There are other factors that also should be
5 considered. What effect do GMP criteria have on the amount
6 of pharmaceutical compounding by veterinarians and
7 pharmacists and perhaps others? Do GMP criteria contribute
8 to drug costs that encourage black market or homeopathic
9 remedies? That may be a little bit of Sue's comment.
10 The concept of developing separate GMP criteria
11 for animal drug products appears to have a great deal of
12 support from organizations, including AVMA. In a December
13 12, 1995 letter to Steve Sundlof the AVMA wrote, the AVMA
14 believes that separate criteria could be established for
15 animal drug CGMPs that would not be deleterious to safety or
16 effectiveness of the products, but could allow more
17 flexibility in the process. We hope CVM will proceed with
18 development of criteria that would allow continued marketing
19 of time-tested, clinically effective and necessary limited
20 use animal drugs.
21 We understand that the current Senate
22 Appropriations Committee report to a company in 1976
23 contains language asking FDA to develop separate GMP
24 criteria for animal drugs. We believe our request is in

1 keeping with the intent of the Senate Appropriations
2 Committee.
3 In a 1992 document, titled, "Animal Drug
4 Availability: Current Impediments and Recommendations," the
5 Animal Health Institute included a recommendation for
6 attenuation of manufacturing guidelines, and you have heard
7 Mary speak to that subject.
8 The Animal Drug Alliance that Jess is representing
9 has in the past attempted to introduce federal legislation
10 to accomplish a change in GMP criteria for animal drugs. I
11 don't believe he mentioned that.
12 And, of course, the U.S. Senate Agriculture
13 Appropriations Committee in its report on the FDA's budget
14 allocation for fiscal year 1996 stated, and I will quote
15 this, the committee expects the FDA to establish, where
16 appropriate, current GMP requirements for animal drugs
17 separate from requirements applicable to drugs for human
18 use. If two trade association groups, a professional
19 association and a congressional committee are all urging
20 that GMPs for animal drugs be separated from the
21 requirements for manufacture of human drugs, it would seem
22 that the time for change has arrived.
23 The key concept, of course, as has been mentioned
24 previously, seems to be flexibility in the process. The

AVMA would certainly not object to allowing manufacturers the option to adhere to human drug GMPs, but there is a definite need for flexibility in GMP requirements for those small drug manufacturers.

Veterinarians who are members of AVMA often blame the Association for failing to resolve the problems that they are experiencing. For example, several veterinarians elected to drop their membership because thiamylal had been removed from the market and AVMA had failed to prevent it. One veterinarian wrote, where was AVMA when Biotal was pulled? We are snowed under by government fees and regulations, many of which are supported or even asked for by AVMA. I have some problems with that but, anyway--

[Laughter]

The vast differences between the human and animal pharmaceutical businesses, wherein animal drug and biologic market is less than five percent of the human market, have played a role in the emergence of a number of animal pharmaceutical firms. Without a change in the GMP requirements, it soon may be that only a few remaining major firms can afford the equipment necessary to meet those criteria.

A few years ago FDA issued a proposal that, if finalized, would have required all injectable animal drugs

to be subjected to terminal sterilization. After receiving some considerable negative feedback on that proposal, it was dropped. Some individuals associated with industry have speculated that GMP enforcement is another way of invoking terminal sterilization requirements.

As demonstrated by many of the questions that some of you previously asked and by the examples provided by Jess and Mary, unequal enforcement of FDA's regulatory requirements is a constant issue. The question of how uniformly GMP requirements are enforced by FDA inspectors is another concern of some small manufacturing firms who continue to have problems meeting the expectations of individual inspectors, and I suspect that you are going to hear from at least a couple of those this afternoon.

Now, that perception may persist, that changing GMP requirements for animal drugs would somehow dilute the quality, purity, safety and effectiveness of those products. That is not necessarily true. The AVMA believes that changes in the process can be made without significantly adversely affecting the final product. The present situation, I believe, will in the long-run result in decreased animal drug availability, evoke hardship on drug manufacturers and animal owners and ultimately damage the health and well-being of the animals themselves. Clearly,

1 something is wrong and it needs to be fixed. Thank you.
2 DR. LEIN: Questions for Joe? Yes, Dr. Wolf?
3 DR. WOLF: I guess just a couple of
4 clarifications. First, in the case of thiamylal, you
5 indicate that the manufacture was out of compliance in 1990,
6 1991 and they finally pulled the product in '93. I assume
7 the manufacturer was aware of this problem? Were they, or
8 were they not making efforts to comply?
9 DR. GLOYD: I think there was a problem with the
10 raw material that came to them and where it didn't meet the
11 requirements, the raw material that went in. You heard some
12 examples.
13 DR. WOLF: So, in other words, they really had no
14 control over the raw material that was coming to them?
15 DR. GLOYD: Yes.
16 DR. WOLF: So that was the major problem.
17 DR. GLOYD: That was the problem but, at the same
18 time, the same raw material had been used for--I don't know
19 how many--years that thiamylal has been approved and, by
20 FDA's own admission, there were no real-world problems with
21 the use of that drug, and I think that is the important
22 point here.
23 The other part of that is that there are thousands
24 of kilograms of that product lying in a warehouse some place

that will never be used unless there is some way to allow it back on the market.

DR. WOLF: One other question, clarification on the PZI insulin, that 36,000 research animal days without an abscess, as I understand it, those are rat and mice days, not dog and cat days for which the product is intended to be marketed. Just different species.

DR. GLOYD: I don't have that kind of information.

DR. LEIN: Other questions? Yes, Dr. Koritz?

DR. KORITZ: Joe, on the injectable iron, do you know what GMP requirements were not met by those products?

DR. GLOYD: No, I don't, but I do know that they were taken off the market because of GMP problems.

DR. LEIN: Can anyone answer that question?

DR. GLOYD: We don't know the specifics; we sure know that it happened.

DR. LEIN: Other questions for Joe? Yes, Dr. Kemp?

DR. KEMP: Joe, on this list of products that are no longer available, except for the amphetamine, I believe they are all available. I am having absolutely no trouble stocking them in my pharmacy. ACTH has gone to a more concentrated form in the 40 unit but is this an accurate list? Do you still think there are problems with them?

DR. GLOYD: There are certainly problems with the manufacturer out in California.

DR. KEMP: But they are available?

DR. GLOYD: Yes, they are available from other sources. I will return the question to you, sir, has that price increased?

DR. KEMP: No. Mine hasn't. You know, I have not seen this massive price change you are talking about. The price change, as was mentioned earlier about lidocaine, they used an Astra price, which is obviously the Cadillac and the highest price on the market against a veterinary product. We can buy human generic for a whole lot less than the Astra product. I am not seeing the big price changes that are being mentioned out here so I am a little confused on some of what is being stated.

DR. GLOYD: Well, I am too because practitioners are certainly reporting an increase.

DR. STERNER: Supplies of phenylbutazone are currently on back order.

DR. KEMP: That is the tablet.

DR. STERNER: Right.

DR. KEMP: Okay, the tablets. Most of these things I think are back on the market, although we did have some problem with atropine for a while. For some of the

other products I am just not sure if this is a current problem or a past problem.

DR. LEIN: Yes, Dr. Blackwell?

DR. BLACKWELL: I just wanted to emphasize, as we look at a list such as the one that has been offered, that we be reminded that the regulatory process requires that companies present information indicating their ability to market a quality product, and an approval results based on that information. The real world being what it is, these conditions will change. Sometimes the raw material is no longer available or they go to a new supplier. What is required then, of course, is to validate that the product is still going to meet the standard for which it was approved.

So whether a company for business reasons decides to do that, I believe, may be a different question and I personally take a bit of an exception when it is characterized as the FDA's requirements driving products off or taking products off the market. These are not issues where the standard changed at all. These are issues where other conditions changed, resulting in a business decision in some cases to no longer market the product.

DR. GERKEN: That is the question that I have. Dr. Gloyd, how many of these products were taken off because of this change that may have occurred in 1990 that resulted

in veterinary drug GMPs being the same as human drug GMPs? Or would these products have been taken off just because they didn't meet the veterinary GMPs, if you will, because of the general standards? Can you answer that question?

DR. GLOYD: I can't answer it directly but I can certainly tell you that prior to 1990 those products were available from a number of firms and they all shut down for a while, and now they are back on the market, but only three of them.

DR. GERKEN: Yes, but that is not direct evidence that it was the result of the change or the increased standards. They may have been taken off because of just what Dr. Blackwell said, that the product that was being purchased by the company was no longer the same as before, or there was some other manufacturing problem. I am just asking--

DR. GLOYD: You certainly may be correct, but we have had two previous speakers who have indicated that in 1990, that is when the GMP requirements for veterinary drugs were invoked to be the same as human drug requirements.

DR. GERKEN: Yes, I recognize that. I just wanted to know how many were casualty to that particular change.

MR. STRIBLING: Dr. Gerken, the only one that I can speak to with some knowledge is the iron dextrin. When

there were three manufacturers, one of the manufacturers might have been in the category that Mr. Schinze mentioned of companies that should have been shut down ago. But one of the manufacturers was a member of both the Animal Health Institute and the Animal Drug Alliance, and a manufacturer that had been compliant with everything and then suddenly got caught up in the new requirements.

DR. GERKEN: Thank you.

MR. SCHINZE: The issue for sodium thiamylal and tribrissen product from Cooper was an assessment based on GMPs, claimed by the Kansas City District, not able to be validated to be sterile. So it was a catchup from what took place in 1990, '91, and they were both regarding sterilization validation.

DR. LEIN: I think Sue had a question, and then Dr. Fletcher.

MS. DURAN: I wanted to mention, some of these products that I am purchasing on the list, some of those products have fallen in the category that they don't have an NADA number but they are filling the void I think.

DR. FLETCHER: Joe, I want to ask you sort of a process question. AVMA I think has a council on biologic therapeutic agents, and my question is, has this issue been discussed by that council or any of the other councils of

the AVMA, and what recommendations have come from groups like that?

DR. LEIN: Deja vu.

DR. GLOYD: I might ask Dr. Lein that question. He has been Chairman of the Drug Advisory Committee--

DR. LEIN: I certainly have, sat and gone through this same repertoire we are going through now. Actually, letters have gone to CVM FDA over this concern and Animal Health Institute. Animal Health Institute also is a consultant to COMTA and the drug advisory group. So, yes, there has been a lot of discussion and a lot of concern.

DR. BLACKWELL: I would like to also ask that the committee look forward to a presentation this afternoon by Dr. Bataller having to do with medically necessary veterinary products. The point being, the Center does now have a policy and a process whereby we will try to find ways to address what appeared to be impending shortages or actual shortages which have occurred. Those solutions may reside in a shift in our application of certain standards or the approval process itself and taking an expedited track. We will become very proactive under those circumstances with companies to try and have the shortage situation addressed.

So, the point being here, I think that although I alluded to the reality that things happen and those things

may result in shortages, we do, in fact, try to be responsive and address them.

MR. MARNANE: My comment was going to be quite similar to what Dr. Blackwell just addressed.

DR. LEIN: I think both of you really sort of brought that out in your presentations too this morning. Yes, Steve?

DR. BARKER: As far as the drugs that are on the list, shortages in the State of Louisiana are not being experienced. These all show up in the race horses in the state.

[Laughter]

DR. LEIN: That has an international trade though that we don't all have.

DR. BARKER: Of course, selling beanie babies as an intentional shortage is always a concern--

[Laughter]

You noted in your discussion that there have been congressional actions that are, I assume, directing the FDA to enact what you are requesting.

DR. GLOYD: That is correct.

DR. BARKER: What is the FDA doing? Have any of these become law, or are they something that you are just going to address based on a resolution?

DR. LEIN: We should recognize Steve Sundlof has arrived. Welcome, Steve.

DR. SUNDLOF: Thank you, Mr. Chairman. In response to the question of what have we done in regard to congressional mandates that we address this issue, well, this is part of it. In the 1996 budget appropriation the language from the House of Representatives, through the Agriculture Appropriations Committee, suggested that we look at the issue of GMPs for animals and where those could be different, to try and start looking at that process, and this is all part of that. So what you are doing right now is in one way in response. It is certainly not the only reason for this. We also recognize that there are some differences of opinion and we wanted to get those out on the table.

DR. LEIN: Further questions? I think we have run over about 15 minutes--not too bad for the type of discussions. I want to thank everyone for keeping on time as well as we did and for the presentations and questions this morning.

[Whereupon, at 12:15 p.m., the proceedings were recessed, to be resumed at 1:15 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. LEIN: The presentations this afternoon will deal first with chemistry, manufacturing and controls, an FDA perspective to begin with, and the first speaker this morning again will be Mr. Bill Marnane.

Chemistry, Manufacturing and Controls, Bill Marnane

MR. MARNANE: First of all, I would like to once again point out to the Veterinary Medical Advisory Committee that the narrative that I have provided you refers to specific portions within the big book you have received. You know, at some future time you may wish to refer to that.

(Slide)

This morning we heard a number of criticisms regarding the application of the current quality standards to animal drug products. Essentially, what we will be doing this afternoon, at least what FDA will be doing, will be trying to reply or provide a perspective on many of these issues.

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This presentation that I will be giving will cover many of the general issues pertaining to CMC, or chemistry, manufacturing and controls, and CGMP quality standards which have been brought to our attention.

These issues include the issue that CVM objected

to inclusion of veterinary drug products in a proposed amendment to the CGMP regulations that would have required sterile human and animal drug products to be terminally sterilized rather than aseptically processed, and that the Center was not provided the flexibility to be exempted from this CGMP requirement.

Secondly, I will discuss the issue that when the economics of the human and animal drug industries are compared, it makes no sense to impose the current quality standards on animal drug products.

(Slide)

Thirdly, I will discuss the issue that there was a sudden change in the application of human drug CGMP requirements to animal drug products.

Lastly, at least as part of the planned talk, the issue that in light of full initial equipment, process and product validation, some in-process controls with some of the finished product testing requirements would no longer be necessary to assure animal drug product quality.

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Again, the first issue that CVM objected to inclusion to the proposed rule-making and was not provided the flexibility to be exempted from that rule-making. Indeed, the Center for Veterinary Medicine attempted to be

1 exempt from a proposed amendment to the CGMP regulations.
2 The proposed rule, entitled, "Use of Aseptic Processing and
3 Terminal Sterilization in the Preparation of Sterile
4 Pharmaceuticals for Human and Veterinary Use," was published
5 in the Federal Register on October 11, 1991. This proposed
6 amendment would have required that human and animal drug
7 products be terminally sterilized rather than aseptically
8 processed when possible.
9 As discussed in the proposed rule, there are two
10 principal processes for the manufacture of sterile drug
11 products. Aseptic processing of a drug product requires
12 that each process and component for the drug product be well
13 controlled and monitored through in-process control and
14 testing and then brought together in a controlled
15 environment. The many manipulations of the separately
16 sterilized components during the assembly of the final drug
17 product, in absence of a final sterilization process after
18 the drug product has been sealed in its final container,
19 limit the degree of sterility assurance that can be obtained
20 with an aseptic process. Therefore, careful control and
21 validation of all operational phases of aseptic processing
22 is imperative to achieve the necessary degree of sterility
23 assurance.
24 In contrast, terminal sterilization is a process

whereby a drug product which may or may not be pre-sterilized is filled and sealed into a container, and then subjected to final sterilization. The advantage that terminal sterilization offers over aseptic processing, other than the increased assurance that the drug product will be sterile, is that in-process control and testing in general is significantly less for a sterile product manufactured by a validated terminal sterilization process.

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Once again, the Center believed that this proposed amendment should not be applied to veterinary injectable drug products. The Center came to this conclusion largely on the basis that the Center and veterinary industry were unaware of the proposed amendment until it was published in the Federal Register, and the Center did not have adequate opportunity to participate in the development of this proposed rule-making, or inform the veterinary industry of the proposed change in CGMP regulations for sterile injectable drug products.

It became very clear during the Center's attempts to be exempted from this proposed amendment to the CGMP regulations that the FDA's position on CGMPs that comparable drug products, such as sterile injectable dosage forms, should meet the same or similar quality standards takes

1 precedence. The Agency appeared to believe that it should
2 treat like products alike, not because the different centers
3 may be regulated under the CGMP regulations but because the
4 drug products themselves are viewed by FDA as the same and
5 we, meaning the Center, did not provide an adequate
6 scientific justification to demonstrate that they may not be
7 the same.
8 The Center discovered that merely saying we don't
9 want it or that there was no demonstrated need was not
10 sufficient to convince FDA that a lesser quality standard is
11 appropriate for sterile animal injectable drug products.
12 What was missing from the Center's efforts to be exempted
13 from the proposed amendment to the CGMP regulations was a
14 scientifically supportable justification for why veterinary
15 injectable drug product quality would not benefit from the
16 proposed amendment to the CGMPS regulations.
17 Clearly, there would need to be something unique
18 about sterile veterinary injectable drug products or
19 processes that made the proposed amendments to the
20 regulations impracticable for animal drug products. If
21 provided with this type of information, the Center could
22 have made a persuasive argument for flexibility in the
23 application of these proposed regulations to veterinary drug
24 products.

As I mentioned in my opening comments on veterinary drug quality, the regulatory scheme, the Center is considering the need for additional flexibility within the regulatory scheme that may be appropriate for animal drugs. This would include the flexibility to evaluate proposed changes to the CGMP regulations that may not be appropriate for veterinary drug products and if necessary, exemption from the proposed requirements.

However, even with additional flexibility, the Center will need to base its decisions on the appropriateness of a CGMP requirement or differences in quality attributes for veterinary drug products on scientifically sound premises. The animal drug industry should be prepared to assist the Center with necessary information to support a sound scientific basis for these types of decisions.

Likewise, the animal drug industry should be willing to accept the fact that if aseptic processing of animal drug products, rather than terminal sterilization, is found to be acceptable to FDA for animal drug products, there will continue to be a need for more extensive in-process control and testing than if the drugs are manufactured by a terminal sterilization process.

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1 Next issue, that being the issue that when the
2 economics of human and animal drug industries are compared
3 it makes no sense to impose the current quality standards on
4 animal drugs.
5 The Center is very aware of the cost-sensitive
6 nature of animal drug products and the industry as a whole.
7 The issue, as the Center sees it, is not one of veterinary
8 drug products needing the same requirements as human drugs
9 but, rather, one of meeting appropriate quality standards
10 which, in most cases, are the same or similar for human and
11 animal drug products. The burden on the Center and on the
12 animal drug industry is to identify those areas where there
13 is a scientific basis for different means to fulfill the
14 CGMP or CMC requirement that is more cost effective.
15 The Center recognizes that a significant portion
16 of the veterinary industry does meet the current quality
17 standards, and will continue to meet the latest technology
18 and CGMP standards to assure the quality of the veterinary
19 drug products. Therefore, one of the challenges for the FDA
20 is to keep the playing field level for CGMPs and to assure
21 that all segments of the industry meet the same quality
22 standards, unless there is a scientific basis for different
23 quality standards, within the pharmaceutical industry.
24 One additional thing that should be considered is

1 whether the cost to maintain the current level of quality is
2 unreasonable in light of the economic impact that lower
3 quality standards could have on the long-term economics for
4 the animal drug industry.
5 There are currently a number of initiatives under
6 way within the FDA and Center for Veterinary Medicine that
7 will provide for international marketing of domestically
8 manufactured animal drug products. These initiatives
9 include the European Union Mutual Recognition Agreement,
10 also known as the EU-MRA, that provides for mutual
11 recognition of European Federation member states CGMP and
12 compliance infrastructures with those of the U.S.
13 Likewise, the Veterinary International Cooperation
14 on Harmonization, which we discussed this morning, VICH,
15 provides for drug product quality standards based on the ICH
16 standards for human drug products. My experience has been
17 that the tripartite members of the VICH initiative generally
18 want animal drug products with the same quality attributes
19 as the human drug counterparts.
20 Clearly, both of these initiatives are built upon
21 our current quality standards for animal drug products,
22 which just so happened to be similar to human drug product
23 quality standards. Any change in our current quality
24 standards could significantly impact on the current

initiatives to establish an international marketplace for domestically manufactured animal drug products.

For its part, the Center will consider different quality standards when they are scientifically based. The challenge, once again, lies with the veterinary industry to provide a sound premise on which the Center may make these decisions. We, meaning the animal drug industry, need to carefully consider any and all changes in the quality standards for animal drug products and the possible long-term negative economic impact of these changes on the domestic animal drug industry's ability to compete in the global marketplace.

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The third issue, that there was a sudden change in the application of human drug CGMP requirements to animal drug products--certainly, we have heard quite a bit about that today. The CVM has received comment that in 1990 there was a sudden change with the application to veterinary drug products of the same procedures, processes and methods as are required for human drug companies.

The CVM has not been able to confirm that there was a sudden change in FDA's application of human drug CGMP requirements to animal drug products, or that FDA investigators had previously applied a more common-sense

approach of "what" and "how" criteria to the evaluation of animal finished pharmaceutical drug products. However, the Center did note that the FDA had implemented the pre-approval compliance program and that the timing for the implementation of this program coincided with when the sudden change appeared to occur.

The pre-approval compliance program was significantly revised from prior programs to expand the number and scope of pre-approval inspections, thereby improving surveillance and enforcement activities related to pending applications. The program provided for inspections to be conducted not only with reference to CGMPs, but also with reference to the specific requirements and commitments contained within the application. This program, which continues to evolve, was a sudden change for both animal and human drug products and not the sudden application of human CGMP standards to animal drug products.

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Issue four, that issue being that in light of full initial equipment process and product validation, are there some in-process controls or some of the finished product testing requirements that may no longer be necessary to assure animal drug product quality.

I will speak to the general issues associated with

processes validation, in-process control and testing and final product testing.

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Assurance of drug product quality is derived from attention to a number of factors, including selection of quality components, adequate process design, demonstrated control of the process, in-process control and testing, and end product testing.

In the guideline on general principles of validation, dated May, 1987, the FDA defines process validation as established, documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. It is through careful design and validation of the process, in-process testing and controls and final product testing that a manufacturer can establish a high degree of confidence that all manufactured units from successive batches will meet their quality attributes.

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Generally, this is the purpose of prospective validation, which the FDA defines, in the same document cited above, as validation conducted prior to the distribution of either a new product or product made under a

revised manufacturing process where the revisions may affect the product's characteristics.

Please note that I have indicated with suprascript a necessary point of clarification to the definition of prospective validation.

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I will spend just a moment on this because it will be covered I believe in the next presentation. But, essentially, there is a significant difference between manufacturing processes validation, which is generally post-approval and prior to marketing, and sterilization process validation, which must be completed prior to approval. I think the reasons for that are generally fairly obvious in that the batches which you manufacture to do your prospective validation--they are going to be marketed so, therefore, sterilization process validation, demonstrating assurance that those prospective batches are sterile, has to be done prior to their manufacture.

Many of the issues that have been placed before CVM involve sterilization processes validation and the in-process controls and testing for sterile animal drug products.

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The FDA recognizes, in the May, 1987 guidelines,

1 that successful validation of a process may reduce the
2 dependence upon in-process and finished product testing. As
3 we heard this morning, this statement seems to be one of the
4 primary points of contention. We have received criticism
5 that there is the appearance that even with FDA's increased
6 emphasis validation there has not been a relaxation of in-
7 process control and testing and final product testing
8 requirements.
9 We have already partially addressed this issue in
10 our earlier comments. Those comments stated if a sponsor
11 chooses a manufacturing method, such as aseptic processing
12 which requires a great deal of in-process control to achieve
13 its intended purpose of manufacturing a sterile product,
14 rather than terminal sterilization that requires less in-
15 process testing to achieve its intended objective, then the
16 burden lies with the sponsor for the choice of manufacturing
17 methods.
18 It would not seem, in our opinion, reasonable for
19 a sponsor to select a procedure, such as aseptic processing
20 which provides a minimal level of quality assurance that the
21 product will be sterile, and then expect the Center or the
22 FDA field to agree that the necessary in-processing controls
23 should then be reduced. Nevertheless, the Center has
24 offered the comment that there may be some instances where

there is a scientific rationale for a different means to fulfill a CGMP requirement, such as endotoxin, and I am again stating that if this information is available and supports a different means to fulfill a CGMP requirement, then the Center will give this information serious consideration.

Where process validation and limited in-process control testing and final product testing cannot adequately measure the outcome of the manufacturing process, more in-process control and testing, along with process validation, are required to provide an adequate level of assurance that the product will meet its predetermined quality attributes.

Likewise, validation of a sterile fill process with consecutive media fills has little relevance to the sterile fill of a drug product on the same line unless the end product's control, such as environmental monitoring, had been maintained within the limits that existed during the validation of the sterile filling process, hence, the need for more in-process testing and control throughout the aseptic fill process.

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The Center for Veterinary Medicine and FDA field understood that there were many issues throughout and the need for in-process control and testing to assure the

1 quality of sterile veterinary injectable drug products,
2 particularly if they are manufactured by an aseptic process.
3 This is one of the primary reasons that the Center will
4 invest a significant amount of effort in the evaluation of
5 sterilization processes validation information. These
6 efforts consisted of the development of a comprehensive
7 guidance document, entitled "Guidance for Industry for the
8 Submission of Documentation for Sterilization Process
9 Validation in Applications for Human and Veterinary Drug
10 Products." Additionally, CVM, CDER and FDA field
11 investigators offered four domestic and two foreign
12 workshops to explain the FDA's perspective on these
13 important issues.
14 Interestingly, what got the Center involved in
15 these activities was a series of complaints from the animal
16 drug industry that there was an unlevel playing field in the
17 FDA field assessment on sterilization process validation
18 requirements for individual manufacturers of veterinary
19 sterile drug products. The Center's reaction was to help
20 level the playing field across the board regarding FDA's
21 expectations for validated sterilization processes and
22 appropriate end-process control and testing. Our purpose
23 was to get uniform buy-in from headquarters' review staff,
24 FDA field investigators and t he pharmaceutical industry as

to what FDA's expectations are for validation and in-process control of sterilization processes.

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We believe we have been very effective as a Center in leveling the playing field and working with our industry, as evidence by the bumper crop of approvals that we had last year and comments that we have received from our industry. For example, a trade organization that represents animal drug manufacturers noted that many animal drug companies are located in the Kansas City District. They are inspected and, therefore, the sterile validation is reviewed by KCDO investigators. It is essential that the KCDO investigators know, agree with an enforce whatever is taught at the workshop.

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What we taught at the workshop was that aseptic processing of a sterile drug product requires sterilization processes validation, accompanies by extensive in-process control and testing, and final product testing to ensure that the sterile product meets necessary microbial attributes.

Having said this, it is important to again make the point that I made during my opening comments about the regulatory scheme, this point being that if the Center

1 received the necessary scientific information to support a
2 different quality standard for animal drug products, then a
3 different third-level of CGMP for the means to fulfill the
4 CGMP regulations could be developed by the Center and FDA
5 field. Thank you very much.
6 DR. LEIN: Thank you. Questions? Jess, you had a
7 question?
8 MR. STRIBLING: As Bill has mentioned, Dr. Giest,
9 as Center Director, and Dr. Teske made a manly attempt to
10 get veterinary drugs out of the proposed regulation for
11 terminal sterilization, that is well-known and documented.
12 It may not be as well-known that the Director of Human
13 Drugs, Carl Peck, who was born on a farm in Nebraska, sat
14 there unbelieving that the Agency could want animal drugs to
15 be terminally sterilized, knowing the way these drugs are
16 used out in the field.
17 But, as Mr. Marnane said, what happened was that
18 the compliance folks overrode a center director and a deputy
19 center director and enforced and required human drug
20 requirements on animal drugs because they did not see any
21 reason for having different standards. That is a fact we
22 are all grateful to the attempt that the Center made to keep
23 animal drugs out of that regulation. But that whole event,
24 recall, and the statement that Bill has made, that I think

is absolutely correct, that in order for a veterinary drug to be different in any way from a human drug in terms of manufacturing practice there must be a scientific basis for a different standard underlies the reason that the Animal Drug Alliance has sought a separate CGMP requirement for animal drugs in the law than that for human drugs, something that the American Veterinary Medical Association has endorsed.

But it also raises the question of the difference between human and animal drugs, and at this point I should let Dr. Sundlof rebut what Mr. Marnane said but, because that would be awkward, I will do it for him.

