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FOOD AND DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

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ANIMAL DRUG MANUFACTURING

Wednesday, November 12, 1997

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P R O C E E D I N G S

Opening Remarks

MR. GUIDOS: Welcome to the Center for Veterinary Medicine's Advisory Committee Meeting for November 12, 1997. Today, we are going to discuss issues relating to the manufacture of animal drugs.

First of all, I would like to introduce myself. My name is Robert Guidos. I am Dr. Sundlof's special assistant at the Center for Veterinary Medicine. I am here today to fill in for Dick Geyer who is the Executive Secretary for this committee. He, unfortunately, is not able to be here because he had a death in his family this past week.

I am told that Dr. Lein is such an expert at running these meetings, I won't have to do anything. So I am going to hold him to that.

First of all, I would like to thank the members here today and the consultants for the work that they have done in preparing for this meeting. I would like to thank Dick Geyer and Jackie Pace for the incredible amount of work they have done preparing for this meeting, as well, and the other employees of the Center for Veterinary Medicine, as well as industry representatives and the representatives from the veterinary profession.

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Before we get started, I am going to need to read the Conflict of Interest statement for the meeting of the Veterinary Medicine Advisory Committee for November 12 and 13th of 1997.

The following announcement addresses the issues of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

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

In accordance with 18 U.S.C. 208(b)(3), a waiver has been granted to Dr. Steven A. Barker, Dr. Diane K. Gerken, Dr. Keith E. Sterner, Dr. Alice Wolf, Dr. Janis L. Cleland, and Dr. William A. Ravis.

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Under the terms of the waiver, Drs. Barker, Gerken, Sterner, Wolf, Cleland, and Ravis will be permitted to participate fully in the discussions and deliberations relating to the quality standards for manufacture of animal drugs, such as Current Good Manufacturing Practices, CGMPs.

A copy of this waiver statement may be obtained through the agency's Freedom of Information Office at HFI-35, Room 2A-15 of the Parklawn Building.

The statement was prepared by Dick Geyer on November 4, 1997, and Dr. Sundlof concurred on 11-7-97.

Now, for a few housekeeping items. I am going to pass around a phone list to members just to make sure the list accurately reflects their current addresses, and that will be coming around.

Also, for the members and other participants who received a notebook prior to this meeting, there are some extra inserts that may have been produced since your book was prepared. They are on the back corner on the left on the table.

Jackie Pace also standing in the back of the room will be able to provide any other attendees here today with other materials if they are interested in receiving them. Just ask Jackie and she will put your name on a list and then she will send you those materials next week.

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I have some envelopes I need to pass around also to the members for them to -- basically, it's return receipt envelopes for your travel vouchers. I don't know if there are members who have received them. They are addressed to Susan Simmons. If your travel voucher package already includes that, please don't take that.

Also, Jess Stribling from the Animal Drug Alliance has asked me to pass around a letter that was sent to him by Dr. Sundlof on October 3rd, just for you to include in your package. I don't think it was included in your material.

With that, I just want to make an announcement about lunch. Lunch will be served between 12:00 and 1:00. It is going to be promptly over at 1:00. I am going to try and keep the members and the participants to a strict schedule here. Lunch will be next-door behind the salad bar. For those of you who have already participated, you know where that is. If you have any questions about that, just let me know.

If you have any other comments or questions, please, either Jackie Pace is in the back of the room or myself can help you.

With that, I would like to introduce Dr. Stephen Sundlof, who is the Director of the Center for Veterinary Medicine, and he has some introductory remarks that he would

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like to make.

Introductory Remarks

DR. SUNDLOF: Thank you very much, Bob.

I would like to welcome all of the members of the Veterinary Medicine Advisory Committee in addition to the consultants that we have asked to attend this because of their expertise in the area of manufacturing chemistry.

I would like to pass along Dick Geyer's regrets that he could not attend this today. As Bob indicated, Dick has been intimately involved in this issue, putting together this program, and he sincerely regrets that he could not be in attendance today, but we are in good hands with Bob Guidos and with our chairman, Dr. Lein. I am sure we will be able to carry on admirably in the absence of Dick Geyer.

I would also like to mention that tomorrow, most of the senior staff at FDA and CVM will not be attending this meeting and we very much regret that. We are scheduled to have our management meeting in Charlottesville, Virginia, and the only dates that we could get in a whole year was the date tomorrow and the next day.