[Laughter]

I mentioned this morning that the great contribution that Dr. Sundlof has made to FDA and to the Center for Veterinary Medicine is redefining the meaning of the word "safety" as it applies to animal drugs, and herein lies the distinction between human and animal drugs that has nothing to do with the scientific base for different standards but, rather, the real-world use, whereas, prior to Dr. Sundlof--Dr. VanHouweling tried it but I wouldn't let him--whereas, prior to Dr. Sundlof a product was looked at in itself in terms of its quality, safety, etc., Dr. Sundlof came in saying--I am paraphrasing, these are my words but I

1 think they are a faithful reflection of what he said and the
2 mission statement of the Center for Veterinary Medicine, we
3 have to understand safety in a wider context. It is
4 important for there to be FDA-approved animal drugs out on
5 the market so that we protect the human food supply because
6 we know that FDA-approved drugs have had the residue
7 requirements met in everything else, and the alternative to
8 FDA-approved drugs, as we have heard so eloquently this
9 morning, is unapproved drugs, compounded drugs in bathtubs,
10 illegally imported drugs, counterfeit drugs, drugs used
11 extra-labelly, none of which enhances the human food supply
12 and, therefore, it is important for us to make sure that
13 drugs we approve are safe, effective and have quality but it
14 is important for us to deal with the issue of drug
15 availability.
16 Now, I would suggest to you all and to Mr. Marnane
17 that Dr. Sundlof has rightly articulated the difference
18 between the two and the reason that the Agency is acting
19 inappropriately and the Center, if it buys what the Agency
20 says, in simply looking at the scientific basis alone.
21 Enough said.
22 DR. LEIN: There are many components in that
23 statement. Questions? Dr. Sterner?
24 DR. STERNER: I guess this is directed to Jess

Stribling. As a practitioner, do I have any assurance that if CVM were to, in fact, the quality standards that I would see a plethora of NDA approvals? That is inferred by your statement.

MR. STRIBLING: Keith, that is absolutely right. It is certainly true that since Dr. Sundlof has been in the Center there has been an increase in approvals. That has coincided with some decreases, both by the Center and under law, with the effectiveness requirements that need to be met to get products onto the market. And, to the extent that--again, Dr. Barker I believe asked about whether the industry has met the current requirements and I said our concern is more with the continuing requirements than with what has gone before--I think that there could be an adverse impact on animal drug availability and, again, the issue is for the vet. Do you want to use an FDA-approved drug? I sure as heck hope so.

DR. LEIN: Other questions? Yes?

MS. HARRIS: Just to amplify on just this response to your question, in the AHI comments presented we did mention that some veterinary companies would redirect costs for compliance, let's say for sterile process validation, if they could take those costs and instead turn them into their IND programs there would be more approvals for other

indications for use and possibly other species. Those costs are significant and they could lead to more approvals for new uses.

DR. LEIN: Other questions? Yes, Dr. Fletcher?

DR. FLETCHER: This is maybe for Mr. Marnane. I am a little bit confused by the examples in which aseptic processing of a sterile drug and the more extensive end-process control that is being made. I understand that a company might say that they cannot do terminal sterilization because that would destroy the product. But are there other circumstances by which a company could elect to do the aseptic processing versus terminal sterilization? Because what I am hearing and the impression I got is that imposing terminal sterilization was a requirement that many felt went beyond what was needed and imposed additional costs to the manufacturer of animal drugs, and I am just wondering are there those that elected and defended it, for whatever reason, other than destruction of the product, aseptic processing as opposed to terminal sterilization?

MR. MARNANE: Basically, I didn't get into the proposed rule-making all that much but they did have provisions-- and you are very close to being entirely correct. I mean, the exemptions that were provided for within that proposed rule-making were for instances where

1 either you could, let's say, use an over-kill cycle which
2 is, you know, a lot of heat for a certain amount of time and
3 you could demonstrate that there was the appearance of new
4 degradance or that you would significantly impact on the
5 breakdown of that product. So it provided for exemptions in
6 those two circumstances, and also when it was harmful to the
7 packaging of the product, in other words, a lot of products
8 come in pre-filled syringes and not all of those would be
9 acceptable or, I should say, would remain intact after a
10 terminal process. Those were basically the only types of
11 exemptions provided.
12 However, realistically I think we have to look at
13 this rule-making and say, gee, it was proposed in October,
14 1991, what happened to it? Well, basically it is an
15 inactive rule-making. Okay? It is still on the books. I
16 don't know if it will ever come back or if it will remain
17 inactive but, obviously, I think there were a number of
18 significant issues that came up across the board, you know,
19 regarding that particular proposal. So I think we need to
20 take that into consideration. Perhaps if it were the best
21 scientifically sound proposal that the FDA ever has come up
22 with, I think we would have seen it come back to us a little
23 bit sooner than this. It certainly is not a high priority.
24 DR. KOONG: I guess I have some clarification I

1 wanted to ask. Throughout this morning's presentation by
2 the Center staff and this afternoon by you, I have had a
3 feeling, Mr. Chairman, that the phrase that has been used
4 throughout the presentation is CVM and FDA or CVM and FDA
5 field. The last time I checked the CVM was part of FDA. Is
6 that still correct?
7 MR. MARNANE: Yes, sir.
8 DR. KOONG: It sounded to me that we are having
9 two agencies working against each other. I am very appalled
10 by the statement here. It says when this was proposed, the
11 amendment, the Center and the veterinary industry were
12 unaware of the proposed amendment until it was published in
13 the Federal Register. So, in other words, FDA as an agency
14 can propose an amendment about animal drug use without even
15 talking to the Center for Veterinary Medicine. Obviously,
16 that is six, seven years ago. I would like to ask Dr.
17 Sundlof, does this still exist today? Because it really
18 bothers me.
19 DR. SUNDLOF: No, it doesn't exist any more--
20 [Laughter]
21 The FDA is a big organization that is dispersed.
22 There are about 9,000 people in the FDA, of which 260,
23 roughly, are from CVM. And it is possible for regulations
24 that are promulgated in one center--usually regulations come

1 out of an individual center. They have to go through the
2 Office of Policy within the Office of the Commissioner, so
3 within the big FDA, the overall umbrella FDA, and everybody
4 is supposed to be in that loop, that they know when new
5 regulations are being written. Since I have been here the
6 administration in the FDA has been very, very responsive to
7 the needs of the individual centers, and if there is a
8 regulation that has an impact on another center, for
9 instance, if the Center for Drug Evaluation were to write a
10 regulation which inadvertently affected the Center for
11 Veterinary Medicine we would be alerted to that. Back in
12 the early '90s, I wasn't here at that time.
13 I'm not exactly sure how things worked out, but we
14 are constantly involved in interacting at the level of the
15 Commissioner's Office with the other centers to make sure
16 that any regulations that come out of the FDA have broad
17 support and buy in.
18 If one center wants to be exempted from that and
19 those centers make it very clear that the regulation only
20 applies to specific centers.
21 DR. LEIN: I believe that Mark Lynch from CDER
22 wanted to say something to this question.
23 MR. LYNCH: Thank you. I was just going to echo
24 what Dr. Sundlof said. I think the Agency has been

chastised recently with the Indiana Citizen's Petition to be much more careful about making guidance, and also policy, by fiat. The Center for Drugs, I know, has taken a real hard look at the way that it develops policy and guidance and there is a very detailed standard operating procedure or Manual of Policy and Procedures Map, we call it, that talks about how we share information with industry groups and other centers via the Internet to get a wide perspective before we interact either regulations or guidance documents.

So I think the way to Agency does business that way in regards to these kinds of things has changed. But he is correct when he said that these guidance documents and these issues come from a variety of different places within the agency, within the Center for Drugs.

It is not always clear in the beginning when they take on a life of their own how much they need to be shared with the Center for Biologics, the Center for Vet Medicine and these things coalesce at different times. So you probably have access to and you might be very interested in looking at the public document, the comments, the particular comments, that were received in regard to the terminal autoclaving Advance Notice of Proposed Rulemaking that exists to answer your question, to see what the pros and cons were.

DR. LEIN: Thank you.

Other questions?

DR. BARKER: Just as a point of clarification. The terminal sterilization is a required process for human drugs?

MR. MARNANE: No; it is not.

DR. BARKER: And it is not being promulgated as required process for veterinary drugs.

MR. MARNANE: Not currently; no.

DR. BARKER: That leads to the next question. Do you anticipate--

MR. MARNANE: The only thing I can say and, perhaps, Mark--as a matter of fact, I went to Mark Lynch to ask him what the status of that proposed rulemaking was. The comment I received from Mark was, "Inactive."

DR. BARKER: Is this a new regulation? It is not a new regulation, is it?

MR. MARNANE: No; it was proposed in 1991 but, for some reason, the issue seems to just not want to go away.

DR. BARKER: I think we can see why. Thanks.

MR. STRIBLING: Mr. Chairman, may I respond to Dr. Barker on the human drug area since I do have experience with that. There is no regulation requiring terminal sterilization. In about 1988, the Center for Drugs decided

that terminal sterilization is CGMP and began refusing to approve applications of drug companies for sterile drug products unless they used terminal sterilization.

In the case of drug companies that were using aseptic processing, one that happened to be a client but wanted to move into a new facility, refused to transfer the applications to the new facility until the company installed terminal sterilization.

Two months after that happened, the Director of the Office of Generic Drugs gave a speech to any industry trade association and said, in the course of that speech, "Oh; by the way, we now believe that terminal sterilization is required for drugs unless the packaging of the product won't withstand the heat."

It was some two or three later that the proposed reg was published. So, the answer to the question; yes, human drug companies are being required to do it under what I call the "we have our ways" enforcement of the agency rather than through regulation or guidance.

DR. LEIN: So, an indirect way.

MR. STRIBLING: That is a nicer way of putting it. Yes, sir.

DR. LEIN: I think we should move on. Further perspectives from FDA. Dr. Patricia Leinbach.

1 DR. LEINBACH: Good afternoon, Mr. Chairman,
2 ladies and gentlemen. For about the next 20 minutes, I am
3 going to briefly discuss issues relating to sterilization
4 process validation for veterinary drugs from the perspective
5 of a reviewer of sterile drug applications.
6 I want to just point out that the handout that you
7 have of my presentation has more detail in it than I am able
8 to present here because of time constraints.
9 Since only a very few veterinary drug products are
10 terminally sterilized, my comments will be confined to
11 aseptic processing. As you will recall from earlier
12 discussions, aseptic processing is where the containers,
13 closures and drug product are sterilized separately and
14 brought together in a controlled environment.
15 After that, there is no further sterile processing
16 after the product is put into the market container.
17 [Slide.]
18 This slide lists the four topics that I am going
19 to discuss. The main purpose of my presentation is to
20 address issues that have arisen concerning validation of
21 sterilization processes. That is item No. 3 on the slide.
22 But, in order to do that, I first need to briefly acquaint
23 you with the kinds of sterilization process validation that
24 should be filed to support approval of a sterile drug

product.

After that, I want to briefly discuss what the role of the Headquarters reviewer in the approval process is. Then I will generally address some of the issues relating to sterility requirements. Lastly, I want to update you on our involvement in FDA's continuing efforts to reduce filing requirements. These are associated with sterile products that have already been approved.

First of all, I would like to discuss briefly the kinds of sterilization process validation information that should be provided to support approval of a drug product. I want to point out that my remarks today are directed strictly toward parenteral solutions and they do not apply to sterile, solid, bulk-drug substances or powder substances.

Additionally, I should clarify, that I will only address issues relating to sterilization process validation. I will not address other issues relating to the chemistry associated with those kinds of applications.

Before we discuss the information that should be provided, I want to briefly review some definitions relating to validation.

[Slide.]

Process validation is defined as establishing

1 documented evidence that all specific processes used in the
2 manufacture of a drug product will consistently produce a
3 product meeting its specifications and quality attributes.
4 [Slide.]
5 Sterilization process validation is defined as a
6 series of protocols and scientific experiments designed to
7 demonstrate that the sterilization processes will
8 consistently produce a sterile product. An issue that needs
9 to be clarified before I move on is to define the difference
10 between the manufacturing process validation and
11 sterilization process validation.
12 [Slide.]
13 This slide shows both manufacturing process
14 validation as well as sterilization process validation. The
15 manufacturing process validation begins with the formulation
16 of a product and it includes all processes, components, et
17 cetera, all the way through to the point when the drug
18 product is put into the market container.
19 The sterilization process validation is only a
20 part of this. Listed on the overhead there, you can see the
21 different components that go into making up sterilization
22 process validation.
23 [Slide.]
24 Now, process validation, which is the overall

manufacturer process from the beginning of formulation right through to putting the product into the container must be completed prior to marketing but not before approval and it requires three production lots of product to be made.

[Slide.]

Sterilization process validation must be completed prior to approval but it does not require the actual product to be made. The reason for this is that aseptic processing, an aseptic fill procedure, can be adequately validated by using media fills. Autoclaves can be validated by using physical means such as thermocouples.

[Slide.]

On this slide, I am showing the cover of the guidance that was mentioned by Mr. Marnane. I showed this to you. You have this under Tab 8(b) of your big book. The information that I am going to briefly talk about concerning sterilization process validation is in that guideline in some detail so that if you need more information concerning some of these topics, that is where you can find it.

[Slide.]

What I am going to do is just mention these different categories because I really don't have time to go into these. But some of the areas of information that we are looking for in the drug application are what is the

1 product composition, what is its container closure. We need
2 a facility description, what is the manufacturing procedure.
3 Is it aseptic processing? Is it terminal
4 processing? Or is it something else? We need to know how
5 different components are sterilized. We need to know--if it
6 is an aseptic filling process, we need to have information
7 on how that is validated. We need to know something about
8 what happens to product if you are in a production mode, you
9 perform a media fill and that media fill fails. What do you
10 do with product that is made before and after that media
11 fill.
12 We need to have some information about filter
13 validation, the sterilizing filter that is used for that
14 product. The batch record should contain a certain amount
15 of information relating to the sterilization process
16 validations, procedures that are used. Environmental
17 monitoring is a concern. That has already been discussed.
18 Container-closure integrity testing is a concern.
19 So this list contains the main categories of
20 information that we are looking for. I would like to point
21 out that once this information is generated, it can be
22 shared by a lot of different drug products. It is not
23 necessarily product-specific.
24 So it can be applied broadly across a variety of

1 different aseptically filled products, et cetera.

2 [Slide.]

3 The next thing that I want to discuss is the role

4 of the headquarters reviewer. We often get the question,

5 why does sterilization process validation information need

6 to be submitted in a drug application. Our response to that

7 question is if it were strictly a GMP issue, we wouldn't

8 need to see it. But it is not strictly a GMP issue.

9 It is true that 21 CFR Part 211 requires

10 validation for GMPs but it is also true that 21 CFR 514

11 requires validation information to be provided in the drug

12 applications. However, in the applications, we don't ask

13 for complete information. We only ask for a description of

14 the protocol, how was the study performed, and a summary of

15 the validation data.

16 We actually perform a scientific review of the

17 protocol to determine if it will accomplish its intended

18 purpose which is, obviously, to sterilize some process or

19 product, et cetera. And then we look at the data that is

20 submitted, the data summary, to see if enough data was

21 generated to prove that the process works.

22 Once the reviewer has ascertained that the CMC

23 section, including sterilization process validation is

24 satisfactory, a preapproval inspection is requested. The

FDA field investigator then performs a facility CGMP inspection. During that inspection, the investigator will confirm that the sterilization process validation data was generated according to the protocols that were approved in the drug application.

From this discussion, you can see that the reviewer and the investigator evaluate different aspects of sterilization process validation. It should be clear to you that the approval of a drug product is a cooperative effort among the reviewer, the sponsor and the FDA field investigator.

[Slide.]

So, just in summary, the headquarters reviewer receives the drug application and evaluates the information that is in the application. Then the reviewer will interact with the firm to resolve any problems that existed with the application, itself.

After those problems are solved, the reviewer will request a preapproval inspection. After that, the reviewer works with the investigator to resolve any problems that might be found during the inspection that are solvable without an intense amount of work.

Then, after that, when all that is done, then the reviewer will recommend approval of either the CMC section

or of the drug product, whichever is appropriate.

[Slide.]

At this point, I want to discuss some of the issues about the filing requirements that have come to our attention during this process of setting up this workshop. The issues that I am going to discuss are listed on this overhead.

The first is container-closure integrity. The issue is that CVM requires container-closure integrity testing for all containers and closures a firm uses. First, I should tell you that container-closure integrity testing is necessary to demonstrate that the container closure will maintain the microbiological quality of the drug product during its shelf life.

CVM does not require that all combinations of containers and closures be tested. We accept bracketing to minimize the amount of work that must be done. This means that the validation may be documented by performing the integrity testing on the largest and the smallest container-closure systems on each filling line.

Once the smallest and largest containers are validated, we consider that all sizes of containers between the smallest and the largest are also validated. The bracketing concept also applies to other processes such as

media fills so that we really try to minimize the amount of work that has to be done to validate these processes.

It is necessary, however, for each facility to perform its own validation testing. This is because the environmental conditions, equipment, personnel, et cetera, are different for each facility. Validations are not transferrable from one facility to another. They must be conducted under the conditions that will be used for routine manufacturer of the drug product.

The second issue is on-line filtering and filling. The issue here is that the homogeneity testing of a true solution processed by an on-line filtering and filling operation must by proved by excessive testing.

Before I address that issue, I want to tell you want on-line filtering and filling is. This is a process where the product goes from a bulk tank into the sterile filter and then immediately goes into the containers and closures. It is not filtered first into a big holding tank and then, at some point later, filled into containers.

It is one continuous operation. The critical issue for on-line filling operations is homogeneity of the product from the beginning of the fill to the end of the filling operation. I cases where there are problems which affect homogeneity, protocols are designed to determine if a

product is homogeneous from the first container.

If not, the protocol is designed to determine how many containers must be discarded due to nonhomogeneity. In the event that the product is not homogeneous, it is critical that enough samples are collected sequentially at the beginning of the fill and at specific points throughout the fill.

The reason for this is to determine how many containers have to be filled before the product reaches homogeneity. All of the samples that are collected are not necessary assayed but a large number is required because it would be impossible to go back and collect proper samples once the filling process has been completed and the containers have been packed into boxes or whatever they are packed into.

Any unused containers are not wasted, however. They are returned to the lot and they are generally sold. Homogeneity testing is not applied to all parenteral solutions processed in on-line filling operations. This type of validation is necessitated only because of the problems associated with achieving homogeneity of particular drug products.

The next issue is filter validation. The issue here is that filter manufacturers certify filters to be

bacterially retentive. So why does the user, then, have to validate the filter?

When filter manufacturers such as Millipore or Pall rate their filters, they routinely use water or aqueous solutions of saline lactose broth to demonstrate the bacterial retentivity of the filters. They do not use individual drug product solutions.

In order to demonstrate that the chosen filter can render the drug product sterile, it is necessary to demonstrate that the filter can remove microorganisms that are present in the drug product. This is because most aqueous drug products and nonaqueous, as far as that is concerned, are composed of multiple ingredients in addition to water for injection.

Since the size, shape and pliability of microorganisms are influenced by pH, ionic strength, anticoagulants, active ingredients, et cetera, it is necessary to demonstrate that the filter will remove low levels of microorganisms that are present in the actual non-sterile bulk product.

Therefore, the filter validation must be product-specific. Sponsors, however, do not have to have Millipore or Pall perform their filter validations. They can set up their own filter-validation operations. In fact, CVM has

assisted firms in setting up these filter validations.

The other thing that I need to point out about filter validations is this is a one-time validation. It is done one time and it is done sometime during product development. It is not done again. It is not done for different lots of filters. It is only done one time to show that that particular filter will remove microorganisms from the product.

The next issue is media fills. The issue is that media fills must be done at least twice a year which is expensive and unnecessary. The aseptic filling process is validated using sterile media to fill containers, as I have pointed out earlier.

Aseptic filling procedures are often validated by using the bracketing approach for container closures which mean they use the largest and smallest. Once the initial media fills are performed, it is necessary to perform the revalidation runs periodically to assure that the conditions which existed during the validation continue to exist in the area where products are aseptically filled.

Media-fill revalidations are generally performed only once per year for each size container. When you think about how many lots of product are processed during the year or during six months, one media fill is a very small

1 percentage of that number.

2 The next issue is sterilization by autoclaving.

3 The issue here is that autoclaves should be revalidated

4 using the single biological indicator in the cold spot.

5 First of all, let me explain, and I am sure that probably

6 you already know this, but I will explain it anyway, what a

7 biological indicator is and how autoclaves are normally

8 validated.

9 Biological indicators are usually microbial spores

10 which have been applied to a strip of paper for ease of use,

11 and they are used to insert into autoclave loads, et cetera.

12 An autoclave, when it is validated, it is necessary to

13 demonstrate two things. Number one, you want to demonstrate

14 the physical delivery of heat to all parts of the autoclave

15 contents.

16 Number two, you want to demonstrate that that heat

17 is lethal to microorganisms. It is generally accepted that

18 12 minutes at 121 degrees is an overkill sterilizing cycle.

19 But if you are using a 12-minute overkill cycle, it is quite

20 likely that your total cycle is going to run longer than

21 that.

22 For instance, it could run 45 minutes or an hour.

23 This is because all parts of an autoclave load will not heat

24 up equally and longer times are often required for the

hardest-to-heat areas to achieve the desired 12 minutes exposure at 121 degrees centigrade.

Validation studies should document that all parts of the autoclave load receive the minimum amount of physical heat and that the delivered heat is lethal to microorganisms. Therefore, both thermocouples and biological indicators are required to properly validate an autoclave.

So, in summary, autoclaves are validated and revalidated using thermocouples and biological indicators. This is because, with continued use of an autoclave, the cold spot does not remain in the same place throughout the life of an autoclave. It actually migrates around within the chamber.

So, as you can see, it would be scientifically invalid to use only biological indicators even if you knew where the cold spot was and if it stayed the same all the time.

The next issue that I was going to discuss is water for injection. But I think enough has been said about water for injection. So I am going to move on to bioburden testing. The issue is that bioburden testing on bulk-drug product is required indefinitely.

The proposal is that testing should be performed

only on the first reproduction lots. Our response to that is that monitoring of bioburden and bulk product is necessary to assure that microbial levels are maintained at a low level during the manufacture of the drug product. This is important because microorganisms produce many kinds of toxins in addition to endotoxin.

Drug products are generally only ever tested for endotoxin. We do not test for other toxins because of the economics, the amount of work that would be involved in identifying the organisms and identifying the toxins, in developing methods to quantitate the toxins and in developing some sort of limits.

So the simplest and the most economical approach to controlling microbial toxins in drug products is to monitor and control the level of microbial contamination during the production of the drug product.

The next issue is endotoxin levels. It has been stated that a demonstration of a three-log reduction of endotoxin is not necessary for containers and closures used for veterinary products. We have stated repeatedly in the past that if a firm demonstrates that there aren't any endotoxin levels on containers and closures, then this kind of testing wouldn't be necessary. To this date, we have received that kind of documentation from one drug firm.

To briefly summarize this slide, I have attempted to clarify some of the issues relating to container-closure integrity testing, on-line filtering and filling, filter validation, media fills, autoclave sterilization, bioburden testing and endotoxin levels.

[Slide.]

The last thing that I want to discuss is CVM's efforts in developing post-approval changes for sterile aqueous solutions. These are products that have already been approved.

We are working with an FDA task force to lessen or to minimize the filing requirements or changes that are made to parenteral drug products after they are approved. The categories that we are considering are shown at the top of this overhead. These are solution composition, the container system, manufacturing location, manufacturing equipment, manufacturing process, product specifications and tests and batch scale.

At the bottom, you can see the three levels of changes that we are trying to develop in each of these categories for each of the items listed above. We are trying to develop changes that can be put into effect immediately which can either be reported in a supplement or, perhaps, in an annual report.

We are trying to develop changes that can be put into effect and reported in a biannual supplement. Of course, there will always be changes that require approval before it can be put into place. So we are looking to make changes in all these categories to make it easier for firms to make post-approval changes to sterile products.

The FDA task force is working with the Parenteral Drug Association, the PDA, to conduct an open forum on the post-approval changes issue. This forum has been scheduled for August 18 and 19 at the J.W. Marriott in Washington, D.C. The purpose of the open forum is to allow individuals and groups to present the types of changes that would be most beneficial to them.

In this way, we hope to concentrate on the changes that are the most needed and also, at the same time, to lessen filing requirements for those changes that are the most needed. The FDA task force's goal is to have a draft document in about six months after at forum.

This information is sketchy but I wanted to present it to you as an update so that you will get the feel that we are continuing in our efforts to facilitate drug approval and availability.

[Slide.]

So, in conclusion, I would just like to summarize

very quickly by saying that we have briefly discussed the kinds of information that we request for sterilization process validation. We have talked about the role of the headquarters reviewer. I briefly discussed some issues relating to sterility requirements and briefly talked about post-approval changes for products that are already approved.

I want to close by saying that CVM continues to be amenable to working with sponsors to minimize the amount of sterilization validation information needed to support approval of parenteral drugs. The microbiological quality of parenteral drugs is a safety issue. The bottom line is that we must have sufficient information in the drug application to convince us that a parenteral drug product will be safe and effective for its intended use.

This concludes my presentation. Thank you very much.

DR. LEIN: Any questions for Dr. Leinbach?

DR. POUST: I have a question. Actually, I have two questions. I am Roland Poust, University of Iowa. It sounds like this PAC SAS is a joint FDA industry effort; is that correct?

DR. LEINBACH: Right.

DR. POUST: And there are a number of other of

1 those efforts that are going on.

2 DR. LEINBACH: Yes.

3 DR. POUST: There is SUPAC IR, there is SUPAC SS

4 and there is BACPAC. The PAC is common and it talks about

5 post-approval changes, but I think the important point I

6 would like to bring out and I want to emphasize is that this

7 is an industry-FDA effort. Some of these are done through

8 PDA, as you mentioned.

9 Some have been done through AAPS, which is the

10 American Association of Pharmaceutical Scientists. They are

11 all scientifically based but they do have a regulatory

12 overtone in that they want to reduce the filing requirements

13 for the industry.

14 A question on your container-closure integrity

15 testing. You talked about bracketing different sizes of

16 vials. You are talking about fill volume, when you say

17 different sizes of vials?

18 DR. LEINBACH: No. We just talk about different

19 sizes. Usually, what we accept is the media fill which,

20 most of the time is around 40 or 50 percent of the fill

21 volume.

22 DR. POUST: No; I understand that. I was looking

23 for some clarification if you are talking about 5 ml versus

24 10 ml versus 50 ml vials.

DR. LEINBACH: By size.

DR. POUST: That is what you mean by size. But I want to suggest an alternative philosophy. That is why I wanted clarification. Have you considered an approach looking at it from the point of view of the neck opening of vials?

DR. LEINBACH: The neck opening? Yes; we do.

DR. POUST: Most vials come in three different-- you have 13 millimeter versus 20 millimeter versus 28 millimeter.

DR. LEINBACH: We actually say the smallest container with the smallest and largest closure, and the largest container with the largest size--

DR. POUST: Given that you are looking at the integrity of the seal between the stopper and the neck, it seems like you ought to be looking at it from the point of view of the diameter of the neck, and if it is a 20-millimeter neck, does it really matter if it is a 10-ml vial or a 20-ml vial or a 50-ml vial. You are looking at the integrity of where the rubber, to paraphrase a saying, where the rubber meets the glass.

DR. LEINBACH: But the bracketing takes care of what you are talking about.

DR. POUST: Okay; so there is some willingness to

1 look at diameter size versus filter--

2 DR. LEINBACH: I tried to simplify it. But we do

3 look at neck openings as well as size, sizes or volume.

4 DR. POUST: Okay. Thank you.

5 DR. LEIN: Other questions?

6 MR. GARZA: If I may comment on that container-

7 closure integrity issue. Depending on how many different

8 sized vials you have, as you said, the purpose is to show

9 that you have an intact seal. If you do bracket and you do

10 have a lot of extremes in between, my concern is

11 compatibility of the stopper and the opening on that vial.

12 Depending upon your specifications for receiving

13 stoppers and vials, that would impact on how I would

14 evaluate what you have done. If you have 15 different sizes

15 between largest and smallest, I would think you would want

16 to do a little bit more to show--or at least show your

17 incoming specifications, the inside diameter of the opening,

18 the outside diameter of the rubber stopper, its composition

19 and so forth are, in fact, in control so that you can assume

20 that they do, in fact, make an intact seal.

21 DR. POUST: So you are suggesting that you ought

22 to look at teflon stoppers versus non-teflon-coated versus

23 something else all within the same vial diameter?

24 MR. GARZA: From the standpoint of the field, yes,

because that can have an impact on the seal on that vial. Container-closure integrity versus media fills are different issues. At times, they can be interpreted quite liberally. In a given case, that may not be adequate.

DR. POUST: But you could to both of those experiments in the same run.

MR. GARZA: Yes; you could.

DR. POUST: Thank you.

DR. LEIN: Other questions, clarifications?

DR. STERNER: I have a plea to those reviewers and approval people who look at two particular types of solution that are found in the types of food-animal practice that I am in. As the victim of multiple thumb lacerations, because of these self-contained aluminum caps, we don't always work under ideal conditions, at least in Michigan where we have nine months of winter. Your hands are often wet and cold.

That seal is viewed much more of an impediment or a liability rather than an asset in terms of protecting the animal's welfare and particularly my welfare.

DR. LEIN: You are not part of the regs, though.

MR. SCHINZE: I might add this container-closure integrity issue was not really an issue for veterinary firms prior to 1991 unless--and I am not sure, even then, to what

extent it was you were a subsidiary of a human pharmaceutical firm that was producing product in their facility.

It is one of those issues that I am certain all of you who are end-users and in the clinics can attest to how much more integrity and quality we have added by adding the container-closure integrity test to the products. We haven't been able to figure it out in industry.

Those container-closure systems are the same ones that were used in the '50's and the '60's and the '70's and the '80's. In many cases, the polymers or the rubber systems and the seals haven't changed at all. There is not a great deal of technology that goes into stopper design in the seals, and the bottles are made by the same Wheatons and Cornings or whomever that have been made in producing those products, the stoppers, the seals, the whole bit.

DR. LEIN: Thank you.

Other questions?

DR. BARKER: Dr. Leinbach, all these different processes that are required in the application to demonstrate their meeting regulations, is there a follow up as to compliance?

DR. LEINBACH: Yes. The question was, is there a follow up by compliance to these processes that we look at

in the application. Yes; the investigator does look at that information but they look at it in a different way than we look at it.

DR. BARKER: It is preapproval.

DR. LEINBACH: It is preapproval. This is preapproval; right.

DR. BARKER: How about postapproval?

DR. LEINBACH: Postapproval--I should let Manuel address that. I am not an investigator.

MR. GARZA: Are you looking for differences between pre and postapproval requirements?

DR. BARKER: Just in terms of what Dr. Leinbach has gone through here, all these different qualities of the product.

MR. GARZA: If, during the preapproval inspection, all these were reviewed and found satisfactory, postapproval inspection is primarily to look at if the process validation issues have been complied with as well as if there have been any changes in the operation, in the controls, in the training of personnel, in the building structure, and so forth, we would look at that from the GMP standpoint.

But, postapproval, validation can stand the test of time. If it is done adequately, it is a matter of verifying that there have been no changes in the validative

1 process. We will look at that from that standpoint.
2 DR. BARKER: In the human drug industry, the
3 product is actually taken off the shelf and tested. Is that
4 done for veterinary drugs?
5 MR. GARZA: Do you mean surveillance samples?
6 DR. BARKER: Yes.
7 MR. GARZA: To my knowledge, there are
8 surveillance samples. I can't speak to the amounts of CDER
9 versus CVM. I am not familiar with that.
10 DR. LEIN: Does anyone have that answer? We will
11 leave that unanswered.
12 DR. GERKEN: The validation process; was that
13 instituted then in the '91 preapproval compliance program
14 changes?
15 DR. LEINBACH: No.
16 DR. GERKEN: That validation was always there?
17 DR. LEINBACH: Yes; it has always been in the
18 regulations.
19 DR. GERKEN: It was not significantly changed in
20 1991? It has always been there and these kinds of
21 requirements have always been there?
22 DR. LEINBACH: The thing that happened in 1991 was
23 that we developed a guideline to sort of give an idea of the
24 kinds of information that should be generated for process

validation. That was in request to industry's inquiries about what kind of information do they need to provide. That was the reason we developed the guideline and then had the workshops was to try to disseminate that information so that--prior to that, the main deficiencies that we were seeing and applications for sterile drugs was absence of either all the validation information or just parts of it.

The reason was that there was a lot of confusion as to what kinds of information should be there. So, at the request of industry, we endeavored to write a guideline to give them guidance and then to have a workshop--well, a series of workshops--to try to educate the industry as to what some of those--the information in that guideline was really saying because it is very difficult to give a specific set of information that has to be generated for process validation because drug products, even all penicillin products, are not equal, or all of anything is not equal, because there are different processes and there is really no way to do it other than in general terms.

DR. GERKEN: Thank you.

DR. LEIN: Any other questions?

Hearing none, we will go on to our next speaker, Dr. Dennis Bensley, further on FDA perspectives.

DR. BENSLEY: Good afternoon. I promise I will be

brief, maybe ten minutes, tops. As part of the FDA perspective, I would like to discuss some points of clarification regarding chemistry, manufacturing and control, or CMC filing expectations--

[Slide.]

--including a brief discussion on the CMC filing requirements for the approval of original animal drug products or drug applications, I should say, a brief discussion on supplemental or post-approval CMC changes to approved animal drug applications and CVM's perspective on some specific CMC issues.

CVM's chemists and microbiologists perform scientific evaluations of the chemistry, manufacturing and control information submitted in original and reviewed according to current FDA and CVM policies and regulations and the U.S. Pharmacopeia and National Formulary.

CVM determined whether or not manufacturing and control information submitted in original animal drug applications are adequate to assure that a drug product will maintain the conditions of use, labeling, safety, effectiveness, identity, strength, quality and purity over its marketed life including the adequacy of the manufacturing methods, facilities and controls to preserve them.

The major CMC review areas for an original application consist of the following.

[Slide.]

Labeling, primarily the chemistry and the control information on the labeling; information on the components and composition; information on the manufacturing and/or control facilities; chemistry manufacturing control on the bulk active ingredients; raw-material control information;

[Slide.]

Manufacturing process information; sterile process-validation information; analytical control information including the release specifications and limits including validation studies; information on the marketed container and closure; and stability information to determine expiry dating.

[Slide.]

Once an animal drug application is approved, FDA's responsibilities continue regarding the regulation for the chemistry, manufacturing and control of the drug product. A number of CMC changes will likely occur after the original approval including the following commonly seen changes: new sources of bulk active ingredient; new finished drug-product manufacturing facility; formation changes; the manufacturing process including sterile process changes;

[Slide.]

Changes in the analytical methods and/or specification limits; changes in the marketed container or closure; exploration dating changes; and manufacturer reprocessing.

[Slide.]

All these changes may impact the quality, safety and/or effectiveness of the approved drug product and, therefore, must be reported to the agency. Also, these changes typically may not be implemented; that is, the product manufactured with these change cannot be marketed prior to approval of a manufacturing supplement.

Again, CVM reviewers assess the supporting data to determine whether the CMC changes will impact the approved conditions of use, labeling, safety and efficacy including identity, strength, quality and purity of the drug product.

Supporting information and data are submitted to the agency by the drug sponsors for review. This data typically consists of chemical and/or microbiological testing results: for example, comparing the release testing results of product before and after the proposed change, stability testing on pilot lots, et cetera.

If the data is comparable to the data generated on the approved product--that is, prior to the proposed change-

-then CVM typically approves the supplemental change and no clinical studies are required. Therefore, a well-controlled quality drug product with appropriate in-process and end-product specifications and tests can be approved for a large number of manufacturing and control changes without requiring additional supporting clinical studies.

To give you additional insight into some specific types of CMC information recommended by the agency to insure the quality of an animal drug product, I will comment on a few issues raised by the animal-drug industry regarding CVM's chemistry, manufacturing and control filing recommendations.

Other raised issues in our comments are provided in the handouts.

One issue that was raised in regard to the use of compendial-grade material, specifically excipients or components of finished animal drug products are required to be USP or NF grades if such grades of material are available. Instead, other grades of material--for example, those listed in the Food-Chemical Codex--should be permitted if the finished animal drug product meets its release specifications.

The U.S. Pharmacopeia, or USP, and the National Formulary, or NF, are the official compendia recognized by

the Federal Food Drug and Cosmetic Act. The USP and NF provide, in large part, a compilation of monographs for active ingredients, finished dosage forms and other common components or excipients used in drug formulations.

The monograph mechanism provides public standards of acceptance for the identity, strength, quality and purity of drug products. Therefore, excipients of finished pharmaceutical animal drug products should be USP or NF grade if a monograph exists.

A manufacturer may make changes to the USP monograph. However, prior FDA approval may be required before these changes are implemented. If no USP or NF monograph exists for an excipient, then appropriate testing and specification limits must be established.

As elaborated in earlier talks, quality cannot be tested into a product. Quality must be built into a product. Therefore, the use of USP- and NF-grade excipients provides that the finished drug products are of good quality. Also, USP- or NF-grade materials have successfully been used in veterinary pharmaceutical drug products for decades.

[Slide.]

Another issue was raised with regard to the specification limits, USP limits, for assay testing.

1 Specifically, FDA requires that the potency or content
2 specifications for the active ingredient in a finished drug
3 product be 90 to 110 percent of label claim. This
4 requirement conflicts with the USP specification limits; for
5 example, 90 to 115 percent or even 90 to 130 percent
6 established for some antibiotic products. The
7 specifications of 90 to 110 percent may not be so rigid for
8 animal drug products.
9 As I described earlier, the USP and NF are the
10 officially recognized compendia for all drug products.
11 Although the tests and specifications provided in the USP
12 and NF monographs are typically acceptable to guarantee that
13 a product meets its approved acceptance for identity,
14 strength, purity and quality, these requirements are,
15 nonetheless, minimal requirements.
16 Additional testing or tightening of the
17 specification limits may be required depending on the drug
18 product--for example, the product-specific pharmaceutical
19 profile such as its impurity and stability profiles.
20 The release specifications for an active
21 ingredient concentration in a finished drug product are
22 usually 90 to 110 percent of label claim. If a drug product
23 has an active ingredient content-specification limit of 90
24 to 100 percent, the product must meet this limit throughout

its shelf life.

CVM policy specifies that all animal drug products should be formulated with active ingredient at 100 percent of label claim. However, overages, or over formulation of the product with the active ingredient, may be allowed under extenuating circumstances such as consistent loss of the active ingredient during manufacturing.

The limits for overages are no more than 3 percent of non-antibiotics and no more than 5 percent of antibiotics. All overages must be justified. However, overages in excess of 3 or 5 percent will likely require supporting data in support of the over-formulation.

Wider USP specification limits for the concentration of typical antibiotics, for example--for example, 90 to 130 percent of label claim--were originally established because of large variations in the precision and accuracy of the analytical methods; typically, microbiological tests.

Since the original methods were established, many microbiological tests have improved or are being replaced by more precise and accurate tests--for example, high-performance liquid chromatography--therefore allowing for tighter specification limits for the active ingredient content.

Manufacturers also request larger overages for antibiotics--for example, 15 to 30 percent overage--to compensate for the product's poor stability and to maintain the product potency above the lower limit of 90 percent of label claim at the end of the product's shelf life.

However, CVM must consider additional factors before proving such large overages including, one, the effect of higher concentrations of active ingredient on human food safety if the drug product is intended to treat food-producing animals and target animal safety.

Two; the effect of the degradation components on human food and target animal safety. For example, if the product is overformulated with 15 percent more active ingredient in order to maintain a shelf-life of two years, then, at shelf-life, the product may be at 90 percent label claim and the concentration of the degradation products can be as high as 25 percent.

Three, whether the expiration dating period is reasonable to justify an overage; for example, is it reasonable considering the potential safety problems to overformulate a drug product just to extend the shelf-life from two to three years especially since most products are probably used within the first year.

[Slide.]

The final issue I am going to address is with regard to degradation compounds in generic drug products. The specific issue was the requirements for identification and measurement of degradation compounds in the generic animal drugs is excessive and unnecessary since this information was either already developed for the pioneer product or the safety of the pioneer product has been demonstrated.

The Federal Food Drug and Cosmetic Act states that for abbreviated drug applications for generic drug products that one, the methods used in or the facilities and controls used for the manufacture, processing and packing of the drug should be adequate to assure and preserve its identity, strength, quality and purity and two, information submitted for the active ingredient should be the same as those approved in the new animal drug application--that is, the pioneer drug product.

Specification limits for individual degradation compounds and total degradation compounds are typically established for new animal drug products for product release and stability testing. The adequacy of these limits are also assessed by clinical studies including target animal safety and toxicological studies.

Many factors can affect the degradation profile of

the drug product including changes in the formulation, source of bulk active ingredient, manufacturer processing, container closures, et cetera. Though approved generic products are quality products, some aspects of the generic products chemistry, manufacture and control typically differs for the pioneer's product including different formulations, if it is tested for bioequivalency, different sources of the bulk active ingredient, different manufacturing processes, all of which may generate the different degradation profile.

Therefore, measurement of degradation products for generic drug product release and stability which provide a necessary assurance that the product will be safe and efficacious are largely independent of the data in the pioneer application. This data must be developed separately by the generic-drug manufacturer.

In conclusion, I briefly discussed, one, the chemistry manufacturing and control filing requirements for the approval of original animal drug applications; two, supplemental or post-approval chemistry manufacturing control changes to approve animal drug applications; and, three, CVM's perspective on specific chemistry, manufacturing and control issues.

Hopefully, my discussion helped you understand

some of FDA's functions in regulating the drug product's chemistry, manufacturing and control and our goal in CVM is to approve quality safe and efficacious animal drug products.

DR. LEIN: Thank you.

Questions?

DR. POUST: In one of your early slides, you mentioned that, I believe, you require approval of a special supplement to extend an expiration date; is that correct?

DR. BENSLEY: Yes.

DR. POUST: But in the human side, they are not requiring that?

DR. BENSLEY: If you have full data to support it, the extension of expiration date, then you can implement that change prior to approval, submit it in an annual report. However, if you want to extend the expiration date based on limited data--for example, if you want to go to two years based on 12-months data, then you need prior approval from FDA.

DR. POUST: But if you have full data, do you not need prior approval?

DR. BARKER: You do not need prior approval. It has to be reported to us in an annual report.

DR. POUST: Okay. I had one other question. It

is a topic you didn't talk about but it seems to me that there is a comment in here about the rigor of the stability protocols for marketed products that is a rigor that I did not see in my twelve years of managing a stability program in the human pharmaceutical industry.

I am kind of wondering why that rigor is there.

DR. BENSLEY: I believe that is the testing of containers in the inverted upright--

DR. POUST: Inverted, upright, accelerated conditions; it sounds like it is being required for every production batch that goes on stability.

DR. BENSLEY: No; we just require that on the first three production batches.

DR. POUST: So there is a misconception in the criticism?

DR. BENSLEY: Yes. That is in our current stability guidelines that specifies for the first three production batches.

DR. POUST: Even that is rigorous from what I saw on the human side.

DR. BENSLEY: Right, but especially for new drug entities, we like to have a history because you have to remember, a lot of supplemental applications are based on accelerated stability studies. We need something to compare

it to once supplements come in. So we need some sort of history, something to compare it with from a degradation profile perspective.

DR. POUST: I guess it just gets back to what people have been talking about this morning. This is a bad place to say this, but there is probably more than one way to skin a cat. If we get into the how of doing things, maybe there ought to be some consideration given to some flexibility of some of those requirements.

I was trying to figure out why such rigor was required and the only thing I could come up with is maybe people in this industry aren't doing the in-depth development work that people are in the human side. So maybe that is kind of a make-up requirement. I don't know.

DR. BENSLEY: We commonly see that companies may come in with a supplement requesting dropping the accelerated testing. Usually, we honor that request.

DR. LEIN: Other questions for Dr. Bensley?

Hearing none, what we are going to do is give you a little rest, Joe. We will take our 15-minute break here at this point and try to come back right at let's say 3:10 and start in again.

[Break.]

DR. LEIN: Dr. Joe Bertone will give a

veterinarian's perspective on quality animal drug issues.

Quality Animal Drugs, Manufacturing and Control

DR. BERTONE: Good afternoon.

[Slide.]

What I wanted to do, even though I am listed under FDA perspective, I don't think this is just an FDA perspective. Also, I don't like to do what I am going to do next, but I thought I had to do that so that people kind of knew where I was coming from.

[Slide.]

This is just about me. I am a diplomate of the American College of Internal Medicine. I am the Chairman of the Large-Animal Program at the Internal Medicine meeting. I am a Therapeutics Committee member for the AEP. Also, I have an equine internal medicine private consulting practice so although I do work at the Center, and I do spend a lot of my time there, I do some other stuff as well relating to this area and my concern in this area.

[Slide.]

These are, again, some of the research areas that I think also relate to this. I spend a lot of time worrying about endotoxin. That is why this issue is very sensitive to me. Platelet-activating factor; I have written papers on critical care, cardiology, infectious disease and now,

thanks to people at the agency, I have some specialty training in pharmacology as well.

[Slide.]

The question to me is should the quality standards for veterinary drugs be relaxed in comparison to drugs for use in human beings and with the purpose to reduce cost, as highlighted in yellow. And then will this action improve drug availability.

[Slide.]

In terms of me, I am being, I guess from my upbringing--I am not necessarily the standard Yankee, so to me more is not necessarily better. To me, drug availability means the ability to establish an armamentarium of medications to manage animal suffering and improve animal use. Because I do equine work--however, I don't do any racetrack work--improving animal use is always an important issue.

[Slide.]

Drug availability, to me, is not simply an issue of drug numbers. In fact, to me, drug numbers are greatly outweighed by the flexibility of drug use. So I am not as much interested in how many drugs are available for a specific condition but, basically, how many ways can I take one drug product and use that. Being an equine medical

1 person, I didn't know that there was such a thing as
2 extralabel use until I came to CVM.
3 Basically, AMDUCA, in and of itself, improves drug
4 availability. I think that is a major impact. So, in terms
5 of using a drug in a flexible manner, the common paradigm
6 that says "first do no harm" is very, very important. To
7 me, that requires massively quality of product.
8 So what I am going to give is what I like to use
9 as an example of extralabel use.
10 [Slide.]
11 This is Gentocin solution which is basically
12 approved as an intrauterine infusion for the control of
13 endometritis in mares. What is key to this issue is that
14 the drugs are evaluated only under conditions of use which
15 means that this drug, for safety, was evaluated by infusing
16 Gentocin into the uterus of mares.
17 I will tell you right now that if I had to make an
18 estimate, I would say that maybe only 2 percent of all the
19 Gentocin used in this country is used in this manner.
20 [Slide.]
21 Here is a bottle of the drug. It's nice to see
22 that once in a while.
23 [Slide.]
24 Extralabel clinical uses in horses for Gentocin

solution. All ages of horses, mares, geldings, stallions. These were never tested in this situation except in mare. IV and IM use, intraarticular use. To me, I will tell you that very tiny doses of endotoxin give you a wonderful model of synovitis to look at chondropathies in horses associated with inflammation.

So, to me, this drug's use in this situation was predicated by the need to have a very clean, sterile, pyrogen-free drug substance. Also, I did want to say it is recommended in most of the literature that the drug be compounded with other IA drugs--for example, Adequon, that it is actually compounded with that to protect against infection.

So it is very important for that use.

[Slide.]

Clearly, this is a horse that I did not real long ago, a pleuritis case. This is a rib resection. You can see that I don't have any drugs that have claims for pleuropneumonia in horses that I could use in this situation. So, again, to me, drug availability is using drugs in a flexible manner, not necessarily in number of drugs.

[Slide.]

I don't have any claims for pulmonary abscessation

in a horse. I don't have any drugs that are approved for that--never will, I'm sure.

[Slide.]

So what I did, and I am glad that Joe--Dr. Gloyd, who, also, I consider a friend--indicated that I had done this list-server survey. The answers were pretty clear but what I was most interested, actually, in was the people who did not answer the questions in the clearly obvious way that you would answer these questions.

[Slide.]

What I did is I used two--actually, I used three. Equine Clinical Network was another one that I did, but their answers created dishomogeneity amongst the population of answers. So I kind of left them out.

I will tell you about that in a second. Okay, okay; calm down. I wanted to be honest. Hold on. I can tell you what the answers are, actually. I will tell you what they are. One is FAACVIM, which is basically for only people who are boarded in internal medicine or who have other boards who are interested in internal medicine and it is only for residents in training.

ACVIMLA is an area for internal medicine people to discuss issues of relevance to internal medicine but not specifically internal medicine; for example, "What do you

1 think about the way residents are trained?" It is those
2 types of issues.
3 [Slide.]
4 There are 215 active ACVIM diplomates with a
5 large-animal specialty. 90 members of that group are
6 members of the two list-servers I indicated and there were
7 53 respondents. With the Equine Clinical Network
8 respondents, there were 18 more respondents in that number.
9 [Slide.]
10 These are the questions. The answers are obvious.
11 But, again, that is not what I wanted to focus on. I wanted
12 to focus on the people who did not answer in the obvious
13 manner. "Do you expect that the quality of drug
14 formulations--manufacturing, identify, strength, et cetera--
15 approved for veterinary use is similar to formulations
16 approved for use in humans?"
17 [Slide.]
18 You can see on this table here that clearly 50
19 percent said yes, two said no and there was one maybe. The
20 two that said no and the maybe were people who were actually
21 concerned about the quality of the drugs, saying that they
22 don't believe that some of the drugs are made the way they
23 should be. Not knowing the difference between FDA and USDA,
24 they brought up the issue of vaccines and said they were

very concerned that vaccines contained measurable amounts of endotoxin and do cause reactions, et cetera.

But I am going to discuss those separate issues later.

[Slide.]

"Do you believe that the quality standards and controls considered essential for human drugs which are now, and have been, applied to veterinary drugs continue to be applied to veterinary drugs?"

[Slide.]

The obvious answer is yes. One, no. Two, maybe.

[Slide.]

"Is there a reason to believe that the quality controls for veterinary drugs should be less than those considered essential in manufacturer of drugs for human use?"

[Slide.]

The answer, very clearly, 49 said no. Three said yes. One, maybe.

[Slide.]

Basically, what I did to kind of improve the poll, I basically answered the same type of question in several different ways so that I would get as many answers as I could and corroborate the same type of answer.

"So, do you agree or disagree with the following statement; animal drugs do not need the same quality of production as drugs for use in people?"

[Slide.]

48 said no. Three said yes. And two said maybe. Again, I will get to the smaller numbers. What I can say, too, about the Equine Clinical Network people that I didn't include in this poll, invariably, they said--of the 18 people, 18 said yes, 18 said yes, here. And it follows right down. So, basically, the ECM block of people actually supported these contentions. That is why I didn't add them to the group.

[Slide.]

"Is there a scientific basis which supports that animals are more tolerant of bacteria and their toxins that are people;" in other words, the Uga theory.

[Slide.]

They all said no. Four said yes. Seven said maybe. This was very interesting to me. What they thought is that possible if some type of interspecies tolerance for endotoxins could be developed, then maybe we could reduce the controls. I think that that was a very good, thoughtful, answer.

Again, to me, the critical area in here is why

1 people--who were the smaller people and why did they vote,
2 or why did they choose the answer that was not clearly the
3 obvious answer?
4 [Slide.]
5 This is the long one. Sorry. It is too much for
6 one slide. But, "Controlling the quantity of bacterial
7 contaminants in veterinary drugs, especially injectables,
8 adds cost to veterinary drug production. The control
9 measures that are taken are similar to the control measures
10 for drugs used in human beings. The control measures are
11 considered essential in the production of drugs for people.
12 Do you believe that it is justified to reduce the quality of
13 veterinary formulations, below the standard of drugs in
14 humans, to reduce the cost of drug production?"
15 [Slide.]
16 Again, the answer was overwhelming. Again,
17 though, this one person in these four maybes said,
18 basically--in summary, they said yes; if there is a
19 scientific basis for reducing the quality, then we should do
20 it. I have to say I agree with that.
21 [Slide.]
22 This table here just basically shows you some of
23 the demographics. Many people belong to multiple servers
24 including ECN. There were 14 Ph.D.s, 26 M.S., three ABVP

boards, and then you can see here that we have multiple people that were boarded. This is surgery boards. These were pathology and nutrition boarded individuals.

[Slide.]

Let me just say about this pilot survey, that it is horrifically biased. I admit that 100 percent. All the members are members of a recognized specialty college, members of the AVMA. There is clearly a bias. They were all computer literate. They mostly associated with referral hospitals and, invariably, they are training all the veterinarians.

Another bias is that they published all the literature. If you look at the group of people in here, all the active people have published all the literature on veterinary drugs and medications and pharmaceutics and everything else that is available.

So I would say my question to the VMAC is how can we improve the survey or do we need to improve it. Maybe that is the more appropriate question.

[Slide.]

So what I am going to do is I am going to address the small minority of people that did not answer it in, as Joe said, the clearly obvious manner. First of all, the vaccine issue; the general thumb rule is you don't vaccinate

animals that are sick.

We vaccinate animals that are well. The reason for that is because when you get a vaccine reaction, you want to know that it is due to the vaccine and not due to the disease that you are dealing with.

I would have a hard time knowing that an animal with pleuropneumonia that I was treating was actually getting ill because of my drug, because they are essentially so ill to begin with, it would be impossible to make that dissection. It would be easy to say, "My animal died acutely. He died from pleuropneumonia." So I going to not know that my drug wasn't safe in that situation.

The last one was yes; "Reduce standards to scientifically identify species tolerance." Again, I thought this was very thoughtful although I will say this--I don't want to mention names, but I will say people who are doing all the research in endotoxin and were doing it when I was doing it all agreed that this would be impossible to do, to determine an interspecies tolerance.

[Slide.]

So what am I going to focus on? I am going to focus on injectable drugs and on gram-negative endotoxin. As I mentioned earlier, endotoxin is given a lot of credit and it is kind of the dull canary in a coal mine, I guess,

that we use to identify bacterial toxins.

The fact of the matter is gram-positive to endotoxin and other bacteria and fungi, et cetera, all produce toxins that can be as lethal or more lethal than endotoxin. So, although we focussed on that, that is the blunt tool with we look at contamination of pharmaceutics.

[Slide.]

I am going to throw, for those of you who know a little bit about endotoxin but not a lot, and for those of you who don't know anything about it, that is fine, too. Basically, this is a cell wall. This is the lipid-A fraction which is embedded in the cell wall of a bacteria.

This is the core protein which is relatively stable across genera of organisms. Then the O-antigen is species specific. As long as the organism is alive, there is no issue. When it dies and this is released, that is what causes the toxicity.

The thing is, what used to be thought, is that the toxicity of lipid A, which is this fraction, was well conserved. That is not true. It turns out that lipid A does vary in toxicity.

It was identified that the core protein was not toxic. It has turned out now that, with molecular biological work, that they have identified that it is toxic.

1 Also, O-antigen is toxic. How they determined this is
2 basically they can cleave this, they can build the molecule
3 that they want and they can show that the toxicity varies.
4 So, really, what we are dealing with here is three
5 toxins, not one. Not lipid A. This is not homogeneous. So
6 what I am trying to get across is that endotoxin is not
7 endotoxin is not endotoxin. It is very changeable from
8 batch to batch of the drug that is identified, or the batch
9 that is identified, to use research studies.
10 [Slide.]
11 Just briefly--believe me I have given three-hour
12 presentations on septicemia, on the pathogenesis, so this is
13 a very easy synopsis. Bacterium and bacterial toxins are
14 absorbed. You get mediator release. You get endothelial
15 damage and then you get metabolic dysfunction.
16 If this toxin goes systemic, then you get the
17 systemic exposure indicated here. You get cardiopulmonary
18 dysfunction. What happens is once you get cardiopulmonary
19 dysfunction because of translocation of bacteria and
20 bacterial toxins from the gut, you actually end up having
21 the cycle just recirculate.
22 So this is a horrible scenario. I have injected
23 endotoxins subcutaneously. I have infused it chronically
24 for seven days and I have decided I don't want to do that

research any more because I don't think it is humane.

[Slide.]

Rationale for reduction in quality standard requirements. The assumption is, and again this came out of the survey that I did, that the quality standards for manufacturing drugs for human beings have been established to reduce the risk of adverse responses. That is why the approaches are there. It is to reduce the risk of having an adverse response.

[Slide.]

The rationale for reduced standards; it should be scientifically based and it should be in the patient-client and veterinarian's best interest even if it is Uga.

[Slide.]

Let me go back. What are the two rationales that I can identify for reducing the standards. One is we do not need to have the same concern. They are just animals. I will tell you right now, this is insulting to me. It is also a disaster to public perception of veterinary medicine and I would be strongly against this approach.

What I have heard this morning, to some degree, I think that is the approach, the way that we are being attacked. This is absolutely ludicrous and it should not be considered under any circumstances.

[Slide.]

Basically, what this approach says is we can hurt a couple. Don't worry about it. You can still sell the drug. I am absolutely opposed to that.

[Slide.]

The rationale for reduced standards? What would be the reasonable approach to that is that animals and humans can tolerate a degree of bacteria and bacterial toxins which is septicemia. When I use the term "septicemia," that means bacteria or bacterial toxins. Then that level can be determined.

In other words, animals for some unknown, nonbiologic reason, are more resistant to endotoxin than people are, so they can handle it.

[Slide.]

What variables would need to be addressed in this thesis? I can tell you, if I can get the funding to do this thesis, I wouldn't be at FDA very long because this is about five years worth of work.

[Slide.]

The issues for study. You have to look at species variability, target species. You would have to look at individual variability and that means animal to animal, from me to Dr. Sundlof. There is a big space there, but, anyway-

-and then you would have to look at microbial-associated variability in the toxin potency, itself.

[Slide.]

Let me just explain this, again using the Uga theorem. Rabbits are coprophagic which means they eat their own feces. They do this at night. Yet they are the most sensitive species.

When I looked at the literature, the only study where they actually used one batch of endotoxin and has even some type of close relevance to look at individual species variability and sensitivity was done in Germany by Dr. Van Miert in 1968 who was a Ph.D. student at the time. Basically, he exposed all the species without quotes to endotoxin.

This is the way he ended up; basically, rabbits, horses, goats, dogs, cows, sheep, cats, swine and chickens. What I did is to kind of try to put humans in that perspective, I took some of the human NSAID studies where they inject people with endotoxin and try to put humans somewhere in this place.

I could say that you could argue with me easily that humans could probably be moved up to around the level of cattle, and they probably fall someplace between the level of cattle and swine in sensitivity. That is what is

accepted, accepted right now, and that is used as the test, the rabbit test. Clearly, the rabbit is the most sensitive.