So, the fact that I won't be here tomorrow and a number of the other senior managers in CVM won't be here tomorrow is not an indication of the importance that we place on this meeting. It was an unfortunate conflict of

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interest that we felt we just couldn't reschedule.

So, again I apologize for that. I will be here all day to try and answer any questions, so if there is things that anybody needs to talk to me personally about or other senior managers in the Center, grab us today and we will be glad to try and answer any questions you have.

We have a really outstanding meeting I think scheduled for today. This is a very complex issue, manufacturing chemistry, and there are not a lot of people that know a whole lot about that, and most of the experts here on the VMAC panel are not experts in this area.

I think it is a tribute to the pharmaceutical industry that we just more or less take the quality of these products for granted, and we don't need to know as much -- for most of the people here -- don't need to know all the intricate details that are associated with manufacturing chemistry, but it is a very, very important process and again one that, as you found out through reading, very complex.

So, in order to help us all learn a little bit more, myself included, we had discussed at the last meeting whether or not it would be possible to have a tour, an actual GMP inspection-type tour through a veterinary drug manufacturer.

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We debated whether it should be a seminar or an actual tour, and we determined that the best use of everybody's time would be to have a seminar that directly preceded this meeting. We are very, very fortunate I believe to have Dr. Rolland Poust, who is going to be giving the seminar on that. It is going to be kind of a virtual tour I guess through the pharmaceutical industry. He indicates that he will not only try and pass on a lot of good knowledge on the subject, but also pose some questions that the committee can deliberate on during the next two days.

Let me just give you an introduction of Dr. Poust. Currently, he is the Director of Pharmaceutical Services and Professor of Pharmaceutics at the University of Iowa in Iowa City, and that is a post that he has held since 1991.

At the University of Iowa, Dr. Poust is responsible for all classes of pharmaceutical services department. It is an FDA-registered contract research and development service and it works with the university hospitals, government agencies, and pharmaceutical industry.

Previous to his position at the University of Iowa, in 1991, he was an adjunct associate professor at the University of North Carolina, and before that, associate professor of Pharmaceutics at the University of Pittsburgh.

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He originally received his pharmacy degree in 1966 from the University of Pittsburgh and his masters from the University of Pittsburgh, as well, in 1968, and his Ph.D. in biopharmaceutics from Purdue University in 1971.

He also holds many positions in industry and that would include section head at Pharmaceutical Research and Development Laboratories at Burroughs Wellcome Company in Greenville, North Carolina, from '79 to '91, and at Burroughs Wellcome, Dr. Poust reported to the Director of Pharmaceutical Research and Development Laboratories and was in charge of two groups, the Physical Pharmacy Group, which completed preformulation studies for 44 compounds that resulted in 36 investigational New Drug Applications, and also in the Stability Studies Group where he carried out stability evaluations on new drug candidates, new formulation of marketed products.

Dr. Poust wrote all of the standard operating procedures that were necessary for stability program to comply with Current Good Manufacturing requirements. He has been involved in 33 publications, has three book chapters, 22 presentations, and two major lectures.

It is a great pleasure again to welcome Dr. Poust and I think you are all going to enjoy the next two hours of your virtual tour through the pharmaceutical industry.

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Dr. Poust.

Seminar Presentation - Drug Manufacturing

DR. POUST: Thank you, Dr. Sundlof. I didn't realize I had done all that.

[Slide.]

This morning I intend to cover a number of topics. I want to cover four major topics, give you a brief overview of Current Good Manufacturing Practices, interject a little science into this discussion in discussing the formulation development process, talk about the manufacturer pharmaceutical dosage forms, talk a little bit about validation, and then -- and I guess this is the virtual tour part of it -- I have some slides of our operation at the University of Iowa, so we thought if we can't take this group to the industry, maybe we can at least bring a little flavor of the industry to the group, and that will be the virtual tour that Dr. Sundlof mentioned.

You really can't do justice to any of those four topics in an hour and a half. Indeed, at the University of Iowa, in our Pharmaceutics Graduate Program, we have a one-semester course on formulation development and I am going to cover that in probably five minutes or 10 minutes, I don't know how long it is going to take, so this is going to be an overview, it is intended to be informative,

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hopefully, I will say a few things that may stimulate discussion.

I may omit a lot of things that would hopefully also stimulate discussion. If you don't hear some things you are expecting to hear, ask about them. I am going to try and make this somewhat noncontroversial.

I know there are a lot of controversial topics related to the how of complying with GMPs. I am going to try and make this somewhat noncontroversial, but perhaps introduce some of those topics as we go through this presentation, and not just in the first section, but in some of the other sections, as well.