So coprophagy is not an issue. Again, when I made that comment about the environment does not determine endotoxin sensitivity, I think you can see this unless, of course, I don't know what these people have done at home in the privacy of their own homes, but, certainly, on a social level, they are probably not to the level of being coprophagic.

[Slide.]

This is where the data came from, studies with humans and then Dr. Pete Constable did some studies from the AJBR that he had published. In fact, I had been there when he was doing those and we looked at calf sensitivity.

[Slide.]

I think that is another issue here. You can see here is cattle and here is calves. Calves are extremely sensitive to endotoxin, much more so. As they age, they actually become less sensitive. At least, that is what is felt.

[Slide.]

What other issues would we have to look at. That is a difficulty. I will describe that. This is the difficulty is doing septic research. I was one of the crazy

1 people that would try to do endotoxin research in horses.
2 One of the problems is establishing a model based on the
3 dose.
4 What is used, often, in other studies like mini-
5 pigs, et cetera, is they use a clamp where they actually
6 infuse a rate of toxin until they get a certain response and
7 then that is where they establish the model, and also the
8 response with repeated challenge. I will talk about that in
9 a second.
10 [Slide.]
11 So this is just one of my studies which is
12 nothing--it wasn't brain surgery. Basically, I used
13 15 microg/ml at 100 ml/hour infusion rate. Then I injected
14 drug until the pulmonary-artery pressure in these horses
15 rose 10 mm of hg. Just to tell you the difference in the
16 variability just within those five animals, the total dose
17 was between 0.96 and 2.5 microg/kg.
18 So this is the variable dose I had to get to get a
19 fixed response.
20 [Slide.]
21 Let me also say this, and this just shows you here
22 that I gave the endotoxin infusion and when they hit 10 mg
23 of hg, I cut it off. Some of them--in fact, most of them--
24 overshot that.

I think what is important there, and I do want to say this, two of the horses that I used in this study did not respond to the infusion at all, or hardly. Two of the horses that I used for this study died. So they are not included in that 0.96 to 2.5 microgram range which would probably set the range way out.

[Slide.]

There are some other things that add to responses to endotoxin. Environmental temperature; colder animals don't respond to endotoxin. They all die, but they don't respond to endotoxin as much. Amino adjuvants, caloric state, gut maturity. This is a really nice study using rodents and they showed that gut maturity is very important in the degree of endotoxin response.

[Slide.]

Protein deficiency. Age. It turns out that as you get older, when you reach a certain point, you don't get the same febrile response, but you are more likely to die. So, not only with age do we disconnect, we disconnect the interspecies and individual effect, but we also say that this animal will not get as pyrexic but he is more likely to die. So we have disconnected the model as well.

I hope what I am doing is really confusing you to death so that you realize that this would be a tough issue.

In this study here, they actually showed that dexamethasone treatment enhanced the response to endotoxin.

[Slide.]

Theophylline treatment? I don't know. The last time I treated an animal with one drug, so I would want all the drugs looked at. Immunocompromise; you are more likely to die. Previous endotoxin challenge; a nice, small study done by Dr. Merritt, presented at the Equine Colic Symposium, showed that horses have differential responses the more they are exposed. We know that.

[Slide.]

Here is, again, with a species. This is E. coli 0127:B8. This is one strain of mice. This is the other strain of mice. The LD50 is 2240 microg/ml or 60, just by changing the strain of mice.

You can show the same thing with Salmonella typhosa.

[Slide.]

There is microbe-associated variability. Lipid-A variation in toxicity, polysaccharide and core-protein actions that are variable. And then the LPS density. LPS is not LPS. Again, the density between strains of E. coli, Salmonella, whatever you might be look at, will vary just simply on the strains.

[Slide.]

This just shows some of those strain issues; E. coli, 055:B55. What they did here is they take human monocytes and they expose the human macrophages to doses of endotoxin. So this is a stable dose of endotoxin from each one of these. These are phenol extracted. This just shows you the differential bursts from phenol-extracted amounts of endotoxin from each one of these.

So, basically, E. coli K235 is much more toxic or much more reactive than E. coli 055:B55. So, figure that tolerance out.

[Slide.]

Now, where we really get more complicated is the issue of toxin-toxin interaction. Endotoxin responses with Pseudomonas proteases, differential responses when you have streptococcal pyrogenic exotoxin. Pseudomonas proteases actually increase the toxic activity about a thousandfold.

[Slide.]

Endotoxin and E. coli hemolysis and endotoxin and intravascular exotoxin challenge in lung injury so, basically saying, not only do you have to worry about interspecies, microbial, et cetera, but then start putting this milieu of the 280 at least known bacterial toxins together and try to figure that one out.

[Slide.]

I could just go on. Endotoxin and Staph-A toxin, basically, again, about a 100- to 200-fold increase in toxic activity. Take a burn patient and expose them to Pseudomonas exotoxin A. You can just keep going on and on and on.

[Slide.]

What are some other issues? Minor species uses. Am I going to be happy with these drugs that I can use them in a partridge or whatever else I might be using it in if it doesn't have the quality and the cleanliness that I need to use. This I throw in here although I did not think of it. One of the reviewers at CVM told me she is on an emergency IND right now for the use of equine hyaluronic acid in her joint, equine hyaluronic acid injected into her joint right now.

That is another issue when we say veterinary drugs can't be used. Also, there is the issue of using veterinary drugs for emergency treatment under disaster situations for human beings as well. So if we reduce the quality, we have to realize what we are going to have to address.

[Slide.]

In summary, then, the issues relative to individual sensitivity to septic media must be addressed and

to identify a safe interspecies tolerance. I hope what I have shown you is that that will be a hell of a task. Quality in manufactured products are essential to drug availability and extralabel use.

Although Dr. Blackwell said that we can't regulate on that basis, that is essential to the way I practice and, I think, to the way that most veterinarians practice, is that you approve a drug and then you find other ways to use it because there just aren't enough. Any reduction in manufacturing must be supported by scientific information.

In conclusion, what I would say is until a tolerance across all treated species can be identified, a reduction in quality standards cannot be justified. There may be some issues, but if it can be justified in veterinary drugs, then it would have to be justified across species and that includes the human species as well.

Any questions?

DR. LEIN: Questions for Dr. Bertone?

DR. FRANCIS-FLOYD: I am a little concerned by some of the comments that you made. I do a lot of clinical work. My patients are a lot smaller than yours and they are not worth nearly as much money. But they are animals. Because we don't have any drugs that we can use legally in our species--

DR. BERTONE: What is that?

DR. FRANCIS-FLOYD: Fish; usually guppies, goldfish. I have people come in with tears streaming down their face because their goldfish are sick. But, usually, I work with people that produce these animals for their living so we are dealing with livelihoods. And we have no drugs approved.

I don't understand. Instead of saying they are just animals, we are always saying, "Fish are animals, too," because we are trying to elevate them to the level of being an animal. I am a little concerned that since we are trying to get up to zero, that your assumption or your thesis is that if we relax the regulations that are currently in place, that that is going to suddenly, number one, put dangerous drugs out there and I don't think that that is the case, from what I have heard.

It sounds to me like the people that spoke earlier this morning are not proposing that at all. They are saying, "Let's specifically look at how we can put these drugs out on the market and try to get them out there safely but, possibly, with a little bit less cost so that we would have more availability.

The one issue is drug availability which, for my industry or the industries I work with is a huge issue.

Also, there is the issue of cost. I know if you are dealing with really expensive horses and you are running a specialty practice, your clients probably are not as concerned about cost as my clients are.

But we get down to the nitty-gritty where they can't afford to buy a drug, they can't afford professional service and so the animals go untreated. That is reality. That is something that I think we really need to address when we are dealing with economic issues.

DR. BERTONE: Yes; I agree 100 percent. I don't think what I said actually is not in line with that because, again, if we developed a drug for guppies, we would have target-animal safety work for guppies. However, if that drug was an injectable drug and found to be useful or the active molecule was found to be useful in horses, and it were not done under a quality production, then I probably would not use it. And so the drug uses its flexibility.

Again, because we look at drugs under conditions of use, it would be evaluated in guppies. But the question is could someone else, then, use it?

DR. FRANCIS-FLOYD: That is what we do now. We have extralabel use is the only way we can practice.

DR. BERTONE: That's right.

DR. FRANCIS-FLOYD: But we still have the issue of

if we maintain the high cost of these drugs, we can't get companies right now to help us. So if we want to work with a drug, I get veterinary students in there. We get money from industry. We get money from anywhere we can get it to try to evaluate safety and efficacy because that is all we can do.

But if we had some support from the companies, it would be so helpful.

DR. BERTONE: I agree.

DR. FRANCIS-FLOYD: I think that anything that we do that makes these standards harder to reach is going to make that less likely.

MR. GLOYD: I have a couple of questions for our good friend Joe. Joe, you said you surveyed 93 board-certified veterinarians.

DR. BERTONE: 93?

MR. GLOYD: I don't have the number. It is what I wrote down, but it is probably incorrect.

DR. BERTONE: It is. It is 53.

MR. GLOYD: You had 53 responses, but you surveyed 93.

DR. BERTONE: Surveyed 90.

MR. GLOYD: My question is, and I know you didn't ask this question, but it would have been an interesting

1 question to ask, how many of those folks were exclusively
2 dependent on fee-for-service for their income? Neither you
3 nor I are dependent on fee-for-service.
4 DR. BERTONE: I think probably most of them are
5 not dependent on it.
6 MR. GLOYD: That is what I would expect.
7 DR. BERTONE: I figured that is where you were
8 going with this.
9 MR. GLOYD: The other one was, you were talking
10 about the endotoxins that you injected. Were any of those
11 endotoxins isolated from drug products that failed to meet
12 GMP requirements? This is the real world.
13 DR. BERTONE: Joe, I will have to give my whole
14 talk to you later on because, clearly, that is not the
15 point.
16 MR. GLOYD: That is the real world.
17 DR. BERTONE: It wouldn't matter. Basically, that
18 is what I hope my talk indicated. It wouldn't matter.
19 MR. GLOYD: I suspect you can't do that.
20 DR. BERTONE: What?
21 MR. GLOYD: Isolate those endotoxins.
22 DR. BERTONE: If I could culture an organism out
23 of a drug or identify an endotoxin and serotype it, I could
24 grow it and inject it into an animal, a naturally occurring

endotoxin. But endotoxin is not the issue.

MR. GLOYD: You would have to enhance that endotoxin.

DR. BERTONE: Strep, for example; strep don't have endotoxin, per se, and yet they still have other toxins. So the toxin is not the issue. It is your level of tolerance that you are willing to accept. For me, my level of tolerance is the rabbit because I know that is a sensitive species. So that is where my tolerance is going to lie.

I will say this. I should say this. I have given endotoxin to, I kind of figured out once, somewhere around 80 horses. Several of those horses died with pulmonary edema after supposedly recovering from it. That occurred later on, probably as a slow response. That does happen commonly with endotoxin.

So what I would be concerned about is small amounts of endotoxin that are in drugs that will generate in responses as well such that animals will die after multiple doses. It happens.

MR. GLOYD: I would like to see that data.

DR. BERTONE: I can show it to you. It is not FOIable. I did it before I came here.

DR. CLELAND: Dr. Bertone, the basis of your survey was a comparison of human versus veterinary drug

requirements. Your questions were related to lowering the standards on veterinary medical products from the human side.

I think a concern from a lot of people that I have heard at lunch and through this morning is that the human requirements are being touted as the gold standard without looking at those requirements on an individual basis to determine if, in fact, that requirement is necessary for a veterinary product.

DR. BERTONE: Why would you say it is not necessary? You would say, then, that it is not necessary for any product?

DR. CLELAND: No; I am not saying that.

DR. BARKER: Then, if it is not necessary for any product, it isn't necessary for veterinary species. In other words, my contention is that if a method--there is no basis to say that anything that has been considered important for human products, we can somehow lower that standard because they are animals. That is absolutely fallacious. Is that a strong enough word? It is absolutely ludicrous to take that approach.

DR. CLELAND: I agree with you.

DR. BERTONE: Thank you.

DR. CLELAND: I agree with you that if you say

1 that a standard is being lowered because the target is an
2 animal, that that is incorrect. I don't think that any
3 standard should be lowered because we are dealing with
4 animals and not humans. But I think that the concern from a
5 lot of people is that we are automatically saying just
6 because the human industry, the human side of FDA, has
7 decided that this particular requirement should be in place
8 that then we move and say, "Okay; if it is good enough for
9 the human side, it has got to be the same for the animal
10 side."
11 I think that is the concern. I think that the
12 individuals in this room--there is not a person in this room
13 who doesn't want quality products. There is not a person in
14 this room who doesn't want safe and efficacious products. I
15 will lead anybody out of the room who doesn't want that.
16 But what I am saying is that we are assuming that
17 because the human side has said it is necessary, therefore,
18 that is the gold standard and that is what we should do. If
19 there is good science that says we should do that, then,
20 fine. I think that everybody in this room would agree with
21 that, too.
22 DR. BERTONE: And I agree with that 100 percent.
23 Again, that wouldn't change anything to my presentation. In
24 fact, I presented that as an assumption. The assumption is

that if the evidence would indicate that those issues are necessarily needed to reduce risk, then there is nothing to indicate we can reduce risk for veterinary species just because they are animals or because we need cheaper drugs.

Again, I still contend very strongly; it is not the number of drugs that is important, it is how many ways you can use them, because if I looked at the permutations of Gentocin, for example, there are about 100 drugs there, approximately 100 drugs across different classes of animals in that one application based on the fact that it was a quality product when it was first made.

DR. CLELAND: But I think there is a certain amount of bias by saying do you want the product that is less than a human product.

DR. BERTONE: And I said that. I said it was clearly biased. And I said we should come up with a way to make it better. So I agree with you. I am just saying that, at this point, I don't see any reason to change that.

DR. LEIN: There are four other questions here.

MR. STRIBLING: I have a comment and a question, if I may. I won't say that I am insulted, but I am concerned about continuing to be heard in a way that I don't believe the industry has presented, and it picks up on Janis' comment. I agree; there is nobody here, particularly

from the industry, who wants any decrease in quality of animal-health products.

The issue that I tried, obviously unsuccessfully, to pose was that once you have got a quality product, you know that it is safe, you know that it is effective, you know that it is made with quality, how far do you want to go after that in dealing with theoretical levels of statistical assurance to show that it is safe, not just to a certain 20 percent but to 40 percent or 60 percent or whatever the correct statistical mechanisms would be for demonstrating that.

There is a difference between quality of the product on the one hand which we certainly want, my members want, I want, and the quantity of statistical data over and above that brought about by additional tests to say yes, we know it has got quality but now it has got quality prime and quality whatever, whatever, whatever.

DR. LEIN: I think you are looking at risk assessment there.

MR. STRIBLING: I am looking at risk assessment.

DR. LEIN: Is it 0 or is it 1 percent or something like that.

MR. STRIBLING: Exactly. Thank you. What we are saying is, "Let's look at those areas once we have given

quality." I would love to work out a questionnaire with you.

DR. BERTONE: We don't need a questionnaire.

MR. STRIBLING: To ask to veterinarians because it would make clear not "Do you want drugs--do you think they should be the same quality as human drugs?" but, rather, "Do you want to pay x amount of dollars for such-and-such a test of this already safe, effective, quality drug in order to--well, take terminal sterilization--to assure the level of assurance of sterility from 10^{-4} to 10^{-6}?

I think a veterinarian trained in science, as I am not, but trained, also, in the real world could answer that.

DR. BERTONE: Clearly. Let me just say this.

MR. STRIBLING: So let's work together.

DR. BERTONE: Again, I think what you did is you paid attention to what I didn't want you to pay attention to and that was what was the answer. What I did was, in fact, I addressed that answer and I said "If, for the few people that answered against the majority," those are the people I actually addressed.

What I said was if you can determine a way to do that, then that can happen. I think that is what Dr. Marnane has said. In fact, I think Bill said that three or four times.

MR. STRIBLING: That was my second point.

DR. BERTONE: Basically, what Bill said is to present the data that shows that that won't increase risk, that that is reasonable. That is what I am saying, present the data that says that animals are less sensitive to endotoxin and bacterial toxins than people. You won't be able to do that.

MR. STRIBLING: Right. As a matter of law--

DR. LEIN: Now, you are in your field.

MR. STRIBLING: FDA's lawyer is here--the agency has the authority to ask whatever is necessary to show safety, effectiveness and quality. That is a given. There is, though, a related issue to what I talked about this morning of you can sit there and fantasize something may happen, therefore, go develop data to show that it won't happen.

That is just as much an ethereal risk-assessment thing as what I was talking about. Sure; industry has an obligation to develop data to show a product's safe, effective quality. Then the agency can go on and say, "All right; now there may be this problem and go show us the data to show that there is no problem."

That is risk assessment.

DR. LEIN: Some of that may come back, though, in

at least the reporting from veterinarians and producers of adverse reactions.

MR. STRIBLING: Which brings me to my next question.

DR. LEIN: Obviously, a product that does have that doesn't stay on the market very long. We have seen that more with vaccines than we have with chemicals or antibiotics.

MR. STRIBLING: May I see your last slide on the board as I ask this?

[Slide.]

"Until a tolerance or reduction in quality cannot be justified." I guess my question is whether you would have been able to make that statement ten years ago. My guess is that you could have on the basis of whatever the requirements were ten years ago.

The way we can prove that, I concede you have confused me but convinced me that it is impossible to demonstrate tolerances or certain levels for endotoxins. But it is not impossible to look at the adverse-reaction reporting from 1980 to 1985, 1985 to 1990, 1990 to 1995, and the number.

You can get from IMS the number of doses of product that were administered and you can come up with a

number of animals dead, percentage, in order to see whether, in the real world, all of these additional requirements are necessary because if the data, pre-'90 data, showed no problem, or no greater problem than the '90 data, then I would say that I would have agreed with this statement back in 1985 and you probably would have, too.

And you would be appalled by what the Center is requiring now.

DR. BERTONE: Neal, are you going to cover that issue at all about the adverse response? I would basically say that, in general, and I am very honest about these things, I didn't know you even had to put those in until I came to the Center. And I was training vet students at three universities. I talked to a lot of faculty members and they don't know that, and students aren't trained to do that.

The fact of the matter is that the number of adverse responses--when you give these drugs to sick animals, you cannot dissect out the fact that this animal died because of this drug or this animal died because he died from the disease.

To me, dependence on the adverse responses to make up the differences is questionable. I just don't think you will be able to identify the responses that occur. One good

1 example is flu vaccines for horses which, many times, cause
2 reactions in horses and you don't get, at least in my--I
3 mean, I didn't even do much herd health work and I can tell
4 you that I would doubt the number of horses that I have seen
5 with adverse responses have ever even reported because
6 people said that is just a natural thing that goes along
7 with using that vaccine with the caveat that vaccines are
8 used in normal animals.
9 I will tell you right now that I could not dissect
10 out an adverse response from a drug if I was giving it to a
11 horse that had gastroenteritis or enteritis or whatever
12 because, basically, that animal is so sick that if the door
13 opens up too fast, they might die.
14 So that is nice thing and it looks good, but the
15 fact is that that is of no value in identifying those issues
16 with manufacturing at least unless they are grossly--
17 DR. STERNER: It is certainly helpful if everybody
18 knows to submit adverse reactions which I think everybody
19 ought to know and hope that veterinarians as well as
20 companies do.
21 Dick, correct me; my recollection is that the
22 adverse reporting is to be done whether or not or the
23 veterinarian believes that it was because of the drug. If
24 there is a conjunction between the use of the drug and an

adverse event, it is supposed to be reported to FDA.

MR. GEYER: I think that is true. Neal might address that, also.

DR. BERTONE: I will let Neal take that.

DR. STERNER: I think this discussion clearly brings to the fore the fact that we all bring a great deal of emotional baggage to this discussion and these deliberations. From my selfish, myopic practitioner's perspective, my concern and my worry is that in setting regulatory standards, the net effect is one of diminished or decreased drug available.

I think that it is within the scope of the CVM's mission statement or new mission statement to provide safe and efficacious drugs. My worry is the reality of the corporate world tends to be that if there is not a perceived profit margin associated with the sale of a pharmaceutical product, then they probably will not develop them or bring them to the fore.

My concern is that in raising these standards, you have raised the cost of doing business to a point where they are unlikely to bring this product to market and, hence, I am deprived of a potentially valuable therapeutic regimen or therapeutic agent or having none at all, in some practice specialties.

The net effect is one of increased animal suffering. So my caution to those of you looking at drug approvals is is this really and truly necessary. I think we all have some degree of comfort with regard to whether you are designing a nuclear reactor, never or zero is a very, very long time, but in the design of these facilities, there is always, what is your comfort factor, what is your margin of safety.

That has not been established here. Is the tolerance zero, and zero is going to be defined by our scientific ability to define precisely zero. There comes a point, and we have all alluded to the point of diminishing returns and what is acceptable.

The final point that I would make as that Jess's profession gives remediation to those who feel they have been wronged by a product that, under some circumstance, might make it to market by an unscrupulous or inadvertent process, you have set up the safeguards. It seems to me they should be reasonable.

But, beyond that, if there is a failure or even a catastrophic failure, there should be the opportunity for Jess to practice his profession and seek remediation for those who have caused that wrong.

DR. BARKER: The question I had had to do with

1 what Dr. Cleland had brought up. If we do equate animals
2 and their proper treatment with humans, which everyone seems
3 to agree that we don't want to lower our quality standards
4 just because they are animals, then we are attempting to
5 reinvent the wheel.
6 The CGMPs represent standards of the industry.
7 That is an important thing in quality assurance because
8 those are the guiding principles. The industry that we are
9 talking about is drug manufacturer, not veterinary medicine,
10 necessary; drug manufacture.
11 The standards of the industry have been most
12 extensively applied to human drugs and they have kind of led
13 the way. Nevertheless, those standards and the techniques
14 that are involved, all of the procedures that are involved,
15 have very sound, reproducible, documented endpoints.
16 They are measurable. You can apply them. They
17 have their role. They have their function. They do their
18 job. If anything, Dr. Bertone has demonstrated to us that,
19 instead of dealing with one species like M.D.s do,
20 veterinarians have to deal with multiple species many of
21 which cannot have these drugs tested on them because of the
22 costs.
23 It is clearly demonstrated that certain species of
24 animals are more sensitive to the endotoxins and other

toxins for different bacteria than are humans. Again, if we equate trying to provide adequate therapy to animals and not lower the standards, just because they are animals, to humans, then maybe the regulations should be more stringent for veterinary drugs.

I don't think we want to do that but, certainly, the standards of the industry as represented by CGMPs, laboratory work as guided by GLPs, are just good practice.

DR. BERTONE: Can I just comment? Steve, you should have done this presentation. That is kind of the point that I was trying to get to and that is that we can't just lower the standards because they are animals. Lowering the standards because of some of the issues that have been raised is just not adequate.

Again, I don't know if Gentocin is used in guppies--

DR. FRANCIS-FLOYD: Actually, it is.

DR. BERTONE: That's good. Is it injected? Do you give it intraarticularly? The question, to me, is that, again when you talk about drug availability and talking about drugs not being available, I think one of the issues, again, in those terms is how often a drug is multiplied.

I don't know if any of the Schering representatives are here and I am going to say this strictly

1 from ignorance, but I doubt that they approved the drug
2 thinking that all of it would be used intrauterine.
3 There is a certain margin known from how a drug
4 will be used extralabel. So, in those terms, that drug was
5 approved knowing that the drug would probably be used
6 largely extralabel. So that quality product allowed that.
7 To look at it another way, sometimes some drugs, in my
8 opinion, are approved with full knowledge that they will be
9 used in an extralabel way.
10 Under those circumstances, that is calculated into
11 the profit margin. But I can talk to people from industry
12 who would probably make a comment to that.
13 DR. STERNER: But, within the CFR, there is, in
14 fact, a mechanism to deal where evidence indicates that a
15 pharmaceutical product is being used in that manner and it
16 can be remediated.
17 DR. BERTONE: I understand that. But, I am just
18 saying, as far as that margin, the quality of the product is
19 what allows that. So the assumption that the--
20 DR. BARKER: The quality of products is defined in
21 our culture, in our society. by CGMP.
22 DR. BERTONE: And by the use in people.
23 DR. BARKER: Yes.
24 DR. BERTONE: And the fact is you and I agree.

1 You might even make the case that these things need to be
2 looked at more critically because we use them in a wider
3 group of species. So, again, you just said it much better
4 than I did and I took a whole hour to do that.
5 MS. DURAN: There are a couple of points I want to
6 make. Regardless of whatever we decide, and I agree the
7 experts should decide what should be the standard. But I,
8 as a pharmacist who has to make a decision and am legally
9 responsible for what I dispense to practitioners, have the
10 right to know what I purchase.
11 This is a copy of the United States Pharmacopeia,
12 Human Supplement. It says on here, trichlorfon, which is a
13 veterinary product also, if I buy this, I have a standard in
14 this book. I can turn to this page and it says if I buy
15 this product, this drug company and the FDA guarantees that
16 I will get 98.whatever to 100.5 percent of trichlorfon in
17 this product.
18 We are talking about Gentocin because this is--and
19 I am not able to assay all drugs, but I do assay Gentocin
20 clinically because I have to look at those levels to make
21 sure I am getting a right level. The standards for
22 veterinary medicine are real confusing to me because
23 Schering tells me it is plus or minus 20 percent for this
24 particular drug. That may be because it is intrauterine.

1 Even so, if we go with your standard of 90 to
2 130 percent, that means if I buy a 100 ml vial of
3 gentamicin, that is 100 mg/ml. That means the drug company
4 has the flexibility of putting in 90 grams to 130 grams of
5 gentamicin.
6 That is a clinically significant program. If I am
7 treating a guppy, that would probably kill your guppy. If I
8 am treating a horse, I am in the toxic level if they put 130
9 milligrams. But what I see, when I assay the bottle, when I
10 have therapeutic failures, is that there is only 84 mg/ml.
11 Yes; I can report to the FDA and I can call the drug company
12 and they will say, well, we probably got a bad batch.
13 The bottom line is that somewhere on that label, I
14 need to know that I have a range in that drug of 90 to
15 130 milligrams. Right now, I don't know that. I asked
16 earlier today about a bioequivalency sheet. If I had that,
17 it would tell me--or, on the label.
18 This labeled product says in this bottle, I have
19 100 mg/ml plus or minus whatever percent. Then I have
20 something to work with. Right now, I really don't know
21 that. Some of our products are labeled sterile, pyrogen-
22 free. Even if they are, if you buy a human product that
23 says sterile, pyrogen-free, some pharmaceutical company may
24 have gone to great expense to buy that product.

I learned today that some of the products I thought that were not pyrogen tested are pyrogen tested. We haven't told the public that. We haven't told the veterinarian or the pharmacist that. So we need to look at the labeling and know.

And then, again, if it is not going to be that good a product and I choose, as a pharmacist, or you choose, as a practitioner, not to use that, you can say, okay, this animal can't afford this medicine that is four times more expensive, but at least we know what we have because right now I feel very uncomfortable going down the aisles in our pharmacy, and we have 1200 products, knowing what is a good-quality product and what is not.

If I kill an animal because I gave an overdose, is that the drug company's product or is that my problem?

DR. LEIN: I hope you didn't give it. I hope a veterinarian gave it.

MS. DURAN: We are trained.

DR. LEIN: I know you are.

We should move on. Are there any last-minute questions? This really did stimulate--see, that little coffee break really helped.

Hearing no further questions, we move on to the next presentation which is adverse reactions and medically

necessary veterinary products. Dr. Neal Battaler.

Adverse Reactions and Medically Necessary Veterinarian Products

DR. BATALLER: Good afternoon. We are more than one hour over. I don't know if you have any directions.

DR. LEIN: Move along. We are going to have a change in direction here. We won't discuss the hour. We will just move around.

DR. BATALLER: If everyone wants to speed read, I will answer any questions on the presentation.

[Slide.]

I am a veterinary in the Division of Epidemiology and Surveillance. I am the coordinator of the Adverse Drug Experience Reporting Program. I also provide technical support for the drug listing efforts in my division. I also provide scientific and medical support for the compliance people. So I am a jack of all trades and, hopefully, we can just end with the phrase right there.

I have two topics that kind of fit together. And they don't of don't. Basically, I am going to be describing the processes which CVM monitors performance and marketed approved and unapproved animal drugs and, specifically, by use of the Adverse Drug Experience Reporting Program.

Basically, what I would like to get across here is

what it can do and, very importantly, what it can't do. The second part will be to describe how CVM insures a continued marketing of what is called "medically necessary veterinary products," which you might have heard before.

That is when those types of products are in an actual anticipated shortage. Again, I have a short amount of time. I can't hope to go over the details, especially of our ADE reporting system, but I will give you the ABCs and, if you have questions, obviously, I will entertain them afterwards.

[Slide.]

One of our main activities on postmarket surveillance is the monitoring of the adverse drug experience. It is required under federal regulations that the sponsors--we will come back to this later--but the sponsors of FDA-approved new animal drugs are required to submit all reports of unusual or unexpected product performance. That comes out of the regulations.

Depending on the nature and the severity of the real or suspected problems, and it is really not up for the sponsor to determine that, the sponsor, nevertheless, should submit a report to CVM either immediately, within 15 days, or as part of the annual drug experience report.

For the folks in the audience, I have a

1 transparency for those on this side of the table. I am not
2 putting anything up that is not in here, so don't feel
3 advised to turn around. This is for the benefit of the
4 audience.
5 Basically, I think it is important enough we look
6 at what they are required to report immediately, mix-up in
7 drug, or labeling with another article, bacteriologic or
8 physical changes, product deterioration, failure of any
9 batch to meet its specifications. Within 15 days, they are
10 to report unexpected adverse side effects, unexpected
11 increases in the incident of side effects that might be on
12 the approved labeling, unexpected increase in the severity
13 of side effects and product ineffectiveness.
14 There is also an annual report, and I list other
15 reports of animal experience, studies, investigations,
16 tests. Firms do have the option, if they are getting
17 reports, side effects that are on the label, they can submit
18 those on a yearly basis. Quite often, most of the firms, to
19 my understanding, are submitting everything pretty much as
20 soon as they get them. All that alleviates them of the
21 burden of having to decide what is unexpected or an
22 increases or anything like that.
23 Rather than going into the details of how we
24 process reports, let's just relate how what I will call

1 significant deviations in GMPs which result in product
2 defects are identified and processed by CVM. This might be
3 a bit enlightening.
4 Typically, product deviations are detected prior
5 to or shortly after a product has gone into distribution.
6 That is good. We don't have a lot of catastrophes out
7 there, at least that we are aware of. Quite often, it is
8 the sponsors, themselves, that are aware of the problem
9 first and has already initiated action or the district or
10 the field office has picked up a problem either in
11 inspection or they tend to get a lot of the local phone
12 calls of complaints from consumers.
13 It is important to know that, quite often, the
14 recall has been organized and is under way before CVM is
15 even aware of the problem. The way it goes is the district
16 office will contact a CVM recall coordinator who, in turn,
17 looks at consultation to veterinary reviewers to see if the
18 recall was adequate for the situation.
19 Less frequently, it might be surprising to you,
20 and I put of no less importance, that CVM is made aware of a
21 product problem before the sponsor is, or even before the
22 district is. But the ADE report system does allow us that
23 provision. We are trying, with the resources we have, to
24 beef it up as much as we can and get the word out and try to

make it easier for folks to report.

We always do encourage people who have complaints to report to industry but, nevertheless, we make it easy for them to contact us. We typically will get those catastrophic types of situations reported from state officials, especially when it involves food and animals, obviously.

In this case, it will work in reverse. We are made aware of the problem, work with Compliance and the CVM recall coordinator who, in turn, calls the district who, in turn, deals with the firm to work on the recall.

[Slide.]

These are some reasons within the last year or so for some of the recalls that we have had. Ms. Dunnavan will present some, I believe, in her talk later on. But, within the last year, you can see subpotency, stability failure, superpotency, drug-article mixups, precipitates, particles, other contaminants or at least visual contaminants, label errors, misprintings.

Recalls, at least in this time period, and they involve, obviously, a variety of drug articles, antibiotics, vitamins and minerals, injectables, and medicated feeds This next point I just think is important. You can do with it what you want, but one-third to one-half, at least within

the last year, of the recalls involved unapproved new animal drugs.

Class 1 recalls are the most serious. They are the most extensive recalls. They typically result, almost invariably result, from reports of animal injury or death. They are brought to our attention before the firm or about the same time that the firm is aware of it.

Almost all of the other recalls are identified or initiated before CVM is aware of the problem. The district might be, but we are usually the last in the loop to know about a lot of those recalls. If I am misspeaking, Ms. Dunnavan will clarify that later on.

In general, and this is more from a Center for Human Drugs study, if the district or the field office has initiated the recall, it is typically more extensive and it involves more of a Class 2 type situation. Then, there are the recall situations that were initiated by the sponsor and those typically result in Class 3, and of the least concern, recalls.

As I said, Class 1 recalls basically are always initiated by the FDA although the firm and, if it is serious, they are made aware of it about the same time. In general, the recall system does work well. It is a qualitative kind of statement, but I think, overall, we are

1 quite pleased with the low number of reports, or at least
2 recalls, that we have to initiate.
3 Most suspect injurious batches are removed from
4 distribution before any significant animal injury occurs, if
5 it occurs at all. Having said that, I would like to just
6 emphasize that if there is a product recall, there is a
7 problem. Hopefully, and it is kind of a philosophical
8 issue, do you lock the barn after the horse is stolen and,
9 indeed, do you demand the lock and the horse back.
10 I hope we have less and less recalls. I hope that
11 the way we demonstrate that products are safe is by using
12 animal death to have us make some sort of action--basically,
13 I guess, it is supporting GMPs. Adequate GMPs in place will
14 minimize that. Obviously, there are day-to-day problems.
15 The ADE reporting system, as run by CVM, is an
16 important backup but it is not the primary means for
17 insuring drug safety, as far as GMPs are concerned. That is
18 really the FDA inspectors and the manufacturers or the
19 sponsors themselves.
20 I would like to say of the some 3,000-odd adverse
21 drug-experience reports CVM receives, 95 percent of them are
22 received directly from sponsors of approved new animal
23 drugs. That means 5 percent is "other." That is not really
24 good. We will get into that, perhaps, a little bit later.

1 Of the 3,000 reports, about 7 to 8 percent of
2 those reports involved a product defect. Typically, they
3 did not necessarily result in a product recall. An
4 additional 13 to 15 percent of those 3,000 reports involve
5 complaints of possible product ineffectiveness. Therefore,
6 a minimum of 20 percent of the adverse drug experience
7 reports are attributed to potential product defects.
8 But, also, just for your information, I would like
9 to say, of the 3,000 adverse drug experience reports, at
10 least one-third are attributed to extralabel use in animals.
11 Typically, that is a result of different species but,
12 obviously, there are other factors. But different species
13 is the main reason.
14 Establishing the relation of those reports to GMPs
15 has been asked. I think Dr. Bertone responded to that. It
16 is just not that simple. We have a very biased population
17 of reports coming in. If I gave you any definite answer to
18 that, I would not believe me nor would I believe anyone else
19 who gave it.
20 You just cannot do that. It is very hard to
21 establish, number one, that a drug is definitively involved
22 with a certain problem. If you want the obvious test, look
23 to the recalls as far a product defects. But those nuances;
24 it is very difficult for me to give you a definitive answer,

more so definitive numbers, especially when you are comparing from this--I think we are concentrating on pre-1990, 1991.

Our adverse drug experience reports have been increasing over the years, so you could make any conclusion with that sort of information that you want. But it is just we are getting the word out. We have new products coming out and we have a lot of concern--manufacturers and consumers, that are providing us with reports. To make a conclusion from differences before 1990 and after 1991, I just don't think you can do that at all.

The main strength of the ADE reporting system is to characterize drug experience or performance. That really is not captured in the NADA, but, obviously, we won't go into that today.

As I said, GMP monitoring is best achieved by the diligence of drug manufacturers and FDA inspectors who, overall, I think, do a very good job. Which brings us to the very important limitation. I talked about extralabel use. ADE reporting is required only of the sponsors of approved new animal drugs. The manufacturers or unapproved new animal drugs, oddly enough, are not required because they shouldn't be out there in the first place, obviously.

But they are not required by law to submit

anything to us. They are required by law, as Ms. Dunnavan said, to adhere to current GMPs, adequate GMPs. And they are required to maintain a complaint file for two years, but they just stay in the file. Unless we do an on-site inspection and look through that file, they don't come our way. They are under no obligation.

We get very few reports, obviously, from industry. As far as directly from practitioners, it is increasing, especially with the help of AVMA and help promoting their USP program. Nevertheless, it is really still quite small.

For all drugs in general, and, particularly, for the unapproved new animal drugs, the FDA requirements for GMPs are the primary regulatory means of insuring product safety. As I said, there is no approval for unapproved new animal drugs. There is no other guarantee for insuring that product is safe, period.

There is no guarantee for insuring that that product is effective, either, but there is absolutely nothing we can really do about that other than taking these drugs off the market which, I am sure you are aware, is no easy risk and might not be desirable in some situation.

The drug approval process affords a large degree of assurance that marketed products are both safe and effective. I think I got ahead of myself, so let me just

get on.

The main point I would like to bring up next, and this is not a threat. It is just a statement of fact. If there is an alteration of GMPs, and we will be blunt about this, that will decrease the quality of animal drugs, there is no way but for us to have to reevaluate the status of those unapproved new animal drugs that are out there.

They are out there under regulatory discretion, what we call "limited tolerance." If there is more of a concern, and the safety goes away, that is the only thing we have, should we be as lenient with some of those products. It is not a threat, obviously, but we can't avoid that and will have to look at it.

There are quite a number. There are 4,000. For your information, we have 4,000 drug listed products, two thirds of which are unapproved new animal drugs. A lot of those are topicals and things like that that you might think are innocuous. But, maybe not.

The second part of the presentation; let's go on to the medically necessary veterinary product. We certainly acknowledge that the shortage of certain animal drugs could result in undue animal suffering and animal-production hardships. We are veterinarians. We have concern towards animals. We have concerns towards their clients, producers

1 and towards veterinarians.

2 We do not want to promote undue suffering. To

3 anticipate and address the situation, CVM developed, and I

4 believe it is in Section 11 of your books--don't read it

5 now--we developed medically necessary veterinarian product,

6 or MNVP, shortage management policy. We developed that in

7 June of 1994 and it was taken from a similar shortage-

8 management policy that the Center for Human Drugs has. That

9 was June of 1994.

10 Its policy is not, necessarily, industry guidance

11 but rather it is a guidance internally for CVM staff. The

12 purpose is to allow CVM to prevent or alleviate shortages of

13 medically necessary veterinary products. We are committed

14 to doing that.

15 Products can be considered to be a medically

16 necessary veterinary product if either it is used to treat

17 or prevent a serious animal disease or condition or it is

18 needed to assure the availability of safe food products of

19 animal origin. The other component is that there is no

20 other available source of that product or alternative drug

21 that is judged by CVM's veterinary staff to be an adequate

22 substitute.

23 With AMDUCA and other types of non-animal drugs

24 out there, we can take other drugs into consideration. Do

note that inconvenience and non-therapeutic uses are not sufficient causes to classify a product as a medically necessary veterinary product.

Who can ask for an MNVP evaluation MNVP evaluation? Anybody can. We welcome it. We don't want to be adversarial. If there is a problem, if you know there is as problem, let us know of it and we will address the situation. We are committed to doing that.

Quite often, we have charges that, "Well, there is a shortage of products." It is the first I ever heard of it. It is the first we ever heard of it. Perhaps, maybe, we are a little--we put people off sometimes, but we really do welcome anyone to report such a thing.

I would also like to add that the policy does not necessarily exclude economics from being considered, especially in food-animal production. Yes; it can be considered. We are not required to, but we are going to use our common sense to know if it is going to result in undue harm.

As I say, particularly, we will consider economics if the shortage negatively and severely impacts on animal health or the animal production industry.

[Slide.]

Drug shortages may arise from a variety of causes.

I will boil it down to three; the unavailability of bulk materials, especially if that bulk material was used in a human product which the human sector is no longer interested in. That is a big situation. Please do not discount that.

I am not saying it is wrong or right, but that is what happens a lot of the time. Humans move on and we are left holding the bag and there is a no bulk drug to put in the bag anymore.

The other one is market decisions. Yes; I mean, we might impact on marketing decisions to a certain extent, but there are other issues with regard to marketing decisions that, really, FDA or CVM has, we are really not involved with; mainly, the manufacturer, the sponsor, does not think it is worth their effort to market that product any more.

You can put the blame on FDA very easily, but I don't think it is fair in all instances. And there are enforcement issues, and that is basically if there are compliance problems, GMP problems, which is the third one. We can, therefore, classify them into compliance issues or non-compliance issues.

I have, in my notes, just, again, to emphasize those first two, and those, quite often, have a large bearing on the situation. Not to discount the last one,

either. If there are GMP problems, there might be a GMP problem. If the problem is the result of a regulation that can be scientifically discounted, well, perhaps, that is what we are here for.

There are instances where, perhaps, that is a justified reason. All GMP violations are not necessarily an indication that FDA is being exuberant in their enforcement. Sometimes, they are justified.

If a determination is made that a shortage exists, special actions will be considered. I want to direct you to number one; discussions with the industry regarding solutions to the shortage. We harp on this today as far as within CVM, but this comes to the flexibility. We really are committed to work things out.

In the situation of medically necessary veterinarian product shortage, let's talk. You would be surprised what can happen sometimes. Sometimes, there are obstacles you just can't get around, but good discussion is the best solution in a lot of instances. We can accelerate the approval process and/or, in extraordinary circumstances, enforcement discretion.

I am sure all veterinarians have that quandary of it is nice to have those unapproved products. I don't want them to go away but, at the same time, I want the best

1 products, and you can go into this cyclic--I do it all the
2 time, and I try not to anymore. It is not healthy.
3 Enforcement discretion may be exercised when the
4 shortage situation results in compliance issues. It
5 occasionally becomes necessary because of a lack of planning
6 on the part of industry and inadequate communication with
7 FDA, just to put some blame elsewhere besides just on us.
8 In a global, pharmaceutical economy, events
9 sometimes occur over which the FDA has not control and may
10 not even have any knowledge of the situation.
11 Unfortunately, we may be blamed for a drug shortage that
12 results from these events.
13 The decision to exercise regulatory discretion, we
14 really consider carefully. There are consequences of doing
15 it. The impact of the violations on the quality of the
16 products, the risks that would result to them, the other
17 products that are out there. You start opening up a can of
18 worms when you start exercising regulatory discretion. It
19 is really not the best thing to do, but we will do it.
20 Nevertheless, we have and we will exercise
21 regulatory discretion when it is deemed necessary in
22 addition to utilizing those other special actions which we
23 would refer and are the best things to do. The policy does
24 not convey any special legal rights. It is things that we

do anyway. All it does is allow us to officially say, "This product is really important. Everyone put it on top of their pile."

I wouldn't say, "Drop everything you are doing," but put it on top of the pile. We will get this thing worked out as soon as we can. All the mechanisms are available for all other drugs. We do not want to circumvent the approval process. It is a hard line to walk, sometimes.

The policy was made to address approved new animal drugs that, for various reasons, were off the market. It really was not designed to address human drugs that went off the market and especially not to address unapproved new animal drugs. Those last two examples are not precluded but, nevertheless, it is not the best way to do business.

I really don't think it benefits the pharmaceutical industry that much.

[Slide.]

This is a list. Again, this is June of '94. We have instituted the policy. These are drugs. I really can't go into the details. It is not to hedge things and I will leave it to Ms. Dunnavan. Some of these are confidential information, why they occurred and what we did. But I will give you a list of things that we actively looked at as far as having a medically necessary veterinarian

product status.

We looked at the shortage situation. We looked at the negative impact it had. You could say, "A lot of those went off the market. Policy didn't do a whole lot of good." Again, there is only so much we can do. Some of the factors are out of our control, but we really looked into trying to make these products available.

In conclusion--we don't have much time for questions. I apologize--we do have a variety of procedures and policies. Know what they can do. Know what they can't do. They are all intertwined. It is just not that simple. There are approved drugs, unapproved drugs, human label drugs. Sponsors of human drugs are not necessarily required to report to us problems that they are having.

They do it voluntarily if they do it at all. But any changes in GMP standards--again, not a threat--but it will influence--everything is interrelated and it will certainly influence us to take a look at is it the best thing for our consumers.

Thanks for your attention.

DR. LEIN: Thank you.

Any questions?

DR. WOLF: I think some of the spokespeople from industry are saying, "Why do we need to change anything? We

1 don't have any problems with the way things are right now."
2 I guess I would like to address the adverse drug reporting.
3 If I took the time to report every time I had to
4 change antibiotics because my dog with a urinary-tract
5 infection didn't respond, so ineffectiveness, or had to
6 report every time I gave a cat some drug and it vomited, I
7 would probably spend a couple of hours a week writing to
8 FDA, which I don't, rightly or wrongly.
9 Also, I have to admit to being a little bit
10 skeptical of reports coming from the companies, themselves.
11 Please forgive me, but it seems to be that every time I
12 call, which is usually when I have a serious problem, the
13 word I get from the representative at the end of the phone
14 is, "Well, you are the only person we have talked to that
15 has had this problem," or, "We have used 1 million animal
16 doses and this is the first time we have ever heard of
17 this."
18 So I would like to ask you for your guesstimate,
19 if you will, of what proportion of the reports that you get
20 are the events that actually happened?
21 DR. BATALLER: We have not really done that. We
22 have that on the books to do when we have the spare time.
23 Overall, there is 10 percent--90 percent underreporting. As
24 far as what we call filtering through the industry, we have

not looked at that. We should do that. There are, obviously, just as with any other industry in the world, there are some good players and bad players.

The few bad players ruin it for anyone else. There are some firms that are--I guess I don't want to mention any names, but some firms are incredibly good and some are incredibly bad. If it is a problem that is affecting animal safety, then we will send an inspector out to look at the files but we really haven't done that many to do those as a project.

I, occasionally, will get reports directly from the veterinarian and get the same report from the industry. I would love to say that they always mesh. They don't always. I have had some very hot veterinarians because they thought what they said to the firm was misrepresented. Again, that occurs but I do not know to what level.

As far as it all coming from industry, I don't know what to say. It is just the way we have always operated. We are looking to beef up more direct reporting but resources preclude us.

DR. WOLF: Can you think of a way to encourage that among practicing veterinarians?

DR. BATALLER: It is not that easy, either. We do encourage people who worked with the industry. Most of the

firms are conscientious. They want to know how their drugs are performing and they will, hopefully, respond in a responsible way. They like to be able to detect problems immediately as they occur.

There is no faster way than to go straight through the firm, than to go through CVM, and then we got through the CVM recall coordinator. It is the fastest way. The other thing is, too, some of the firms are good about reimbursing veterinarians for expenses incurred. So, economically, they might have good luck, too. So I don't want to discount all the industry because I think it is very rewarding for both parties involved.

DR. BLACKWELL: I would like to just add that, and this is to build a little bit on what Dr. Bataller just said, I think we need to do a better job of providing back information. I believe, as practitioners, clinicians receive information out of that process which will help make decisions. It will encourage use or reporting.

I think, also, we need to find a way to make it easier. I think the computer technology today and the fact that those are very evident in most clinical settings will probably hold the answer to how to best do that where it is going to be reduced down to maybe a few minutes to key in some information that electronically gets sent in.

1 That is a concept that is certainly worth
2 exploring. I think the point is actually an excellent
3 point. We just have to do better.
4 DR. GERKEN: How many of your adverse reports come
5 from the USP? Do you have a sharing of information between
6 USP and FDA?
7 DR. BATALLER: USP, especially if they report it
8 to USP, has not precluded or disallowed the information
9 being passed on to us. USP is very good about sharing that
10 information almost immediately. They will fax it or send
11 it. As far as us sharing with them, I believe the last
12 AVJAMA article, they obtained information for us.
13 I spoke with a USP representative, in fact, this
14 week or late last week, and we are looking to build ties.
15 With regard to USP reports, it is an awkward question. We
16 don't want duplication. A lot of those reports go off to
17 industry. In fact, Dr. Meyers told me 100 percent of the
18 USP reports get forwarded to industry.
19 Industry is obliged to report those to us. So we
20 have to be cognizant of duplication of reports. We screen
21 those reports and we are looking for the obvious sorts of
22 things. But we more or less wait until we hear from
23 industry for the most part unless it is some obviously
24 injurious sort of situation.

DR. GERKEN: We have tried to do the information sharing with our veterinary students about how important this is. But we still get the same kind of response that I suspect many veterinarians and I know some of our clinicians have.

DR. BATALLER: The black hole?

DR. GERKEN: Well, no. The, perhaps, punitive nature of the FDA. I know that is a perception that is there. It is difficult to overcome that. I guess we will just leave it at that, but I think that that is a serious impediment, at least for many people who don't understand that the system is not punitive.

We can tell the students that it is not punitive, that the students still feel that it is punitive because it is a regulatory agency. So it is kind of a circular argument that never gets--I guess they just don't believe it. They can't believe it.

DR. BATALLER: That is up to us to get more positive experience. We are trying to do that by giving more useful information on the Internet. We are trying to have more of a presence on VIN. We do the best we can but, yes, you are right.

DR. LEIN: Any other questions?

Thank you. We are going to make a change in the

program. The two people that have come forward to give some public presentation on this, one has to get to a plane. We need to move that person up so we will do both of them at this point.

The first speaker will be Dr. Eugene Lloyd, who is with Lloyd Vet-A-Mix, who is going to give a presentation.

Public Hearing

DR. LLOYD: Thank you, Mr. Chairman, ladies and gentlemen. Thank you very much for hearing me today. Thank you, Dick Geyer, for also encouraging me to come to this meeting and for accommodating my schedule. You are all in for a treat because I do have to catch that plane.

As I looked around today, it occurred to me that I am maybe the oldest person in this room. I can say I spent about a third of my professional life as a practitioner, small-animal and mixed, and another third in academia ending up as a toxicologist at Iowa State University and two thirds of my life in industry.

I know that adds up to four-thirds which is above unity, but I work a lot.

I have distributed manuscripts to the committee members and the consultants and I think there are some extra ones floating around. We have two case studies which I use as a model. They are in your handouts. I would like to go

over those.

The first involves an NADA, the site transfer of an oral product from an old facility to a new facility. The second one involves a first attempt at a generic drug injectable.

First, though, I would like to address the general prologue questions publicly. Number one, the question is should a product differ between a human and an animal drug. I say no. If it says USP, it should be USP. I am hypothyroid, have been for 20 years, and I happen to take Thyroxin, USP, manufactured by my own company for dogs. But my internist says I am just doing fine. So I don't think there should be any difference in the final quality of the product.

However, when it comes to administration, I think maybe my plan today is to show you that we may be getting beyond the point of diminishing returns.

Case Study A involves a prednisolone. We went to the Food and Drug Administration and we said, "We would like to develop a chewable prednisolone tablet." They said, "Well, why don't you start with a conventional tablet first," which we did. This was approved quite some time ago and we manufactured that product and sold it for four years under an approved NADA.

1 Five years ago this month, we decided to start on
2 a new upgraded facility. In October of 1995, we moved into
3 that facility. It was our intention to do a site transfer
4 from the old facility to the new facility. We conferred
5 with Mr. McDonald of the Kansas City District and Mr.
6 Marnane of the Center for Veterinary Medicine. We had a
7 plan for facilitating that.
8 However, the District Director told us that first
9 we would have to cease manufacturing the prednisolone
10 manufactured in the old plant, cease selling it, the product
11 manufactured in the old plant and, secondly, we would be
12 required to hire consultants to certify our new facility.
13 I am glad to say that after 15 months, the end of
14 January, we finally were approved. Now, Page 2 is the a
15 list of the analytical procedures which we did to do the
16 validation of just one drug product. We do have other drug
17 products.
18 We had 1,642 individual assays. For those of you
19 who have done HPLCs and do your multiplication, you know
20 that we are talking about $6 figures to do just that. FDA
21 inspectors and private consultants insisted that we must
22 show that all batches of product manufactured were
23 statistically the same.
24 We cited references to show that this is an

impossibility when it comes to manufacturing pharmaceuticals, both human and veterinary.

We conferred with Dr. Cox, a statistician at Iowa State University. Dave said what we were doing was the best we could do. We went to Dr. George Milliken at Kansas State. He is also somebody who has worked a lot with CVM. He said, "What you are doing is fine. It is inappropriate to use normal statistical analyses."

To this date, that dilemma is either moribund or dead, I don't know which, but we have not had any official resolution on it. That is a problem with validation when you think about it. As I said, we got the facility approved but we do have over $100,000 worth of prednisolone tablets validated and manufactured in the old facility which we cannot sell and will probably have to be trashed.

At first, I said, "I am going to pay anybody $100,000 if they can show me there is a difference between those two." And I thought, "How about $50,000?" I don't have $50,000. But I would like to have anybody show me the difference in the quality of the drugs that were validated and produced in the old facility and the drugs that were validated and produced in the new facility.

There is another chapter and that is that the manufacturer, the synthesizer, of prednisolone does not have

a current DMF, drug master file. So we cannot sell the new drug that we manufactured because of that despite the fact that that manufacturer's drug dosage forms can be found in pharmacies right now for humans.

Case B study is a first attempt to get a generic drug on the market which was Ketamine. We do not have sterile facilities so we referenced this through a private-labeled contractor. We did all of our own work ourselves in the laboratory. This is including such things as container closure, endotoxins, everything, and even stability studies.

But the district--not the Kansas City District, and Mr. Garza, I hope you don't hold this against me. Another district would not approve our drug from that manufacturer ostensibly because of water. Nevertheless, in the 25 months period, they were producing dozens of both human and veterinary fluids and drugs. I ask you, why did they do that? Is it fair? I don't think so.

I have some final discussions here. I want to take a couple of minutes. Going down to the more specific questions, process validation, what we have happening now is what I call idiosyncratic pet peeves or translations of individual field investigators or consultants. You are jumping through the hoops all the time because they do not coordinate their thinking and synergize their plans.

1 This must change whether it is in human
2 pharmaceuticals or veterinary pharmaceuticals. We must have
3 a consolidation of effort and an idea of what we are going
4 to be doing in validating drugs.
5 Facilities, utilities and equipment, IQs, OQs,
6 PQs, you name it; it has gotten to where, unless you have a
7 blockbuster drug, you are going to find yourself suicidal to
8 go to another plant and upgrade the plant. You might as
9 well manufacture it in your old plant because you won't have
10 to have your drug master file opened up.
11 That is being discouraged now. Components; I know
12 Dr. Bensley talked about drugs must be USP. But USP isn't
13 the sole count, as you may find out from a couple of other
14 people today. What does count is does that USP drug have a
15 drug master file, was it produced under GMPs in a bulk drug.
16 I could go to just about any country in the world,
17 which we are doing, having drugs manufactured whether bulk
18 drugs or USP or BP, and there is no question about it.
19 Analytical testing: right now, a postapproval takes three
20 validation batches, if you are talking about an injection.
21 You are talking about $240,000. I was just talking to Bill
22 Lance and we came up independently with the same figures.
23 One other issue is related to that and that is--
24 this is an example. My company developed xylazine

injections, two of them, under a full new drug application. We did the whole works. It was research-developed. We did the synthesis, dose titration, safety evaluation, validation, expiry dates, the whole works. We know that if xylazine is left out in the sunlight that it deteriorates.

We asked FDA about putting this product in an amber bottle, everything else being exactly the same. They told us, at that time--it may have changed--"You must do a supplement." A supplement would take about a quarter of a million dollars and we would probably lose our three-year expiry date.

My company is almost 40 years old. We haven't gone very far very fast, I guess. I was thinking here a few days ago that I would have been better off to have stayed in academia and invested in the stock market. We spend a relatively large proportion of our product in R&D. We switch people out of R&D now. One-third of all of our people, and about half of our people have degrees of some type in my company, are in some kind of regulatory affairs, QA, QC or regulatory affairs.

It comes down to risk assessment, an everyday risk assessment, which we all do in our lives. As a toxicologist, I have been trained to distinguish the difference between toxicity and hazard. The latter is the

likelihood of a problem, not idealistically, what is the real toxicity. It is the real hazard that counts.

I have a Jewish friend who sometimes practices orthodoxy. He would prefer to buy kosher but he won't if it costs too much. I think we may be in that same situation. I am a devout perfectionist, but I want to say something. I think that idealism and perfectionism do have their limits and I believe we may be approaching that now.

I want to say again that it is not a case, I don't think, of making veterinary drugs and human drugs have a different release specification. It is a difference in how we got there and what it is going to cost to do it.

So, again, I say, are we approaching diminishing returns. I think we are getting there pretty fast.

Thank you very much for your attention.

DR. LEIN: Thank you, Dr. Lloyd. Any questions for Dr. Lloyd?

Thank you, again.

DR. LLOYD: Thank you.

DR. LEIN: The next presenter is Dr. William Lance with Wildlife Pharmaceuticals, Incorporated.

DR. LANCE: First, I want to thank you for the opportunity to speak before this group. Being way out in Colorado, we are the last to find out about something like

this. Again, I appreciate the time. Also, I admire your endurance. None of you look like you are completely immobilized yet.

[Slide.]

I was contacted by Mr. Geyer and very politely asked to come talk about the potential impact of human GMPs on the availability of what I call specialized non-traditional veterinary pharmaceuticals. That is the world I work in. So my comments and everything is going to be addressing the situation we are facing today. It is what I have continued to perceive as a rising bar of GMP compliance and how I believe, in my opinion, it will affect the availability of these drugs in the future.

[Slide.]

This is my world. I tell everybody I live in 3 milliliter world. If I can't everything that I need in a 3-milliliter dart, it is of no use to me.

[Slide.]

Just as some additional background, and we have been talking about, mainly, domestic species, but these are the situations. We are talking about real world. With these animals, job No. 1 is to get your hands on them because I don't care how good a clinician you are, you can't do a thing with them until you get them down.