You have handouts I believe of the overheads. The last two pages are a series of definitions. I am not going to spend time reading those definitions to you. I will allude to a number of those terms as I go through, but those are just there for your edification.

[Slide.]

Let's start by saying a few words about GMPs, Current Good Manufacturing Practices. The last major rewrite of the GMPs was in 1976 and after a period of about three years of industry comment and industry-FDA dialogue, these kind of became official or were finalized and were declared substantive, which meant that noncompliance was a

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prosecutable criminal act.

Basically, what these GMPs said or say are the following - that you must have written procedures for everything you do, you must follow them, you must validate your systems, and you have to document everything.

Some people think that GMPs mean generate more paper, and indeed over the years they have, but there is more to it than that. Dr. Sundlof indicated, I guess as part of his introduction -- I would have never thought of this if he hadn't said it -- but he mentioned that I had written all the standard operating procedures for the stability testing program at Burroughs Wellcome. Well, that is true and that was one of my first assignments when I arrived there in 1979, because these GMPs had just become official and that was one aspect of this GMP rewrite.

[Slide.]

What are Good Manufacturing Practices? I will have to admit, somewhat shamelessly I guess, that I have stolen most of these slides from various and sundry presentations that I have attended over the years. I couldn't begin to give credit to the people who wrote them because I don't remember who wrote many of them.

So, the next few slides are things that you pick up if you ever attend a basic course on Good Manufacturing

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Practices, and there are organizations out there which provide that training. We have sent some of our people to those.

One definition you can read - the systematic and predetermined means of preventing mistakes. In the pharmaceutical industry, people are striving for zero defects. I think zero defects is a concept that arose in the space industry, but it applies to the pharmaceutical industry, as well. We don't want to make mistakes in manufacturing.

[Slide.]

Another definition -- that part of quality assurance aimed at ensuring products are consistently manufactured to a quality appropriate to their intended use.

What do we mean by "consistent"? What do we mean by "appropriate"? I am not sure I can answer those questions.

Somebody on this panel, I believe at the May meeting, talked about what happens when a batch fails, how consistent do you have to be, and what percentage of the batches do you have to pass.

Well, you pass as high a percentage as you can and your goal is to pass 100 percent, but what happens if you fail one? Well, maybe we will talk about that later, either

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in this presentation or as part of one of our discussions.

[Slide.]

CGMPs are based on the fundamental concepts of quality assurance. You will find a lot of this language right in the GMPs. Quality, safety, effectiveness must be designed and built into a product, and I will talk a little bit how we do build and design quality into a product when I talk about formulation development.

Quality cannot be inspected or tested into a finished -- testing quality into a product implies you test it until you get it right. You don't do things like that in this industry. Each step of the process must be controlled to maximize the likelihood the finished product will be acceptable.

[Slide.]

Why do we have GMPs? Well, one reason is the patients don't have a -- or practitioners for that matter -- don't have any means really of detecting that something is wrong with the product, so they rely really on the people making the product that it has been made correctly.

There is an inherent weakness in testing pharmaceuticals because we cannot test the entire batch. Testing is destructive. We consume the samples that we test, so we can only test samples or small portions of a

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batch. You might make a batch of 40,000 vials of a sterile product. The USP sterility test requires that you only test 20 of those for sterility. But how do you know you haven't contaminated the rest of the batch? You don't. I guess that is where validation comes in. So, we can't test every portion of that batch.

[Slide.]

CGMP. People like to say it is good business, it is good science, and it is good common sense, and I agree with that. I am an advocate of that. Sometimes we tend to lose sight of that fact. My feeling is those three phrases ought to be the underpinning of everything we do, whether we are talking about the what or whether we are talking about the how. Let's apply and interject as much as we can good business, good science, and good common sense.

[Slide.]

What I have done in I guess the next four slides is simply reproduce the table of contents to 21 CFR Part 211, which are the GMPs. I am not going to read this table of contents, I will make a few comments on each section or on some of the sections.

I brought a copy of the GMPs with me. We said generate more paper. Well, GMPs are written on very little paper. These are the GMPs, this little book, 63 pages, and

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the print is large enough to read even with my 54-year-old eyes. There is not a lot of stuff here in terms of volume of verbiage.

This is the what, not the how. The how could probably fill this room with paper, but this is the what. I picked this up at the AAPS meeting where I was last week, in Boston. Some of the vendors give these things out.