That buffalo there, he has got all sorts of pathogens and gram negatives on his hide. I will guarantee that a giraffe does.

[Slide.]

Again, sometimes you only get this view of the animal going away.

[Slide.]

And then you have the horse from hell.

AUDIENCE: That is the appaloosa.

DR. LANCE: They say one of the reasons that Indians rode appaloosas into battle so they would be in the right frame of mind when they got there. Believe me, they would be in a better frame of mind if they could get a saddle on one of these.

[Slide.]

But, anyway, the issue that we are faced with is to get the drugs into the animals and then look for some response from them. Again, what I really want to talk to you about is kind of the history of these drugs. We can break the entire history of drugs for specialized veterinary medicine into pre-1986 and post-1986.

Pre-1986, we had one drug that was labeled specifically for use in non-traditional species. That was our old favorite M99 new animal drugs M5050. We have heard

a lot of talk about pre-1991 and post-1991. Those of you that may still have some M99 in your kit, the freshest that is out there is 1991.

I will tell you that this drug right here was a casualty of the increased level of compliance. This was being produced by Lemon. I can tell you for a fact that they quit producing this drug, closed their operation because they said, "For a product that we only sell 450 vials a year, we cannot, and will not, go through the hoops to make this drug available."

And so that is one drug--I don't know about any others--that was a casualty of what I call the Kansas City massacre. Since 1986, due to the research and neuropharmacology, there have been a lot of new drugs developed. Carfentanil is one of them, which we do have approved.

[Slide.]

There is a new drug called A3080 that has come out. There are some long-acting tranquilizers that are in the pipeline. We have some compounds that can be used for reproduction management, both in captive, non-domestic species and possibly free-ranging. These are the drugs that will be the potential casualties of future cost that is associated with GMP compliance in these special niches.

[Slide.]

Let's talk about the size of the need. The drugs that are produced strictly for non-domestic species, some of them are a thousand vials or less annually with, generally, one lot per year produced, maybe three lots if it is a highly active drug. The amount of raw material is 50 grams or less, and that figure will supply the world with carfentanil, up to 5 kilos. The 5 kilo figure is for a drug that is used to treat trichomoniasis in racing pigeons.

So we are talking about hand-crafted drugs. These drugs are filled individually, vial by vial. For us to produce three lots for validation of the process, we would have well over a three-year supply, a 36-month supply, on a drug that may have an 18-month expiration date on it. That is a problem.

[Slide.]

They said, "Well, why don't the major companies do it?" No way. The reason the smaller companies have it is because the major companies say, "We can't afford to do this. We are not going to dedicate and validate filling lines and facilities for 1,000-vial-a-year market." I'm sorry, but the dollar rules.

When you start looking at these special-niche products, the majors will not pursue those. It is a matter

of simple economic. I don't care if your heart is involved. I am emotionally and professionally tied to zoo and wildlife medicine. That has been my life for the last 30 years.

So I have a professional motivation to see these drugs out there because I have killed enough animals using inappropriate drugs. I have a bigger dead pile than anybody I know. But the major companies have consistently said, "We cannot afford to do this. Would you like to take a shot at it?"

Up until fairly recently, we said, "Yes; this equation can work." But as the levels of validation and GMPs continue to rise, then even the smaller companies are questioning, "Does this work in any world."

[Slide.]

What does it cost? If you make the assumption we are producing a thousand-vial lot, we have to put a normal amount on stability, go through the sterility, maintain the validations, both the initial process validations and ongoing.

[Slide.]

Now, if we had no cost in the active ingredient, to break even, we have got to charge you $50 a vial. That is if the active ingredient is free. This is the type of

1 economics that is at play in these specialized
2 pharmaceuticals.
3 [Slide.]
4 What are the facts? If we lost the drugs that we
5 currently have available for these specialized uses, it
6 would be disastrous. You don't have to believe me. Call
7 Mitch Bush at the National Zoo and your local zoo
8 veterinarians, and say, "What would you do if you lost
9 carfentanil today? What if you lost your reversal agents?
10 What would you do?"
11 I guarantee you they would be heading to Africa
12 real quick and smuggling the stuff in. There are new drugs
13 in the pipeline. Whether or not these drugs ever come out
14 will depend upon the level of regulations regarding them.
15 I am just simply addressing the manufacturing
16 issues, nothing about safety and efficacy requirements. I
17 believe that continuing to raise CGMPs regarding these
18 specialized drugs one, is not appropriate and, two, will be
19 fatal to doing any drug development. That is my opinion.
20 [Slide.]
21 Here is what I call the wild-dart equation. We
22 take the drug in this vial that has been manufactured to
23 absolutely 100 percent accuracy that it is perfectly pure,
24 we put it in a non-sterilized dart, we shoot it through non-

1 sterilized air, through an inch of mud, through the hair,
2 the hide and finally get it into the muscle.
3 All that extra cost that one, I'm not sure anybody
4 will pay for in my world, just went into the dirt.
5 [Slide.]
6 The easiest, most comfortable word to say is no.
7 No is safe. You can say no; give me more information. That
8 is safe. That is conservative. The thing that I fear and
9 the thing that I have discerned is that we have two entities
10 here. We have FDA and we have the Center for Veterinary
11 Medicine.
12 I have realized over the years that sometimes
13 there is conflict and warfare; is that not true? I thank
14 god that there is a Center for Veterinary Medicine because
15 if we had to live just under the big FDA, life would be a
16 disaster. I really believe that if FDA took over regulation
17 of airlines, 50 percent of the aircraft would have had to be
18 crash-tested before they would let them fly.
19 The other thing that we are dealing with is what I
20 call the "one size fits all" formula. I do not believe it
21 is appropriate for specialized uses. In many cases, it is
22 not appropriate for veterinary pharmaceuticals. I, too,
23 will stand here and say, "I believe that the animals that I
24 treat should have the best possible drugs available. But I

also believe they should have drugs." That is Job 1.

If the economic environment is created that precludes that, then we need to break the system and build it anew.

[Slide.]

The impact of no will be the loss of future drugs for minor species as well as minor use in major species. The continuing saying of no and asking for infinite amounts of data to give 100 percent reassurance against all possible risk will put the currently available drugs at risk.

I believe--my personal opinion--that this is a retreat from the reality of veterinary medicine in general and I can guarantee you the reality of the world that I work in.

[Slide.]

I believe that FDA and CVM want to say yes. I believe that FDA and CVM has a heart for veterinary medicine and they are currently looking for new ways, innovative ways, to say yes. Those of us in industry want to give them the information that they need to say yes, to make these drugs available.

[Slide.]

When you are in a situation and you are trying to get that one big horn ewe off the top of that fence, you

really appreciate that you do have a drug available to do it because, without them, what you have left is rope and the miracle drug we call "brutathane."

[Slide.]

It is basically going to take a cooperative effort. It is going to take some people within the Center for Veterinary Medicine to really stand up and make a stand for the animal resource, for the veterinary profession and for the publicly served to say, "Yes; there is a difference and there are special situations that require special consideration."

I believe that specialized drugs for use in specialized niches are one of those situations.

Thank you.

DR. LEIN: Thank you, Dr. Lance.

Any questions from Dr. Lance?

DR. WOLF: I have a special feeling for what you are trying to say here. My husband is an exotic-species veterinarian and I don't really want him run over by a rhino. I guess I would ask do you have any thoughts about where you want to draw the line. In other words, if it is a thousand vials a year, then we ought to make an exception, but if it is 2,000, but it is for a major species, we shouldn't.

1 Do you have some thoughts you would like to share?
2 DR. LANCE: Yes; I have thoughts I would like to
3 share. To set a limit, if you want to quantify it in
4 milligrams or kilograms, I think you have to look at the
5 use. If the use is within confined populations where there
6 is absolutely no risk to the human food chain, I think that
7 is one thing to be taken into consideration.
8 If you have a drug that you say there is some
9 possible diversion in the food species, you have to take
10 that into consideration. If you have one source where,
11 through surveillance, you can pretty well monitor how much
12 raw material is going out, I think you need to take that
13 into consideration.
14 Yes; I think there needs to be an appropriate
15 level. But, at the same time, myself as a manufacturer as
16 well a wildlife veterinarian, I want those drugs going out
17 to be first quality because the last thing I want is someone
18 to call me up and say, "Lance, you know, your drugs killed
19 another animal." I have a bad day when they say that.
20 DR. BARKER: You are victim of our capitalist
21 system.
22 DR. LANCE: Yes; I am. And I love it.
23 DR. BARKER: In the human drug market, a similar
24 phenomenon, of course, occurs with orphan drugs. In that

case, a law had to be written to permit private industry to address the need. I think there are tax writeoffs and a number of other phenomena. The industry may want to lobby Congress yet again to try to get that type of incentive to provide quality drugs to exotic and wild animals.

That seems like more of a solution than throwing out regulations that provide quality drugs that you can be assured will not kill your very expensive and rare exotic animals. That type of policy, would you agree or disagree, might be more appropriate?

DR. LANCE: If a policy would be implemented that would recognize the unique position of these drugs. I think the Center has, internally, developed those policies. It has been my recent experience that the Center is trying to find more and more ways to say yes in these issues.

It has been a dynamic process but I am always gun-shy of policy because policy is controlled by politics, perception and public pressure.

DR. BARKER: It seems like you have all three already. Everybody loves animals and we realize that our exotic and wild animals are a diminishing group of living species on this planet. They do need special care. Private industry is not necessarily a victim of capitalism. I think they do fairly well at it and will not address this issue

unless it is profitable, unless government steps in and gives them the ability to do some of the things that are needed, regardless of the capitalist system.

The profit motive and whether GMPs really enter that much into the cost of it is debatable. But some policy like that may be, I think, more appropriate because you need quite different drugs in many cases, higher potency and all that, than a lot of what does get produced.

DR. LANCE: That's true.

DR. STERNER: Dr. Lance, wearing my food-animal practitioner's hat, a couple of concerns here. One is we see a great proliferation recently in captive serve-a-day throughout the United States. They oftentimes become food animals in a sense, at least in the sense of that person who seeks to use them as wild game.

The other is a reference you made in your slides to minor use in major species. I guess I am concerned about at what point do you draw the line with regard to the popularity of a drug, a minor drug, as it were, or a minor use in a major species, particularly those that are food animals or potentially food animals.

DR. LANCE: The labeling on these drugs, at least the drugs that we produce and go out, very clearly have one, a 45-day withdrawal period before any legal hunting season

and no use within a legal hunting season. That is written in stone.

DR. LEIN: Other questions for Dr. Lance?

MR. GLOYD: Just a comment, as long as the word "orphan drug" came up. If you compare the market for veterinary therapeutic products to the market for human orphan drugs, I think that you will find that there are very few veterinary drug therapeutic agents that wouldn't fall into this same category as orphan drugs from a human standpoint from the amount of money that is exchanged on the marketplace.

So, in my opinion, that is not a fair comparison. This is a very small entity compared to the market for human drugs even if you classify them as orphan drugs.

DR. BARKER: So, regardless of any incentives, you wouldn't manufacturer them anyway.

MR. GLOYD: Well, I think that maybe we ought to classify all veterinary therapeutic agents as orphan drugs.

DR. BARKER: Help from private industry may be slow in coming.

DR. LEIN: Other questions?

Thank you, Dr. Lance.

DR. LANCE: Thank you.

DR. LEIN: Would everyone just like to rise for a

few minutes and we will start again.

[Break.]

DR. LEIN: I would like to introduce our next speaker. We are going to go back to at least looking at, now, the field perspective of FDA with the current good management practices. The first presentation will be Manuel Garza from the Kansas City District.

CGMPs: Field Perspective

MR. GARZA: I am Manuel Garza from that hellhole known as Kansas City.

DR. LEIN: You do have a nice town, though. It is a nice town to visit.

MR. GARZA: I have gotten used to the heat; yes.

[Slide.]

Since I will be talking about GMPs, I should give you a little background to give you an idea where I am coming from. I have been an investigator for over 25 years and have served in three different FDA district offices. In that time period, I have made inspections of every major industry regulated by the FDA.

I have been inspecting foreign manufacturers of human and veterinary drug products including finished dosage forms, active pharmaceutical ingredients and pharmaceutical intermediates for the last 17 years in various corners of

1 the globe.

2 I have been focussing, I guess, 100 percent of my

3 time in the pharmaceutical area for about the last ten

4 years. I currently serve as a Preapproval Inspection

5 Manager for the Kansas City District which means when CVM or

6 CDER has preapproval assignments, it comes through my desk

7 and then I make the reviews to see whether there is

8 sufficient information to send the recommendation forward,

9 either withhold or approvable, or whether we need to make an

10 inspection.

11 I continue to make inspections both domestically

12 and internationally and assist the other investigators in

13 the district in accomplishing the various preapproval

14 inspections so I get involved with the GMPs on a daily

15 basis, validation of all the issues, whether human or vet.

16 The first issue I would like to address, and some

17 of these have been raised by the industry and anything else

18 I can't answer, perhaps I can handle during the Q&A.

19 [Slide.]

20 There was a statement submitted to CVM that a

21 company's procedures, processes and methods for complying

22 with the law and regulations are FDA's interpretation of how

23 the requirements of the regulation should be met and these

24 interpretations are imposed upon companies thereby becoming

1 third-level requirements of the GMP."

2 It is true that, during inspection, we do ask how

3 they are complying with the GMP. What is offered to us by

4 the company is what the company, itself, interprets as

5 meeting the requirements of the GMP. If those responses or

6 procedures are adequate, then we do expect the company to

7 comply with them because those are their procedures.

8 If they are found inadequate or if compliance with

9 those procedures are found lacking then, of course, that is

10 reflected in the FDA 483. But it is something that the

11 company, itself, offers to us. I have often said that

12 procedures by one company may be in whole or in part

13 inadequate or unacceptable in another company because of the

14 numerous variables that occur, even in companies that

15 manufacture the same drug product, or within the

16 corporation.

17 There are enough individual variations in

18 personnel, training, equipment and so forth that a given set

19 of procedures would not be compatible at the next facility.

20 [Slide.]

21 Another comment concerned air classification. A

22 process room surrounding a sterile suite is required to have

23 a defined particulate air classification based on whether it

24 is a critical, non-critical or controlled process room. It

was further stated that, "Any air system in a process room which has been adequately validated to support the process within it should be acceptable."

I don't necessarily disagree with this. The key is defining "adequately validated system." If it is adequately validated and you do come up with some classification, there will still be a defined particulate count for that room. We do use the June '87 Guideline on Sterile Drug Products Produced by Aseptic Processing as a general guide in evaluating both the viable and non-viable air quality within these facilities.

But, in any case, if you do validate that, you will come up with a defined spec that you will have to comply with.

[Slide.]

Another comment related to the differential pressure between aseptic and non-aseptic rooms is required to be 0.05 inches of water. The conclusion was that it was excessive and unnecessary and that any pressure differential that has been validated to prevent cross contamination should be acceptable.

Generally, the 0.05 inches of water has been accepted as one that would prevent cross contamination under general operating conditions. That is why it is used. When

the doors are opened, the outward air flow should be sufficient to minimize ingress of contamination.

If less is used then, of course, we would have to look at the documentation to see how that lower amount of pressure differential could give you equivalent or superior control of possible cross contamination.

[Slide.]

There was a comment in one of the letters that CVM requires each and every jug of the same brand of sanitizing solution to be sterilized before use. "This is unnecessary for animal drugs once three consecutive lots of sanitizing solutions have been validated to be sterile. Only the validation of one lot per year should be required."

I was a little confused on the point the author was trying to make. One, apparently, there is objection to sterilizing of the solution but, on the same token, there is concurrence that it should be validated. So I would have to talk to the author and see what is the point that is trying to be made.

But when it comes to sanitizing solutions, they are generally sterilized because they may not be sold as sterile. If the objective for the sanitizing solution, if used in a clean-room environment, is to control or reduce microorganisms, there should be some assurance of its

quality and effectiveness. That is why the firms will sterilize the sanitizing solution because any solution, no matter how broad a spectrum it is effective against, it is not effective against all microorganisms. That is the whole purpose in that, using it in that room to control, if not reduce, organisms.

[Slide.]

There was a comment on cleaning validation. "If a cleaning procedure can be validated for a particular surface finish for a specific product, that procedure should be able to be extrapolated to similar pieces of equipment with similar finishes." Obviously, this person doesn't know that much about cleaning validation. That is not cleaning validation.

A similar finish does not take into account the hard-to-reach areas, right angles, depressions, wells, orifices, nozzle attachment areas and the like where material can accumulate and be difficult to clean.

Neither does it take into account whether a cleaning is manual, semi-automatic, automatic, CIP--which is cleaned-in-place--and/or a combination of these. And the efficiency or consistency of a given cleaning method under worst-case conditions.

It also fails to account for the location of the

piece of equipment and its accessibility to cleaning, its surrounding environment or any ergonomic issues. Furthermore, it doesn't address the time lag between completion of the operation and the beginning of the cleaning operation.

All these can have an impact on cleaning validation. A cleaning validation study that does not consider and resolve these issues is unacceptable.

[Slide.]

Another cleaning-validation comment is related to, "Equipment cleaning procedures must be validated to demonstrate that the active ingredient and preservatives, if present, have been removed from rinse-water levels below the lower limit of assay detection which was considered as being excessive and unnecessary. Visibly clean should be the acceptable standard."

The first sentence, I think, needs some clarification because if you know anything about cleaning validation, testing the rinse water may be inadequate. You may have to do swabs to actually identify the residue and quantify it because, especially the areas I just pointed out earlier, any rough surfaces, right angles and so forth where a product can accumulate, especially if you are doing manual cleaning which is hard to validate to begin with, how can

1 you assure that cleaning the rinse water, especially if the
2 active ingredient is not soluble in water--how can you tell
3 that the rinse water will tell you if a residue is present
4 or not.
5 If it is visibly clean, then how would you
6 validate that? How can you look at the most difficult-to-
7 clean areas and, based upon your observation, consistently
8 state that that residue is not there?
9 The residue is based upon the limit that you have
10 identified will not have a detrimental effect on the animal
11 or the product or in case, if it is used on food animals,
12 perhaps on humans, you need to calculate the complete
13 residue level on the old equipment train which is the
14 cumulative amount of equipment that is used for that one
15 product.
16 If you have equal distribution of that residue in
17 one piece, what happens at the end of the process? So you
18 need to have considered these variables in order to
19 determine for yourself, if not for the FDA, that you are
20 satisfied that your cleaning is sufficient to do the work.
21 Process validation; the May '87 guideline, the
22 comment quoted from the sentence, "Successfully validating a
23 process may reduce the dependence on intensive in-process
24 and finished product testing." The proposal, as discussed

earlier, was that, in light of this, perhaps some of the in-process or finished product testing could be reduced.

But, in the same guideline, after the first sentence there, there is a statement there; "It should be noted that in most cases, in-produce testing plays a major role in assuring that quality assurance goals are met; i.e., validation and in-product testing are not mutually exclusive.

So the point is if, in fact, there is some relaxation or elimination of some of the process controls and documentation, will there still be a means of assuring that the process is still consistent. If there is relaxation, there may be also relaxation in the amount of documentation you keep.

The question from a field investigator is is the validated process that was achieved initially still be maintained when you have less controls in place; that is, the result. If you have some slight drift or trend from your specification that would normally have been picked up when the controls were in place, if they are minimized, could this go unidentified until it becomes a more significant issue that may affect a product on the market.

Again, that is a question I ask, myself, when I am trying to make these inspections depending upon the

complexity of the product, the toxicity of the drug and the other issues that can affect a high-volume operation.

[Slide.]

Another comment related to each piece of equipment used in production is required to be prospectively validated for each product run on the equipment including a piece of equipment that is identical or very similar to an already prospectively validated piece of equipment. Otherwise, a product-validated machine may not be run on an identical machine in the same facility without a validation of the identical machine.

If you have an identical machine, every change and post-validation doesn't necessarily have to be revalidated as a whole. I think that is an oversimplication from my own perspective. From my side, if it is identical or very similar, I treat that with a grain of salt.

After all these years looking at NADA's validation documentation, facts records, written procedures, when the conclusion was that the equipment was identical or very similar and I got there on the site and tried to see this identical nature, in fact, there wasn't. When it was very similar, it was highly dissimilar.

What I didn't find was any equivalency data to show that maybe, in fact, it is dissimilar but you get the

same end result. I think these are, as someone is fond of saying, "in the real world." That's what I get in the real world, this type of distinction.

If, in fact, it is similar, we will consider and entertain not having it validated, but I need to have as much data as I can. Instead of presumed because you concluded similar or very similar, that it should. There needs to be concurrence on this identical or very similar nature.

[Slide.]

"Holding times on powder mixes are required to be validated by all companies in all facilities even though it is impossible for powder mixes to be mixed properly in controlled environments. That is true. In controlled environments, it is very difficult. But hold validation goes beyond the demixing operation. Will there be degradation of the powder.

The stability of a powder if it is packaged as powder or subsequently as a tablet, it is usually done on the final container/closure system in which it is distributed. So what would happen to the powder if it is stored in bulk for over a year, as I have seen it done, in a container which is different from the one in which it is distributed?

1 There was no validation there to assure that there
2 was no adverse reaction. The other issue is if, in fact,
3 there is degradation, the impact on stability. But the main
4 thing is demixing is not the only issue we are talking
5 about. When we are talking about the integrity of the
6 contents, mixing is one of the issues.
7 [Slide.]
8 Blender mixing; once blender mixing studies have
9 been conducted to fully validate a blending process, then
10 those kinds of uniformity tests of the finished dosage form
11 should be eliminated. Blender validation has no impact
12 whatsoever on how the drug product is handled after the
13 blending step. Depending on your process, you can have days
14 and numerous processes post-blending that can affect the
15 content uniformity, again the holding phase, the container
16 in which it is held, the environment around the container.
17 The other operating equipment, for example, in
18 compression, the vibration within the feeder-hoppers may
19 cause segregation depending on the particle size such that
20 you no longer have content uniformity depending upon the
21 degree of vibration. But there are other issues to
22 consider. So blender validation and content uniformity
23 testing are two separate issues conducted at two separate
24 phases of the operation. And they are not synonymous.

1 Those are the basic issues that I individually
2 took out to discuss within the time provided. The main
3 issue I wanted to bring up is that if the objective is to
4 minimize or eliminate some elements of the GMPs, the
5 validation of the operating systems will always be the
6 foundation for establishing their consistency.
7 If, upon reaching the validated state, some GMP
8 elements are minimized or eliminated, will there still be
9 the same high degree of assurance that the validated state
10 is being maintained. With elimination of some elements of
11 the GMP, there might be less documentation and/or assurance
12 that the conditions established for validation batches is
13 still being maintained.
14 That is my final question. If you have any
15 questions, I will try to address them.
16 DR. LEIN: Questions?
17 DR. GERKEN: I have a question. What degree of
18 validation or what degree of assurance are you trying to
19 achieve?
20 MR. GARZA: The degree of validation is provided
21 to us at the initial development of the product. If I have
22 interpreted the comments, if the objective is to eliminate
23 some of the in-process controls that are present now, will
24 there still be assurance that, depending upon the complexity

of the process, if a batch is a couple of hours or a couple of days, are you still having the same degree of control so that, in the end result, you are still getting product uniformity, the stability of the product is the same, and so forth.

DR. GERKEN: I meant percentagewise. Are you trying to achieve 99 percent assurance or 95 percent assurance that the product is--you can choose any percentage that you want.

MR. GARZA: Of course.

DR. GERKEN: And then you set the number of times you determine that. That is kind of set by the percentage of assurance that you want.

MR. GARZA: Yes.

DR. GERKEN: I am just trying to understand what the percent assurance that the current regulations aimed at. Is it 99? Is it 95? Is it 90 percent?

MR. GARZA: I haven't seen percentages. What I see is, depending upon the complexity of the product and the toxicity or the potency of the drug, the firm will do sufficient testing either both of the active and inactive ingredients, the control of the various pieces of equipment, the cleanliness of the equipment, the training of the personnel, the in-process testing. All of these, as a

whole, will provide the assurance that the process is consistent.

Any one, by itself, doesn't tell me it is consistent.

DR. GERKEN: I guess you are misunderstanding what I am saying.

MR. GARZA: If you give me a percent, yes. Why would I want anything less than 100 percent? That is the answer.

DR. GERKEN: But 100 percent means you have got to test everything every time in all phases. It is just one big test, is what it is.

MR. GARZA: Destructive testing tells you the results of the tests on what you tested. Samples that are collected, depending upon the bulk or finished dosage form, as still representative of the product. I don't see products in which 100 percent of a 1000-kilo batch is going to be tested.

DR. GERKEN: I guess the CVM requires each and every jug of the same brand sanitizing solution be sterilized before use. And they have talked about--I don't know whether that is analyzed every single time or not.

MR. GARZA: No; with sanitizing solutions, you can get that in five-gallon jugs. It is a matter of if it is

done at the facility then, the facility will sterile-filter that into individual-use containers for the clean room, perhaps 5 or 6-ounce containers.

I have seen this in human operations in which they would take a 0.22 micron filter to sterile filter a sanitizing solution into a two-piece container--the container is a jar because the tube--after the post-sterile filtration has gone to the container receiving that.

Now, the logic of this individual to use a 0.22 micron filter when there is about a couple-of-inch gap between the receiving vessel and the lid, and this is in a human firm I have seen, the issue is if you are sterile filtering and you take the 5 gallon and you filter a thousand of these, or 500 or 20 of them, it is to assure that did you test one or two to assure that the filter is, in fact, sterilizing that.

I would have to see the conditions under which you are filtering because there is so much variation. But the problem I have is I get a lot of general scenarios that require specific responses. Until you paint the picture and the conditions under which you are providing that, it is difficult to give you, again, a specific response to a very general question.

DR. GERKEN: I have another question. If there

1 were two sets of regulations, two separate GMPs, one for
2 animal drugs and one for human drugs, how difficult would
3 that be for your compliance, your inspection group, to
4 handle those two separate types of regulations?
5 MR. GARZA: It is a non-issue. Right now, for
6 your information, when we do various inspections, we have
7 GMPs for biologics, for devices, for foods, general foods,
8 for canned foods. You have got Type A medicated articles,
9 medicated feeds. That is our job. Whatever the GMP is,
10 that is what we apply to the industry.
11 To presume that if we have another set of GMPs is
12 going to be a problem is not knowing how we function in the
13 field.
14 DR. FLETCHER: Mr. Garza, I thought you were going
15 to begin your presentation with that famous saying, "God; I
16 love this job."
17 MR. GARZA: Well, I thought it was obvious.
18 DR. FLETCHER: My question is relating to the
19 first slide that you talked about, and I need you to help me
20 understand this. Does the industry declare to you what
21 their CGMP is going to be and then you determine the
22 adequacy of that as well as looking at the compliance?
23 MR. GARZA: That's correct.
24 DR. FLETCHER: So the company has the leeway to

say, "We think that this good manufacturing practice will meet the requirements," you look at that and determine, is it adequate first and then do they comply with it.

MR. GARZA: That's correct.

DR. LEIN: Other questions?

Thank you.

MR. GARZA: Thank you.

DR. LEIN: The last speaker that is scheduled on our program here is Headquarters perspective, Gloria Dunnavan.

Headquarters Perspective

6PM MS. DUNNAVAN: Hi. I am Gloria Dunnavan. I am Director of Compliance in the Center for Veterinary Medicine. I am your anchor speaker today. This may be refreshing to you; I have no slides. I have no overheads and I don't have a copy of my presentation. So I would just recommendation that you sit back and relax and listen.

The question asked here today is whether FDA should make any changes in the quality standards for the manufacturer of animal drugs or in the administration of inspectional procedures by which it implements those standards.

I would like to give you some thoughts on FDA's perspective on this question from a compliance point of

1 view. I think you will find that some of what I have to say
2 will end up being a summary of some of the things that we
3 have discussed here today.
4 21 CFR Part 211, the CGMP regulations, establish
5 minimum good manufacturing practice criteria to be assured
6 that a drug product meets the quality it claims. GMP
7 regulations have been in effect for many years and FDA has
8 been inspecting, evaluating compliance, and enforcing GMPs
9 in veterinary drug manufacture using basically the same
10 regulations that we have today.
11 We haven't made a distinction about the quality
12 standards just because these were veterinary drugs. We view
13 the GMPs as a useful tool for guidance in assuring a quality
14 product and in the marketplace and, hopefully, for
15 resolution of some real-world issues.
16 We have pursued enforcement actions based on GMP
17 violations when warranted. Under our law, that includes
18 seizure or injunction and even prosecution. But those
19 actions were taken only after attempts, often many attempts,
20 at voluntary compliance or they were taken when some
21 imminent threat to the health of the animal was apparent.
22 You might find or hear of some individual
23 instances where we have made a case-by-case decision not to
24 require a particular GMP criteria or not to pursue and

1 enforcement action for certain GMP violations. But I think
2 those instances don't occur very often. They are very
3 carefully evaluated by FDA and they often have some
4 extenuating circumstances.
5 The decision to pursue enforcement based on GMP
6 violations for a particular batch of product or a particular
7 product or class of products or a firm's entire production
8 is dependent on a lot of factors. Let me give you some
9 examples of those factors.
10 The significance of the violation is one that we
11 look at very carefully. The nature of the product; by that,
12 I mean, for example, is it an injectable or is it a topical.
13 The condition of use for the product, what it is supposed to
14 be used for, the scope of distribution, how it fits in the
15 scheme of the agency's priorities and our available
16 resources.
17 Has there been prior notification of a GMP problem
18 to the firm? What kinds of promises and attempts at
19 correction have come from the firm. We also consider if
20 there other means to achieve compliance. Examples of that
21 might be a state or local agency action might be more
22 appropriate. And educational effort might be an appropriate
23 way to achieve compliance or a cooperative effort with
24 industry associations.