If you read these things -- and people say that reading these things is a sure cure for insomnia -- if you read these things, you will find three words in here over and over and over again. Those words are appropriate, adequate, and suitable.

What do they mean? Well, I don't know. What it says is there are a lot of ways to comply with this. I guess I hate to say this in this group, but there is an old saying there is many ways to skin a cat. Well, there is many ways to comply with GMPs.

Bear with me. I will read you a couple passages here just to illustrate the point of appropriate, adequate, and suitable. This is Subpart C, Buildings and Facilities, 211.42. Any building or buildings used in the manufacture, processing, packaging, or holding of drug products shall be of suitable size and construction and location. Now, that is part (a).

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Part (b), any such building shall have adequate space. So somebody has got to decide what is adequate. I guess if you in the industry can't do it, FDA will help you.

Part (c) of the same paragraph. Operation shall be performed within specifically defined areas of adequate size, and so it goes - adequate, appropriate, suitable throughout this book.

Another point I want to make about these GMPs or these slides, they encompass all aspects of manufacturing. They cover everything. What do I mean? Subpart A is just general as the definition. Subpart B talks about organization of the company and personnel, qualifications of the personnel, responsibilities of the personnel.

One important aspect of this portion is that it talks about reporting relationships and basically says that it is a conflict of interest for the Quality Control Group, the people who do the testing of the product, to actually report to the Production people, because the Production people could overrule the Quality Control people and say, well, we know your result isn't quite right, but we are going to release this batch anyway. So, it lays out those kinds of principles.

Buildings and Facilities, again, a few comments here. One very important aspect of GMPs and pharmaceutical

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manufacturing is avoidance of cross-contamination. We added a wing to our building in the last few years, and I sent a copy of the blueprints, I mean the thing must have weighed 50 pounds, to FDA and told them what we were doing. I got a one-page letter back that said this is all fine, but what are you doing to prevent cross-contamination.

So, I responded to that and pointed out what we were doing, and I guess that was satisfactory because I didn't hear any more about it.

But basically cross-contamination or preventing cross-contamination means that you are not picking up drug out of one manufacturing group and carrying it through your ventilation system and dumping it into the next room and into the product, into another product in the room next door. That is basically what we mean by cross-contamination.

There has been some discussion of pressure differentials between rooms. You won't find anything in here about 0.05 inches of water pressure as a pressure differential between a clean room and the next stage of cleanliness. That is the how. This is basically the what.

GMPs address equipment, appropriate design, location, how to clean it, and so on.

[Slide.]

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This goes on and talks about raw materials, components, and drug product containers and closures. Here is an example of where we build design quality into a product. A finished product is only as good as the ingredients that it is made of.

You can't take subparts, so to speak, or lower quality ingredients and make a high quality product, so you have got to start with the raw materials. If you don't have good raw materials, you are not going to have a good drug product.

As I mentioned, this is part of building quality into a formulation. This, as you can see, talks about testing of components, not only ingredients of the formulation, but the actual packaging materials, vial stopper seals, plastic bottles for tablets, and so on.

Subpart F talks about production and process controls, manufacturing processes. There has been discussion in this group about the concept of terminal sterilization versus aseptic processing. Those are processes, those are pharmaceutical processes. I will talk about those a little later when I try to interject some science into all this.

[Slide.]

Subpart G talks about packaging and labeling

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control. You used to see a lot of recalls, perhaps not so many anymore, of pharmaceutical products due to labeling mix-ups. People put the wrong label on the wrong product. The how kind of defines these days that you have to do 100 percent accounting of your labels. When you are printing 50,000 labels, that can be difficult.

Subpart (i) talks about laboratory controls, stability testing. There were a couple of issues related to stability testing when we met in May. The principles of stability testing are set forth in the GMPs.

Laboratory operations have been a recent area of emphasis by FDA. Field investigators have been delving more into laboratory operations. If you are at all familiar with the industry, there is the famous or infamous Barr decision that came out I believe in 1993 that talked about laboratory operations and retesting of samples and out-of-specification results. I am not going to get into that.

I believe there are guidance documents in preparation that address that because there is still not a clear understanding of how that is to work and probably not clear agreement on how that is to work between FDA and industry.

Endotoxin testing. I guess this is part of laboratory testing. We will talk about endotoxins I guess a

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little later.

[Slide.]