We have made, I think, serious efforts to try to educate the industry on GMP requirements. That is really done informally every time we do an inspections. A discussion with management is held at the end of the inspection and any deviations are discussed with the firm at that time.

That is especially important when there are significant deviations that warrant reporting on a 483. That is the last of inspectional observations. In addition, informal guidance is provided through correspondence and meetings with firms on a regular basis.

More formally, we have issued written guidance such as the guidelines that are included in your package. I think you have to CVM Animal Drug Manufacturing Guidelines and the CVM Drug Stability Guidelines in your big book. We have participated in and supported conferences and seminars and workshops where GMP issues were discussed and we have even sponsored our own workshops on GMP issues.

One workshop that has been the subject of a number of discussions earlier today, and that was the Kansas City District's workshop on validation requirements in 1990. That was presented in an effort to educate the industry about the requirements of generic animal-drug amendments.

I would like to say that I am very pleased that I

1 don't have to come to you today with a long list of serious
2 injuries or deaths because of GMP problems. Those examples
3 are very rare. I attribute that, in large part, to the fact
4 that we do have a quality standard. We, and I mean the FDA,
5 take that very seriously.
6 We are very vigilant informing the industry, in
7 conducting inspections and in pursuing enforcement actions
8 when it is necessary to insure GMP compliance. I think the
9 industry is well aware of this and they, too, for the most
10 part are vigilant about manufacturing products that are in
11 conformance with GMPs.
12 The kind of GMP problems; we see the impact on the
13 market availability of specific lots of product. I think
14 Dr. Keller talked about this a little bit, things like
15 labeling mixups, batch stability and manufacturing errors
16 the yield potency or contamination problems.
17 One example of that kind of problem was the
18 addition of an organophosphate turf insecticide to a batch
19 of the drug famfur. The trade name is Warbex. That
20 resulted in about 56 cattle deaths and over 150 serious
21 adverse reactions. This was in late 1995, so it is fairly
22 recent.
23 We have had 14 product recalls in our fiscal year
24 1996, which is October to October, 14 as a result of GMP

1 problems in FY '96, and 16 if FY '95. I think those are
2 pretty small numbers. These were, I would like to point
3 out, all firm-initiated recalls on the part of industry.
4 With the exception of the Warbex incident, none of these
5 were classified by FDA as Class 1.
6 Class 1, just so you will understand what I am
7 talking about, is the user exposure of the product is likely
8 to cause immediate adverse-health consequences or death. So
9 we don't often have Class 1 recalls.
10 GMP problems that impact the overall process such
11 as process validation, which we have talked about a lot
12 today, can affect the availability of all lots of the
13 product, a whole category of products or even the entire
14 production line.
15 Again, these don't happen very often but we do
16 have some examples. We had an injunction in the early
17 1980s, Wendt Laboratories. In the mid-'80's, John Capanas
18 Manufacturer was a prosecution. In the early 1990s, Radix
19 Laboratories, also a prosecution.
20 So, again, when you are looking at that time span,
21 it is a small number. Now, some of the products that were
22 identified in earlier presentations as not being available
23 are the result of some ongoing GMP problems. We are in a
24 dialogue with the firm over those so it would not be

appropriate at this point for me to go into details about that. Sometimes, those things end up in a litigation situation.

I would like to give you some thoughts to consider as context for what might appear to be some new standard we suddenly decided to apply to veterinary drugs. Although we have an overriding priority of human health safety, our priorities for assuring public-health safety can change somewhat from year to year depending on information that is available or unforeseen issues that arise.

For example, information on an emerging or existing problem that may be the result of manufacturing practices can trigger the agency to look more closely at a particular section of the GMPs or the overall GMPs of a particular product, class of product or dosage form.

That could be perceived as some new interpretation of the GMPs but, in fact, is only for filling our public-health mission and assuring that drug products are safe and effective. The drug manufacturing industry has changed and GMP standards which represent current practice should change, too.

That may require change in the regulations, themselves, but, more often, the changes in how the GMP requirements are met. Current good manufacturing practice

is not necessarily the same today as it was 20 years ago. The specificity and sophistication of the industry has increased dramatically with the development of new techniques and equipment, advances in science, new technology, computers.

In addition, many of the products being manufactured today are vastly different than those from years ago. They are more complex in their structure and in their required manufacturing steps, equipment, and knowledge skills and abilities of personnel in the plant.

I believe factoring in all of these issues should help to put any program viewed as too stringent into perspective. I think it is not really a change which is too stringent but, rather, changing to keep up with current practice.

There has been a lot of discussion today about the FDA investigators and their consistency in looking at individual inspections at individual firms. So I would like to talk about that just a little bit. FDA investigators are our eyes and ears and they are trained in a lot of areas including food and drug law, investigative techniques, sample collection and handling and industry practices.

They are required to have a basic level of science background. In addition, they are trained in specialty

areas either by FDA or arranged by FDA to enhance their understanding of various industries that we regulate. FDA investigators are further encouraged to seek additional training to keep abreast of industry changes and trends which could include seminars and conferences, trade meetings as well as academic courses.

FDA has embarked on a new initiative to certify our investigators. The primary objective of the certification program is to provide assurance that FDA's investigators have the skills and knowledge necessary to effectively execute their responsibilities. Certification will promote investigator uniformity, enable FDA to maximize the use of its trained resources and formally recognize those investigators who have met specific eligibility requirements and demonstrated a predetermined level of knowledge and performance.

Initial participation in the certification problem will be voluntary. However, the long-range plan is to make participation mandatory for incoming as well as experienced investigators. Investigators will be certified in specific areas of agency responsibility based on the needs of the office they are assigned and the responsibilities and skills of the investigator.

They will be updated as needed to address changes

in the industry and the laws and regulations enforced by the agency and there will be maintenance requirements to continue the certification status.

Right now, that is being piloted with device firms so it has not entered into the drug manufacturing area, but I don't think it will be long before it does. The agency is very serious about this approach.

In conclusion, I would like to say that FDA believes it is appropriate to apply quality standards to all drug products manufacturing in the U.S. and we believe our history of actions and public statements are consistent with that approach.

Here are some reasons I would like to present to you. One is the residue issue. As mentioned before, human health safety is a serious priority for the agency. One way we assure that goal is reached is to be assured that potentially hazardous residues of drug products and their metabolites are not present in edible animal products.

The preapproval process is designed to develop safe conditions of use which can assure the consumer that there is a reasonable certainty of no harm from drug residues in edible animal products. That reasonable certainty of no harm is based on knowing that the drug products are the same as, and consistent with, the product

1 for which the safety and efficacy data was established, that
2 the marketed product will be consistent from batch to batch,
3 will not contain contaminants that will affect the action of
4 the product, and that the metabolism and residue depletion
5 of the product in edible tissue is consistent with the
6 approved product.
7 The institution and adherence to a high standard
8 of quality--and, by that, I mean our current GMP
9 regulations--is the cornerstone and foundation of that
10 assurance.
11 Extralabel use; the extralabel use of approved
12 drugs which has recently been legalized by the passage of
13 the Animal Medicinal Drug Use Clarification Act, AMDUCA--
14 here and after, AMDUCA--puts an even greater burden on
15 approved veterinary drug products to be manufactured under
16 high quality and consistency.
17 When a drug product is used in an extralabel
18 manner, not only must there be assurance that the product is
19 consistent with the product for which safe conditions of use
20 have been established, but that product can now be used
21 under other conditions which can include different dosages,
22 species, routes of administration.
23 They need to be assured about what the user is
24 starting with is critical. Again, our current GMPs are the

cornerstone and foundation of that assurance.

International; the continued application of consistent quality standards for veterinary drug products has far-reaching implications for international trade. The United States has been engaged in negotiations for several years with the European Union to develop a mutual recognition agreement on pharmaceutical GMPs. Such an agreement would provide for the recognition by the U.S. and the E.U. of each other's inspection reports.

This would reduce the duplication of inspections by both E.U. and U.S. inspectors and provide additional benefits in terms of the elimination of certain batch recontrol requirements which have been imposed by the E.U.

The cornerstone of such an agreement is the evaluation of the equivalency of the GMP system including regulatory requirements, implementation and enforcement. Since the E.U. system currently applies the same GMP standard to both human and animal drugs, adoption of a different standard for animal drugs in the U.S. would result in a finding of not equivalent for the U.S. sector of animal drugs.

The animal-drug industry would then be unable to enjoy any of the benefits of such an agreement with the E.U. Since FDA is also engaging in similar discussions with other

countries, a different GMP standard for animal drugs in the U.S. could result in additional impact internationally.

Lastly, I would like to talk a little bit about regulatory discretion. There are a number of veterinary products marketed in this country which have not gone through the preapproval process but which we have allowed to be marketed under regulatory or enforcement discretion.

These products tend to be limited in production and marketing. They may be for topical application and many are for non-food-producing animals. Generally, we have some information on the safety of the ingredients and we limit the scope and nature of the claims and often require the prescription legend to control the distribution and use of these products.

The idea of allowing the marketing of these products under some kind of regulatory discretion is based on the requirement that these products are manufactured under strict GMPs. Therefore, we have assurance of the consistency and control and the manufacturer of the product.

I think, without that assurance, the marketing of these products would likely be vastly different and certainly limited.

With that, I would be happy to try to entertain any questions.

DR. LEIN: Any questions for Ms. Dunnavan?

DR. KORITZ: How many districts are there that are of the same structure and function as the Kansas City District?

MS. DUNNAVAN: We have 22 district offices. At one point in time, they were all structured exactly the same. All of FDA is undergoing some reorganization activities so some districts, now, are organized somewhat differently. Some have more reliance on teams than the traditional supervisor, staff. But all have a district director. All have a management staff. All have investigative staff and administrative.

DR. KORITZ: My next question was is there a difference in, if you wish, the consumer-complaint rate--i.e., pharmaceutical-company complaint rate--as to number of violations that are awarded to their industries in the different districts and are things really homogenous?

MS. DUNNAVAN: That is a fairly difficult question to answer because there tends to be a concentration of veterinary firms in different parts of the country. So we do a lot of business with certain districts and practically no business with others. So, given that, we are going to get more comment from those districts where we have a lot of firms that are veterinary-related.

So it is hard for me to--

DR. KORITZ: Do you think if you divided the number of comments by the number of firms, that this might be a common ratio between the districts or not?

MS. DUNNAVAN: I can't really answer that. I don't really know. I think your question is is there a district that is, perhaps, being more vigilant than another district and, therefore, we get more complaints from firms from that district. I think it would be fair to say that we do hear from some areas of the country more than others.

I would attribute that, in part, to the quality of the inspection staff, that they really know their job and are vigilant about their job. I think the industry could perceive that differently, which may be an understatement. Maybe a better way to look at it is how often we end up with enforcement actions in different parts of the country.

I think that is a more consistent, perhaps, way of looking it. We may be perceiving more vigilant inspectors and so we hear about that a lot. In fact, we are not having to pursue enforcement actions in those parts of the country. So I think it maybe be a balance in that context.

DR. KORITZ: Do you think that communication between the inspectors and the industry is as open and cooperative as it could be because it seems to be the old

phrase, what we have here is, perhaps, a failure to communication and that may be a bit part of the problem.

MS. DUNNAVAN: I would hope, perhaps, Manuel would comment on that.

MR. GARZA: In the last few years, at least speaking for the Kansas City District, we have had much more communication. We are putting on workshops for the industry, the drug industry in general, including human and vet. We have had industry meetings the last couple of years almost every quarter which members of industry and members of our office participate in putting on workshops to discuss the issues that are paramount at the time.

There has been a lot of communication both with industry, the field and CVM in assuring that as much as is feasible that both the industry, the field and CVM have some uniform way of addressing these various issues. At least in the Kansas City District, my Director, Mr. Michael Rogers, has opened up a policy that anybody can, and people in this room will attest to this, have private audiences with Mr. Rogers discussing any issue that they wish.

At times, they involve some of us because we are discussing issues leading to new kinds developments, new submissions, AAP issues, site transfers and so forth, to try to expedite the issue. I think, in our district, we have

had a lot of communication with the industry.

I think, if anything, that would not be an issue to complain about because--and, of course, they also assist us because we learn from each other, in how this works, how we work and what we expect.

DR. SUNDLOF: I would like address that question that Dr. Koritz asked from CVM's standpoint. I don't know if the pharmaceutical industry agrees, but I notice, and I think a lot of people have noticed, a real change in the field in the last three or four years.

They have really become a lot more communicative, as Manuel Garza just indicated, but they have really changed, really made a tremendous effort to change the culture within the Office of Regulatory Affairs which is the field to go away from the "gotcha" attitude to achieve compliance through means other than strict enforcement, writing 483s--that is something that everybody in the industry hates, the 483, because that is what--the field comes in and they write their reports, and it talks about all the violations of GMPs and other things.

Now, the field is taking the approach that if they find a violation and they can work with the firm in order to get back into compliance, then they won't write up the 483. They have held a number of workshops for the animal drug

industry, for feed industry.

They have received several awards from the Vice President of the United States for taking less of a strict enforcement approach and working more towards compliance with the regulations in a partnerships arrangement. So a lot of the things that have occurred that we are talking about here have occurred in 1990.

The field has really changed since that time. I am sure it is not as far as everybody would like it to go and I am sure that that field is not finished. They have a long ways to go. But there is more consistency than there was three or four years ago between the districts.

We have heard lots of complaints about companies that have a manufacturing facility in one district and a manufacturing facility in another district and that the regulations were not applied equally across those districts.

I think a lot of that has really changed. Again, we are trying to work with the field. With veterinary-drug issues, we are trying to get more consistency and less of an enforcement and more of a coaching attitude.

MS. DUNNAVAN: Could I make one additional comment along that line, too? I think we in the Center are engaging in a dialogue with a firm, we are trying to make sure that we include the field, or at least advise the field, when

that is going on so there is not a disconnect between Headquarters and the field.

DR. STERNER: Much of the discussion today has revolved around GMPs and the impact on the industry that it has with regard to availability and the need for change. Some of that discussion, then, relates to the interpretation by investigators and inspectors with regard to conformance and compliance and validation.

It seems to me that a logical outcome of this discussion and recommendation revolves around the people charged with enforcing the regulations, hence your inspector and the certification of your investigators. I am curious to know more about that program. Do you have specific plans to have everybody certified and, if so, when and how much, on an annual basis, will you be retraining these people to be assured that your investigators have the same degree of familiarity with that industry that they are charged with regulating.

MS. DUNNAVAN: I can't give you an exact date because I don't really know. That program is coming through our Office of Regulatory Affairs. But, to be certified is a multiphase operation. So it is not simply you do it on the job and take a training course and take a test and you are certified. There is a series of basic training, an exam.

1 There is some additional training. There is some
2 self assessment. So it is a long process. I think an
3 investigator won't get certified immediately. To get all
4 the investigators certified in all of the different
5 disciplines is going to take quite some time.
6 Now, I may be able to get--I can talk to IR and
7 see if they have some time-line estimate. I don't know
8 that. I might be able to get that for you.
9 DR. STERNER: I think that it is also germane to
10 this discussion, or has very clearly been defined, that
11 communication skills are one of the things that your
12 investigators need training in. I think it is fair for all
13 of us to say we all need improvement in those skills.
14 DR. LEIN: Any other questions?
15 DR. FLETCHER: We had comments from Dr. Lance and
16 Dr. Lloyd. I wondered if you or anyone else wanted to make
17 any comments or any response to the kinds of concerns that
18 they raised.
19 MS. DUNNAVAN: Actually, I had been in a dialogue
20 with Dr. Lloyd on one of the issues that he brought up, the
21 change in manufacturing site, in trying to develop a way
22 that we could deal with the product that is left sitting.
23 But, again, that is sort of ongoing. So I am aware of that
24 one. I have not worked with Dr. Lance on his products.

1 That may be, I think, more a preapproval issue.

2 MR. GARZA: One these issues, the only people we

3 are allowed to discuss that with are the principals,

4 themselves. It is a confidential issue. We are just not

5 permitted to discuss it openly like this. You would have to

6 discuss it with them personally but we are not at liberty to

7 do that at this point.

8 As to communication, just to let you know, the

9 next industry meeting in our district is May 22. Again, we

10 have had about three or four a year. As to communication,

11 at the conclusion of an inspection, when the investigator

12 issues the 483 listing what, in his or her opinion, are

13 deficiencies, that is a time that we seek out the senior

14 management at that site.

15 Frequently, if it is appropriate off-site, they

16 will ask us when we plan to conclude so that if off-site

17 management wishes to be present, they are present. That is

18 the time when we discuss it and if there is concurrence that

19 the deficiencies are, in fact--they agreed on the

20 deficiencies, we do ask if they have a corrective action

21 plan and a tentative time table for that.

22 If there is disagreement, of course, we solicit

23 what is their position and then we are obligated to report

24 that for further review of the latter. But there is

communication. It is mandatory. It is one of the requirements of establishing the inspection report to discuss the deficiencies that are the opinion of the investigator and to solicit and responses, positive or negative, so that the reviewers up the line can make a judgment on how to proceed.

But communication is paramount in the inspection.

MR. HAGGARD: I am Dave Haggard. I am with ORA, Office of Enforcement. At times in the past, I was an investigator, Director of the Investigations Branch, and so forth.

I would say there is far more consistency than what may have been discussed. I think, sometimes, people take the fact that there may be disagreement as a basis to make a complaint over the issues, not one of communications. Communications has improved a lot. Something that we just started April 1 is every single inspector report will be provided to the inspected firm once that inspection report has been reviewed and closed.

This goes for pharmaceutical, for the food, certainly for veterinary medicine. As Manuel said, during every inspection, at the conclusion of the inspection, there is a complete discussion of all observations, reporting management's concern, disagreements.

When they do agree, the correction should be made. That report includes what they are going to do, typically with a time frame. A copy of that, unpurged of all the information that the investigator received from the firm being inspected, will be given back to the firm. This is a part of our move now toward more open communications.

Are there any other questions?

DR. LEIN: Questions?

MR. MARNANE: It sort of got away from me, but I know there was a question about how we may have worked with Dr. Lance to resolve some of those issues. I think it builds very much on what Dave just said in the area of communication. We have worked very closely with Bill Lance as a manufacturer of what you might call "niche products" to fulfill specific minor requirements that we are very interested in in terms of drug availability.

Through the innovative activities that we have had in working very closely with this field, in conducting the specific inspection at the wildlife facility, we were able to, in fact, get a number of these small niche products approved, not by what I would call really inferior GMPs or anything like that, but, certainly, we did stretch the envelope with the consensus of the field to come up with appropriate standards.

1 So I really have to say that those sponsors who
2 are willing to come in and work with us have, in fact,
3 benefitted through this cooperation and we have certainly
4 benefitted through the cooperation that the field has
5 extended to us in trying to meet these extenuating
6 circumstances when we bring to them a drug that certainly
7 has limitation in terms of meeting what you might call the
8 full extent of the good manufacturing practice requirements.
9 MR. GARZA: On that same topic, if I may comment.
10 Having a low-volume product produced by a firm in our
11 district may be a barrier but it is nothing that cannot be
12 overcome. We have dealt with these and it is a matter of
13 the GMP control at that facility that will help expedite the
14 validation of a low-volume drug.
15 It has occurred in our place. We have dealt with
16 this in conjunction with CVM in seeing that these low-volume
17 drugs can be produced and approved.
18
19 The main issue is not that it is low volume. The
20 main issue is the GMP controls at the site that is trying to
21 manufacture the product. That is first and foremost. Then
22 we will deal with the low volume and how do you validate a
23 product that may be produced perhaps once a year.
24 It is possible. We have done it. It is a matter

of trying to assure that the controls being put forth are, in fact, under control.

DR. LEIN: Any other questions from the committee or the audience here? I have two for Ms. Dunnavan. One is are there any of the inspectors that are rotated, basically, or are they always at one establishment, one center? Do you do a rotational situation so that at least they find out what is happening in different areas?

MR. GARZA: Let me make sure I cover the whole picture. We have people that specialize in one area versus another, pharmaceuticals, medical devices, biologics, and so forth. Within that, the ideal is to have different people in the same firm so that you have a more objective view.

If I go into the same factory three or four times in a row, I will start overlooking some issues and, because of the different background and training and education of some of the individuals, it is best to have different individuals. Sometimes, it is not feasible in some of our field offices where you have limited personnel available.

But the ideal is to have different people look at the same facility to get a better rounded inspection.

DR. LEIN: I don't know if I misunderstood you or I wasn't hearing, basically, or getting tired or something, but when you talked about the international, at least

deliberations going on at this point, as we look at the acceptance with a united Europe and other countries of drug products, did you say that it has been verified now that, for this to happen, we have to meet the standard that has been put together for human drugs for good manufacturing practices?

MS. DUNNAVAN: No. The EU does use the same standard. We are in the process of negotiating these agreements. So it is not cast in stone, but it is looking like if we do have different standards, that we may--the veterinary drug industry may be adversely impacted from that. It is not a finalized--

DR. LEIN: Are those standards as rigid as our human standards? That is the next question.

MS. DUNNAVAN: That is a good question. Dr. Tollefson is not here, and I think she could probably address that better, but I think they are equivalent.

MR. HAGGARD: Remember ORA does a lot of foreign inspections. I think last year they did something over 900 foreign inspections. It will vary country by country because some of the foreign countries such as England, France and Germany, I think their standards are equivalent to ours.

There are other foreign countries in which their

standards may not be equivalent but, certainly, the firms we inspect overseas, we hold to the same standards as the firms we inspect here and we do a lot of pharmaceutical inspections and a fair number of veterinary-drug producers overseas.

We are holding them to the same standards. So the answer is it is country by country. Certainly, many of the foreign countries are holding their firms to the same standards that we hold ours to.

DR. LEIN: Thank you.

Any other questions at this point?

MR. LYNCH: I didn't really introduce myself. My name is Mark Lynch. I am the Branch Chief for Investigations and Preapproval Compliance in the Center for Drugs. I would like to make myself available to all the members of this committee today or at any time as it relates to drug-approval mechanisms and any other GMP issues.

I am not a GMP expert but I manage the human-drug preapproval process so I have some information about what happens there and there certainly are parallels there with what happens with veterinary drug approval.

I wanted to paint a slightly different picture of that EU/MRA negotiations because people in my division and branch are involved in that now and we have involved in that

for a number of different cycles. The picture that was painted by Gloria is not really wrong, but she gave the impression that we are actively involved in promoting this deal-making MRA negotiation with the EU when, in fact, the opposite is really true.

The EU has really attached this MRA as a mechanisms to keep FDA investigators out of EU member countries and has attached this issue to the telecommunications acceptance on their end. So we feel a little bit different.

While the standards have been compared to GMP standards in the EU and human GMPs 21 CFR 211 are similar when you compare them on paper, we feel that there may be a difference in the way these things are used in different member countries or in the EU in total.

So we have gone to an insistence, and our negotiations are trying to force comparison of the regulatory system of the EU or of the individual countries. So is the EU mechanism, the regulatory system, capable of doing the same kinds of things that we are doing, not are the GMPs the same on paper as what is really happening.

What are the dynamics of the system? Are there the same protective factors? Does the investigator have the option to do the same kinds of things that our investigators

1 or our mechanism has the option to do.

2 So I would paint it a little bit different. We

3 are a little bit skeptical of the way different EU member

4 states operate, a little bit more collegially with the

5 industry, resolve issues prior to leaving, issues are not

6 recorded anywhere on paper on 43s or any other document,

7 those kinds of things.

8 The statement that she made that was correct;

9 there is a large variety in the abilities, the GMP

10 abilities, of various member states. The UK, MCA, certainly

11 has a lot of capability compared to Portugal, Italy, some of

12 these countries.

13 She was painting a kind of a happy picture and I

14 wanted to paint it a little bit differently.

15 MR. GARZA: I did want to echo Mark's comments.

16 As I said, I have been making inspections all over the world

17 for 17 years. It is one thing having the GMPs or the

18 requirements on paper and another thing having the

19 inspections done. While they may have it on paper, the

20 inspector is, in my view, at least from the inspections that

21 I have done over the world, not as thorough and as in depth

22 as we would have it.

23 Having said that, I have frequently been asked

24 which country has the better firms. Of course, I have seen

very nice state-of-the-art firms here and I have seen very sloppy ones here. And I have had the same thing in Western Europe, the Far East, India, Scandinavia, wherever you look.

It is not necessarily, at least from the ones I have inspected, the facility or the firm itself; it is the corporate mentality at that point, just like it is here.

So the vast majority; yes, they comply. But the inspectorate that I have up there, even in the most Western firms that you think are the most industrialized, how they go about seeking compliance with the new drug applications or new animal drug applications, it is quite different than what we are used to.

DR. LEIN: Other questions?

We are sort of running overtime. We do have here at least a heading that says Public Hearing. At this point, if there is any statement from anyone that has not given us the ability to be registered as a speaker, we would entertain that.

We maybe lost everyone that would want to do that at this point. Seeing no indication of that, we will move directly into our committee discussion.

Committee Discussion

DR. LEIN: I will refer the committee back to at least the questions for the committee. If you have a copy

of those, you may want to pull those out. If not, number one on that is should FDA make any changes in its quality standards for the manufacturer of animal drugs or in the administrative and inspectional procedure by which it implements those standards.

It looked like, in true lawyer form, they were looking for a yes or no answer there. But I'm sure it is open for discussion.

I have just been told, too, that, really, we will be coming back to these questions again in the fall. I don't know if we need any clear decision yet on these. Dick has been telling me that number three is probably the most important element at this point to say when are we going to meeting again on this subject.

He has got some blocks that are open from the standpoint of FDA/CVM. What don't you discuss those, Dick, while people are thinking and then I will come back to this again.

MR. GEYER: Just to repeat the plan that we have and that is that we will come back in the fall and ask the committee to deliberate in some depth on the response to the first two questions. In the meantime, we will prepare a summary of today's proceedings that we will use for refreshing our memories when we come back again to discuss

the issues.

We will also have a transcript of today's proceedings available which can be used as well for that same purpose. We will also have all of the speakers who are here today available for any questions that might arise during the committee's discussion in the fall.

We will also take any other suggestions that any of you might have for things that should be done between now and the fall. So that is why we are focussing, for now, on the third question. We knew that when we got to this point in the discussion that it probably would be somewhere around 6:00 to 7:00 o'clock and that the committee probably wouldn't want to spend the time that it really would take to answer these two questions in a deliberate and thoughtful way.

So that is why we set it up the way we did. We do have the questions. Is there any additional information that the committee would like to have between now and the next meeting or do you have enough? Do you have too much?

We don't want to hand a lot more paper out to anybody because I know you have plenty.

DR. FRANCIS-FLOYD: I definitely don't want to talk for more than a second but it seems like there were a number of questions that were very pointed that were asked

by various committee members today that FDA representatives were not able to answer very well.

Perhaps, as we review the transcript and stuff, we could pull some things out of there that need some more information.

MR. GEYER: That is a good idea. We can do that.

DR. FLETCHER: This is just a thought. I thought Mary Harris did a good job in the written material that she presented us in giving us some recommendations to consider, some draft recommendations, if you would.

A suggestion I would make is that if anyone had suggestions for us that they could make them for us to consider--I mean, specific kinds of statements, yes or no, and, if no, then these are the things we would like for you to address.

That would at least be helpful to me. It is kind of a straw man, so to speak, to say, what do you think about this suggestion.

DR. LEIN: One thing that has been going through my mind basically, and it has been alluded to by both the animal-health industry and the animal-drug alliance which would be really industry, and I am not saying it is one or the other or maybe it is both and maybe it is the whole industry that can get together, it would very nice to have

an industry standard as they see it on at least the part of good manufacturing practice.

It is almost an industry standard that is the minimum that they would like to hold themselves to. Now, that is not always easy to get out of an industry, but an industry that polices itself, frequently government will buy into that.

So if there was at least agreement of the majority of that industry, I think that would be easier for everyone, too.

MS. DURAN: Again, Diane asked this question and several other people. It may be somewhere--is there a place to look to see if I want to look at the 4,000 drugs that are approved to see what percentage plus or minus standard per drug? Is there a database that says for, alphabetically, ampicillin what is required?

If ampicillin says one gram, what are the standards for ampicillin for a veterinary product? Or is it plus or minus 10 percent of whatever the label says? Is that what your standard is?

MR. MARNANE: Actually, the standard varies, as we talked about today, the example that Dennis had given. But, once again, I think the point is, and Dennis did make this point, is the product is formulated to 100 percent of label

1 claim.

2 The variation that we normally provide for in most

3 finished pharmaceuticals is 90 to 110 with the exception of

4 when you have methods that lack specificity and precision,

5 like microbial methods. Then we end up with ranges which

6 are wider.

7 In that case, it may be, for example, 85 to 125.

8 The product still should be formulated to 100 percent. That

9 range is there because of the variation and the method which

10 could be, unlike a good analytical method that will give

11 maybe plus or minus 2 percent.

12 A microbial method might be plus or minus

13 10 percent and we can't have these things appearing to fall

14 out of specifications all the time because of the method

15 even though they are formulated correctly.

16 MS. DURAN: Thank you.

17 DR. LEIN: Other questions from the committee.

18 DR. KORITZ: I had a very specific question. I

19 hope it is not because I failed to read the material because

20 I didn't have all the material to begin with. But it is

21 this. We are having discussions around the issue of

22 sterility and we also have discussions about sterile water.

23 Are there currently injectables that are made with non-

24 sterile water that are on the market?

DR. LEINBACH: I will try to answer that for you. Injectables are made with water for injection. Water for injection is not sterile. There is a very low microbial limit on water for injection. It has to be made to certain standards of purity and it is tested for microbial quality, et cetera. But it is not sterile.

DR. KORITZ: Is it pathogen free?

DR. LEINBACH: I don't know that that has ever been documented but we certainly would hope that it is.

DR. KORITZ: This does really rattle my cage. This is a real eye-opener to me. It is rather amazing that we have gotten away with all this all these years.

DR. LEINBACH: You remember that sterile drugs are formulated and then they are sterilized. So, at the end, it would be sterile but it doesn't necessarily start with sterile ingredients. The active ingredient is, quite often, not sterile. The excipient materials are not sterile. So why would you use sterile water to formulate it?

DR. KORITZ: So, currently, injectables are all required to be sterilized at the end of the manufacturing process?

DR. LEINBACH: Except for the exceptions which are euthanasia products, hormonal ear implants that are used in bovine intramammary infusion products which we recommend

they be sterile but, because there were quite a few of these products on the market before the Center for Veterinary Medicine came into existence and, realizing the economic impact that a change like this would have on the industry, we opted to say that those that had previously been on the market could remain non-sterile but they have to be pathogen-free.

That is even probably more difficult to demonstrate than to produce a sterile drug. And they also have to be labeled as being non-sterile.

DR. KORITZ: Am I hearing from AHI that they would like to, perhaps, have an opportunity to market more non-sterile injectable products to further loosen up the requirement?

DR. STANK: Absolutely not.

DR. LEINBACH: Again, a little bit of bacteria is not as dangerous as when you kill that bacteria. Then you have a pyrogen. So what worries me more is that if we don't have the preapproval and we say we are not going to pyrogen test, then I am worried.

MR. GARZA: May I make a comment, please? On the WFI, yes; it is not defined as sterile in the USP, the monograph. But, essentially, in a well-controlled WFI system, it is essentially sterile and toxin free.

If you were to get microbes in it, as I said, the USP does not require it to be sterile. But, essentially, you are dealing with a very clean product. As Pat said, it is either sterile-filtered or terminally sterilized. So the end product will be sterile.

Now, you try to start with as clean as possible all the various active and inactive components including WFI. But it is different from purified water. Where it says potable water, again, there are different standards. But essentially it is endotoxin free and sterile, but not legally bound to those specs.

DR. LEINBACH: Just to further address your concern, there are controls, environmental controls, that are in place during the manufacturing which controls your concerns about endotoxins.

MS. DURAN: Which gets back to the labeling. Again, I can deal with that but I want to know that. I would like to have that label say that this product is sterile. It doesn't have to say that it is pyrogen free. But if it is pyrogen tested, we need to say sterile, pyrogen free

MR. MARNANE: I am not familiar that even for human products there has ever been labeling like that. I know the USP recently has recommended even the removal of

1 the word "sterile" from obviously sterile drug products, the
2 reason being, and it has come up a little bit in the
3 discussions today, is that there is only a certain level of
4 assurance associated with any sterility process.
5 For example, aseptic processing that is 10^3. In
6 other words, you can expect maybe one out of a thousand of
7 those will not be a sterile unit, a sterile injectable. So
8 I guess there was fallacy in the USP labeling those products
9 as sterile. As a result of that, they took that labeling
10 off.
11 So that is why we use the terminology that we
12 recommended in our policy, manufactured by a non-sterilizing
13 process, because, conceivably, some of those--I mean, even
14 in this room, if we manufactured product right now,
15 conceivably some of these could come out being sterile; no
16 microbes are in there.
17 Therefore, the only thing we could say about it is
18 manufactured by a non-sterilizing process rather than saying
19 non-sterile, or sterile, because those are very absolute
20 terms.
21 DR. LEIN: It is the zero tolerance thing that we
22 are up against. Let's have one more question here and then
23 we have come to a decision on a date.
24 DR. BARKER: I am a little confused. That is

1 nothing new, so don't be worried. I think I called Dick
2 Geyer Dr. Guest and carried on a 30-minute conversation with
3 him looking at me like I was a total idiot.
4 I have heard several representatives from private
5 industry get up and say that you have no problems with the
6 GMP regulations, or at least 95 percent of them--
7 MR. STRIBLING: No; 100 percent on the regs.
8 DR. BARKER: So we are not seeking to change
9 regulations.
10 MR. STRIBLING: We're not.
11 DR. BARKER: That is what I want to make clear.
12 We are not seeking to change regulations. It is to try to
13 make some distinction between what should be done and drugs
14 manufactured for animals versus drugs manufactured for
15 humans and your concern about FDA running amok with new
16 regulations just getting worse and worse.
17 MR. STRIBLING: Your words, not mine, but a fair
18 characterization of what I was saying.
19 DR. BARKER: I put them in your mouth. Swallow
20 them, whatever. However, the letter to Dr. Sundlof lists
21 things that change regulation. Let me give my impression.
22 You can shake your head as much as you like. They change
23 regulation. They exempt certain practices and processes
24 which is not a definition of how. It is a definition of

1 what.

2 There are certain things you don't want to do.

3 That is what confuses me to the point, almost, where I am

4 not really sure what we are arguing about here. The

5 existing regulations are required and I have no doubt that

6 if you developed a veterinary drug that suddenly was found

7 to have a tremendous market in the human drug arena that you

8 would, indeed, meet every regulation required to gain the

9 profit from the sales of that compound.

10 I think that would be true. But if we are not to

11 treat them differently, then, again, what are we arguing

12 about. We have been given plenty of information, I think,

13 from the Food and Drug Administration.

14 Of course, GMPs are regulation. They are in the

15 CFR publications. We know all that. The only real

16 information that we have had from you all says that you are

17 not concerned about the regulations, you agree with the

18 regulations 100 percent.

19 We are being asked should the FDA make any changes

20 in its quality standards for the manufacture of animal

21 drugs. Well, quality standards are regulations.

22 MR. STRIBLING: I would interpret it that way

23 although it could be interpreted more broadly.

24 DR. BARKER: Or in the administrative and

inspectional procedures. Administrative and inspectional procedures you all seem to have a problem with. That has been consistent in your argument, AHI, and American Animal Drug Alliance, that there is a problem, perhaps, in applying some of the information. Again, I am not real sure.

Those are certainly issues where there appears to be mechanisms, flexibility within the agency in discussion with private industry that a lot of that could possibly worked out.

I would like information about what it is we are really supposed to answer. I hope I haven't dismissed and wasted the entire day but--

MR. STRIBLING: Dr. Barker, with all due respect, I hope that the other members of the committee are not quite as confused about this as you are.

DR. BARKER: They are intelligent people. They weren't born in Alabama like I was.

MR. STRIBLING: But I do understand, in part, just from the whole discussion today how difficult this is to talk about and how all of us from our respective points of view are making very fine distinctions that are second nature to us but may not be to you all. For that, I apologize, but I am not sure how we talk about it without doing that.

1 I think, sir, that it would be helpful if Dick
2 Geyer could give you a copy of the CGMP regulations and, if
3 you have time to look through them, because nothing in our
4 letter appears in those regulations.
5 DR. BARKER: It may appear with CGMPs. I act as a
6 consultant for CGMPs and GLPs. I just want you to know
7 that.
8 MR. STRIBLING: Good. Okay. Then nothing in our
9 letter appears as a regulation. Everything in our letter
10 appears as what is required to fulfill the regulation. I
11 know there is confusion. I have latched on to the FDA
12 terminology in the 1978 preamble to the final CGMP
13 regulations where the Commissioner used the words what and
14 how.
15 I have used that simply because that was what FDA
16 said and I tried to be consistent even though I readily
17 recognize that a lot of what I have categorized under the
18 FDA category of how comes out as a what, what you need to do
19 to fulfill the regulation.
20 DR. BARKER: But they are "whats."
21 MR. STRIBLING: They are "whats." That's right.
22 But they are not regulations. They are what need to be done
23 to show it. You asked Mr. Garza the question earlier about
24 okay, the regulations are there, the investigator comes in

1 and the company presents to the investigator what he is
2 doing to fulfill the regulation, and it is up to the company
3 to present that.
4 And he said, "That's right." And it is. And then
5 you decide whether it is compliant. And he said that's
6 right. What we are saying it that 1990 if a company has not
7 been doing what has been done in human drug companies, then
8 they get written up for that and the investigator says, "No;
9 that is not compliant."
10 I agree with Manuel. But just understand the
11 picture.
12 DR. BARKER: But are these not standards of the
13 industry? This is what has been defined to meet a
14 particular requirement?
15 MR. STRIBLING: What did I say; 95 percent? I
16 don't think we have any concerns about 95 percent of these
17 things. The concern is what has happened in very recent
18 years and is continuing to happen. If you were to ask me
19 exactly what is it that you all would like more than
20 anything, I would refer to Mary's paper and to my paper and
21 say what we would both like is an agency Center procedure
22 under which the Center looks at new requirements before they
23 are imposed.
24 This conflicts with good management practices.

Good management practices which all FDAers follow delegate authority down to the reviewer level and try not to micromanage because, yes, you are going to ruin the morale of your staff if you micromanage what they do.

But I have got to tell you it is a thin line between good management and abdication of responsibility. What we would like to see, and I heard the same thing suggested by Mary, are some procedures whereby things can be looked at. That would be a great, great--

DR. BARKER: It is more of an investigational than administrative issue.

MR. STRIBLING: Absolutely.

DR. BARKER: Than it is a current good manufacturing practices regulation.

MR. STRIBLING: Because of the administrative process that is not paying close enough attention to the requirements that are being imposed. Yes.

DR. BARKER: I think I understand now.

MR. STRIBLING: Good. I'm glad you asked, sir.

DR. STERNER: We have listened to broad concerns about CGMPs and we have listened to particular concerns over particular issues. I think that as I have listened to people discussing around here, I am not sure that on this panel with, perhaps, a few exceptions, there is the

collective expertise to make specific regard to some of these issues.

It appears to me that within the scope of the topic you just talked about, good management practices, there needs to be some provision for arbitration over these sticky wickets as you would, perhaps, like to call them. They are serious issues because, as the manufacturer that may involve hundreds of thousands if not millions of dollars in investment, not just in R&D but in bringing this product to market, and you have fallen into a roadblock because somebody says, "Well, we have never done it that way before."

So, to cut to the chase, what is needed is an administration procedure by which these sticking points can, in fact, be discussed and arbitrated by--and I would suggest that a panel of experts could be convened to discuss particular issues. The same panel that would discuss the sterility might not be the same one to talk about analytical testing.

MR. STRIBLING: That would be very helpful but, Keith, understand, we acknowledge and it is in law and it must be, the FDA has the final authority. There is no doubt in any of our minds about that. But what we would like to see would be more--so that I am concerned about arbitration.

I don't think that we are in a position to arbitrate with the agency but I think that there can be mechanisms and procedures set up to make sure that there is input not only from industry but from experts.

DR. STERNER: Poor choice of words on my part but--

MR. STRIBLING: I wanted to show our deference to the agency; that's all.

DR. KOONG: It seems to me the year 1991, the period, was mentioned a number of times. That must be a good year. Our youngest son was born that year, I think. I want to come back to this. I think we are talking about a procedure--it seems to me that there is one unfinished business, and that is the proposed amendment in 1991.

Basically, we talked about it, the requirement for sterilization for human and animal drugs. Given the fact that--let me understand the situation. This proposed amendment has not been passed; is that correct?

MR. MARNANE: Yes; that's correct.

DR. KOONG: It is inactive.

MR. MARNANE: That's correct.

DR. KOONG: And it is on the shelf.

MR. MARNANE: That's correct.

DR. KOONG: It is still on the shelf. It could be activated.

MR. MARNANE: Yes; it could be.

DR. KOONG: Given the fact, also, that proposal was put forth five years ago and without the knowledge or consultation with the staff of CVM, I would like to suggest to this committee--I am following your lead--of what we do between now and the next meeting that the Chair of this committee requests, subject, obviously, to our colleagues' approval, to fully withdraw that proposal or vacate--I don't know the legal term.

I am not saying that is a bad bill. I have got nothing to do with whether that proposal is good or bad. I am talking about it has been six years or five and a half years. It was without consultation with the staff.

So, furthermore, if they wanted to resubmit this proposal, they must give justifications on a scientific basis why we need that and with an impact assessment in the area of social, economical and animal welfare, perhaps.

DR. LEIN: So where would you like to do that? Would you like to have that come off the--

DR. KOONG: From the committee maybe to the Commissioner and a copy to Dr. Sundlof or vice-versa. I don't know the current procedures.

DR. LEIN: To reactivate that again, or remove it.

DR. KOONG: Remove it.

DR. LEIN: Remove it.

DR. KOONG: Because it is on the shelf. It bothers me. I don't know if anybody wants to make a comment about that. I don't know. If you all think that is appropriate, maybe you would like to make it in the form of a motion. But I don't know that.

DR. LEIN: Let's ask CVM. Does that bother them with this sitting there as a potential or is it a moot situation that will never surface.

DR. SUNDLOF: There is some uncertainty about it. There is a proposed rule out there that has not been finalized. I imagine that if it were to be finalized right now, and I am going to ask Mr. Geyer, would you presume that it would have to be reproposed at this time or could the agency move to finalize a proposed rule that is that old?

MR. GEYER: In the abstract, it could be finalized. But I don't know enough of the history about that really to answer the question. When it is five years old, it is always suspect. In that situation, they quite often reproposed.

But I wanted to ask you and Dr. Blackwell a question. I think this specific issue is not one that is

1 really within the scope of the questions that we posed to
2 the committee. So I guess the question to you is do you
3 want advice on that issue at this point or is it something
4 that you would just rather leave as it is.
5 DR. SUNDLOF: One of the issues that it deals
6 with, really, I think, is issue No. 1 which is sterility,
7 and that is do we require terminal sterilization or can
8 sterile process validation serve. So I think that Dr.
9 Koong's comment was in response to that issue, and that may
10 be one issue of resolving issue No. 1.
11 MR. GEYER: I think as far as the kind of
12 requirement that should be placed, it is appropriate, and
13 certainly within the scope of that question. But,
14 certainly, if we talk about should we take a formal action,
15 the committee take a formal action, with regard to that
16 outstanding proposal, that is an agency policy issue and a
17 procedural issue that you may not want specific advice on.
18 That is what I was trying to say because there is
19 at least one other center in the agency that as affected by
20 this, the Office of Policy as well.
21 DR. KOONG: I think it is related to No. 1 because
22 there is a proposal on the table, or on the shelf, that
23 could potentially be activated. That definitely changes the
24 No. 1 question, it would change the quality standards. That

is the way I interpret it.

DR. LEIN: Thoughts? Further concerns?

DR. SUNDLOF: Maybe as I understand Mr. Geyer's concern and it may be if the committee does decide to write that letter that they write the letter not in such a way that it asks the agency to vacate the rule or to repropose it to consider CVM issues separately from that rule, to exempt CVM products from that rule.

That way, the process could be carried on, if they ever decide, which I think is unlikely, but it would raise the awareness that CVM is not, at this time, prepared to-- that the committee has examined the issue and they feel that it is not in the best interest of veterinary medicine to apply the standard of terminal sterility to veterinary drugs and that any rule that would be finalized, the committee would like the agency to know that there is a concern, that it was probably an unintended consequence when they wrote the rule.

DR. LEIN: Does the rest of the committee agree with this? We will need a vote. Do I hear any naysayers? Oscar, you were going to say something.

DR. FLETCHER: I was going to nay-say it to this extent. I think it is maybe premature, given the fact that we are going to discuss this again in a fall meeting, to

deal with that particular issue. It would give us a chance to think about it. I don't think we need to take any action on it.

MR. GEYER: Also, we have had two members that have had to leave and can't be part of this discussion. This could be one of the specific issues or specific questions that could be put to the committee in the fall.

DR. FLETCHER: I think what Steve just said is probably appropriate, and what he has also said today is that the climate is different now in terms of the communication between different centers within FDA. But, to me, the issue is the consultation within FDA before coming out with a proposed regulation. That is something we could speak to in a general way, but I don't think we need to do it now.

DR. LEIN: Why don't we put it on, then, as another question to answer, the rule, itself and tie to this sterility question to be studied and looked at at the next meeting.

Other concerns of the committee?

DR. CARR: Dr. Lein and committee members, my name is Paul Carr. I am a consultant, have been consulting to the animal health industry since 1974. Prior to that, I was in manufacturing, in the pharmaceutical area, both animal

1 health and human health.

2 There is another regulation that was alluded to

3 earlier today that is also of concern. You talked about

4 this one, Dr. Koong, about the terminally sterilized

5 products. There is another regulation that is cropping up

6 that I really think we need to be concerned with and that is

7 the change in GMP that has been published in the

8 regulations.

9 It provides quite a few additional criteria on the

10 industry that is over and above what the current GMP

11 requires. There are reasons for this. FDA has alluded to a

12 lot of these reasons. Some of them are valid and some of

13 them are not.

14 That is one comment I wanted to make. I wanted to

15 make another comment, a couple of other comments, actually.

16 1991 keeps coming up as a year when there were a lot of

17 changes. Believe me, I have seen a lot of changes

18 throughout the industry and through the regulated bodies in

19 my time as a consultant.

20 But prior to 1990, submissions were made to FDA

21 with safety, efficacy, manufacturing procedures and

22 controls. The manufacturing section of these submissions

23 was generally in the neighborhood of 100 pages, 200 pages,

24 maybe one volume.

1 After 1991--and these are where the costs come in,
2 folks--there were changes in the FDA. The last submission I
3 made--not the last one, but one other submission that I made
4 to the agency was 13 volumes for good manufacturing practice
5 to cover the Section 5 of the 356(b) form which must go in
6 as an NADA.
7 A lot of these things are things that previously
8 the field was covering. I have heard that the CVM looks at
9 it from a scientific viewpoint. I kind of wonder, in my own
10 mind, where does that leave the field, but that is all
11 right. That is their problem, not mine.
12 But there are a lot of practitioners here, and
13 maybe not so many anymore, but there are a lot of
14 practitioners and I would ask you one question in that
15 regard of the changes that have taken place, have you seen
16 an improvement in the quality of the drugs that you are
17 receiving today that you did 20 years ago, or ten years ago?
18 MS. DURAN: Yes.
19 DR. CARR: In what way?
20 DR. STERNER: They do what they say at the dose
21 they say.
22 DR. CARR: And they didn't ten years ago?
23 DR. STERNER: Not nearly so well as they do today.
24 DR. CARR: I disagree with that.

DR. STERNER: I am out in the field. I see it in the patients that I treat.

DR. CARR: Another comment I would like to make is in regards to, I think we were talking about if we set up a new set of regulations here in the United States, then that is a problem with the EU countries. And then I hear another person get up and state, "Yes, but the EU countries are not inspecting to the degree to the quality that we are inspecting to."

I am confused with that, very confused.

The last comment I would like to make is also I understand Dr. Bertone said something about an animal is an animal is an animal. I agree with that. But then I hear that there are concessions made or thought about, as far as small-volume drugs. I ask FDA, then, are these small-volume drugs, then, less quality than a drug that is for therapeutic use. If they are not, then why don't we use the same standards for the therapeutic drugs that we are putting out that we are using for these small-volume drugs.

Talk about pigeons. The pigeon, I'm sure, has feelings just like a cow or a horse. Is a pigeon food? Sometimes.

So those are the comments I have. Thank you for your attention.

DR. LEIN: Thank you. Other statements from the committee? Concerns?

DR. SUNDLOF: I will just address Paul Carr's last statement. This is the exact problem that we are constantly faced with, this tension of when do we make a decision that appears rational on its face without giving away everything. If we work with Bill Lance to produce 1000 doses a year of carfentanil, then does every company come in and say, "Now, I want that standard applied to my particular situation."

We have to maintain a level playing field out there. Otherwise, we are accused of being arbitrary and capricious and that is against the law and we can't do that.

Dr. Gloyd talked earlier this afternoon about why are we taking action against drugs that are necessary like thyamilal when they don't meet the good manufacturing standards. The reason is when you start making those kinds of exceptions, then everybody is entitled to the same opportunity to have those.

It is a very difficult situation that we are constantly faced with and we are dumping it on you right now. But you have heard it from the exact opposite points of view. And those are the things that we are struggling with.

DR. LEIN: I think another thing that we maybe

ought to be looking at because of the two speakers from the floor, basically, is the orphan drug situation in the human field. Maybe I would recommend that we see material on that as well so that we would be more knowledgeable in saying that we think that some of our small drug volume could be handled in that same way and make recommendations that way.

At least we have heard that a few times now. It would be nice to have that in there. I just wanted to make a comment that I equilibrate today what we have heard, and really have heard from industry, a little bit in that the testing world that I am in with laboratories and we do GLP testing for at least companies that are doing FDA work.

We also do quality-assurance work, basically, for everyday veterinary clientele. I can tell you that if I did GLP for my veterinary clients in what they needed in diagnostics, I doubt if we would be testing a lot of animals. It would cost them too much to do that.

Still, we use GLP standards but we don't apply them at the rate we apply GLP. There is a difference there. I think we give them a good product in our answer. We don't have the amount of documentation that we have basically in at least GLP.

We probably are not doing as much quality-assurance testing of our tests during that time period, but

it is at a different rate and I think we probably give them pretty good answers. I think we are looking at the same thing here with this drug issue; how much do you need to be put together to give a good product that the company feels safe with, that the veterinarian feels safe with, the food industry feels safe with and still is affordable for the industry.

I think that is what we are really looking at. It really comes down to risk assessment, again, how much risk assessment do we want. The world would like zero. They don't want to think about anything, basically. They just want it completely safe.

We know that the world is not a zero situation in its assessment. So I think those are the things, as a committee, that we have got to start to look at and say how can we work with that.

Again, I get back to industry as saying it would be very nice if the industry would come up with a standard that they, in a majority, would feel is what they would like to see as a minimal thing for at least good manufacturing practices.

MR. STRIBLING: Dr. Lein, I did not respond to that question when you asked it the first time. I will meet with my colleagues at the Animal Health Institute and see

1 the extent to which the industry can speak with one voice.
2 AHI has difficulty speaking with one voice since some of its
3 member companies make human drugs and animal drugs in the
4 same facility and other of its members have dedicated
5 veterinary facilities
6 But, to the extent that we can and we will,
7 although again--
8 DR. LEIN: Maybe some of it is in your thoughts
9 already that you put forward.
10 MR. STRIBLING: Mary had no disagreement with my
11 statement that the industry has no problems with the current
12 CGMP regulations, number one, and, number two, that we
13 probably have no problems with 95 percent of the
14 requirements to achieve the regulation--
15 DR. LEIN: It is maybe what I have been saying,
16 though; how do you apply those and at what rate do you apply
17 them.
18 MR. STRIBLING: Exactly.
19 DR. LEIN: Maybe that is what we have got to come
20 up with.
21 DR. BARKER: Could you say that again, Mr.
22 Stribling, because we seem to keep coming back to the same
23 idea here, that we have got to change GMPs. You are
24 satisfied with GMP regulations?

MR. STRIBLING: I am satisfied. So far as I know, Dr. Barker, the industry, the animal health industry across the board is completely satisfied with the current good manufacturing practice regulations in Parts 210 and 211 of Title 21.

DR. BARKER: Thank you.

DR. GERKEN: I would like to ask one question here. Is that the same as 7(b) of our handout, which you probably don't have but that is what was in the Federal Register, Volume 61, No. 87? The date was May 3, 1996, a proposed rule? So, what you are speaking to is current. It is not the proposal.

MR. STRIBLING: I dodged the proposals.

DR. GERKEN: Okay. Do you have additional recommendations for the proposal? Do you have additional places where you deviate from what the proposal is?

MR. STRIBLING: Both the Alliance and the Animal Health Institute submitted comments on the proposal. Those comments are public record and we will stand on those. I would not want to characterize them.

DR. GERKEN: Do we have those comments?

MR. GEYER: We can get the comments.

DR. GERKEN: That might be something that we would like to have because we have one kettle of fish and then we

1 have another kettle of fish and I am not sure what the
2 difference is.
3 MR. MARNANE: If I could just make one comment
4 regarding that proposal. I checked the other day on exactly
5 where that was, that they had received, to that May 1995
6 proposal or '96 proposal, I think 115 letters and they have
7 sorted out 500 to 700 individual comments.
8 When I say "they," essentially that is being
9 largely done by the compliance group in CDER. Out of that
10 should be a number of specifically related only veterinary
11 issues which, of course, we will be working with that group
12 to try to deal with those things which pertain to us.
13 DR. LEIN: Any other statements from the committee
14 here?
15 DR. FLETCHER: I hate to belabor this, but my
16 simple mind is interpreting this as a major problem coming--
17 if a company offers a GMP and FDA evaluates it for adequacy,
18 that is one point of conflict because if I submit it, and
19 FDA says, "I don't believe it is adequate," then that is a
20 point of conflict.
21 Another one is it is adequate, but am I complying
22 with it? Am I doing what I said I was going to do? So, to
23 me, the issue is kind of boiled down into those areas. And
24 then there are comments like lessening of current GMP

standards and lower GMP standards.

We might ought to be talking about different GMP standards. My understanding is companies can submit different GMP standards based on what they consider to be adequate. Then you have, if there is a disagreement, if FDA doesn't accept that at face value or whatever, then you have got a negotiation process about what is adequate.

I see that sort of as the nub of the problem, not lowering the quality of animal product. I don't hear anybody saying lowering the product. So I tend to focus on those two issues. If am wrong on that, then I would need more information about no, it is a different issue from that.

DR. LEIN: I think you are right. I think that is part of it. I think the other part is, as I was saying, how much do you apply into that GMP standard.

DR. FLETCHER: So I see at least some degree of flexibility depending either on how the company or the agency chooses to work on a particular issue.

DR. LEIN: I think what the industry is saying is that is certainly is there. The mold for this to happen is there and everyone accepts that it is the right mold. But when they submit what they want to do, it comes back to them that, no, you are going to meet what the human drug is going

to do. It is going to be set up that you are going to do this 30 times instead of ten times, or whatever it is going to be.

DR. LEIN: Any other questions? I think this has been good. It has sort of brought us maybe to a leveler playing field of where we are going to make some decisions.

What about dates, Dick? We will get to that for a minute.

DR. FLETCHER: We are looking at a couple of weeks in October and November. Let me just run through the weeks that we are looking at, probably in order of preference; first, the week of November 10 and then the week of November 17, and then go back up into October, the last week in October, which is the week of the 27th and then the week of the 20th.

We would be looking preferably at Tuesday, Wednesday or Thursday in those weeks. For the last week that I gave you, the week of October 20, Wednesday, the 22nd, is not a possibility for us.

This is based on the schedules that I was able to get from the people in CVM. We need to know what others might have in terms of conflicts. Maybe we could go back to that second week in November. Let me just ask you is there any major conflict that any of you see for that second week

in November, particularly the dates 11, 12 and 13.

DR. LEIN: Is there an AVMA, COBTA meeting then?

DR. FLETCHER: The American College of Veterinary Pathologists meets that following week so I think that would be a conflict for some.

DR. LEIN: USAHA and AVLD will be meeting either that third or fourth week in October. I would have to check that. I didn't get the dates on that.

MR. GEYER: I haven't heard any problems with the week of November 10; that is, specifically, the dates the 11th, 12th and 13th.

DR. FLETCHER: Are you thinking about three days?

MR. GEYER: We are going to need one day on this subject and then, probably, we will have another subject for the committee, but that yet will be determined. So it would be a maximum of two days.

DR. FLETCHER: My suggestion would be the 11th and 12th.

MR. GEYER: I think that is our preference, too. We could do it on Tuesday and Wednesday. If there aren't any major conflicts, then we will go ahead and plan on those dates, the 11th and 12th. That's all we need to do right now. Thank you.

DR. LEIN: No more questions from anyone on where

we are going with this?

If not, I move for adjournment. All in favor? There is no one saying anything but adjourn.

[Whereupon, at 7:47 p.m., the proceedings were recessed, to be resumed at 8:30 a.m., Wednesday, May 14, 1997.]