Records and reports. This is where it tells you that you have got to document everything. It tells about the different kinds of records, equipment records, use logs, documentation of component testing, production, manufacturing records, and so on, laboratory records, complaint files, all sorts of records document everything. Finally, it talks about return in salvaged drug products, so basically the GMPs cover all aspects.

If you can think of some aspect of pharmaceutical manufacturing that is not covered here, you are ahead of a lot of people, because I think this is pretty exhaustive and intended to be very exhaustive.

Okay. This is the what. Either directly or indirectly we will start talking about I guess the how.

[Slide.]

Why current practices change. Some people call it the how, some people call it the letter C in CGMP, what makes things current. The answer is in technology, the answer is in science, experience is part of where that comes from.

[Slide.]

Who puts the C in CGMP? Well, FDA determines what

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is current based on their experience with manufacturers of drugs, of biologics devices through a variety of mechanisms - inspection and compliance activities, reviewing NDAs, PLAs, ELAs. Those latter two terms are terms that have arisen in the biotechnology industry in the Center for Biologics.

Comments on proposed regulations and guidelines. We have had a lot of comments here from the industry which I think is hoping to help shape this, whatever we wind up recommending, and that's good.

Meetings, seminars, workshops in conjunction with industry groups, trade associations and PDA, and PhRMA, which formerly used to be the PMA, a new name for an old former trade association of the research-based pharmaceutical industry on the human side, and has its veterinary counterparts, the generic industry is involved in this, as well, both on the human side and I guess in this group.

All my training and experience up until a few years ago has been with the human pharmaceutical industry. I am learning a lot about the animal health industry. I have learned more I guess in the last six months or since May than I ever knew before, but I have had some other experiences with this industry, as well, and I am beginning

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to draw some conclusions about the differences between the animal health industry and the human pharmaceutical industry. There are many similarities, but there are also some differences, not necessarily related to GMPs.

Well, that is my -- I don't know -- 15 or 20 minutes on GMPs, and if I can have the next slide, please, I would like to move into a brief discussion of formulation development. This will be an attempt to interject a little bit of science into all this.

[Slide.]

Formulation development. How do drug products come into being, where do they come from, how does the process work? Well, generally, it works in the industry that a formulator or somebody who has been designated as a formulation development specialist, receives an assignment from management, and the assignment is to develop a pharmaceutical dosage form of this new compound that the researchers have discovered and they think it is good to treat some disease state or another.

Basically, what the formulator is told is here is the structure of the compound, and maybe here is 10 grams of it if you are lucky, sometimes it is less than 1 gram, we would like to have this drug administered in this way, in other words, they are given the route of administration, we

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want to inject this intravenously, we want to give this orally in a tablet or capsule, or something, so they know the route of administration.

They do have some flexibility in determining the actual dosage form, and sometimes -- not all the time -- but sometimes they are given the approximate dose that they think will be administered to humans.

Now, mind you at this point in the development scheme, there has been a little bit of pharmacology done in animals and maybe a little bit of toxicology done in animals, but sometimes it is easy to translate from animals to humans in terms of dosing and sometimes it is not, so they may be given a rough idea of the dose, and that is about all they are given. Well, I guess the other thing they are given is not enough time to do this, but anyway, this is a hot new compound. I am being a little facetious if you don't know me very well.

[Slide.]

The next slide, I have attempted to give you an overview of the process that is followed in the development of a pharmaceutical dosage form, and it all begins, not so much with the pharmacist or the formulator, but it begins with the analyst, the analytical chemist.

In order to evaluate what the formulator has done

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requires, at least at this stage of development, a semi-reliable analytical technique for quantitating the compound and for assessing whether it is stable under certain conditions.

So, there needs to be some sort of method development/validation and sometimes the term validation is used a little bit loosely, but basically, it is employing the principles of good science to come up with a method that works, that is linear, has a fair degree of precision and accuracy, and can be counted on to give reliable data when analyzing certain samples that formulate or generates.

This is all under the umbrella of research and development. The GMPs haven't reached this far back, and I hope they don't, but I see signs that sometimes they do.

Generally, then, the formulator either through his or her own efforts or through a group designated to do this kind of work engages in a series of studies, scientific experiments which are called preformulation.

Preformulation involves the physical/chemical characterization of the compound. People are interested at this point in solubility in the PKA of the compound, whether or not it is compatible with certain excipients that might be used in the dosage form, solid state chemistry, a variety of things.

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The data generated at this stage of development, of research and development, helps the formulator later on to design a rational dosage form to build quality into the formulation, so this is the beginning of the building of the quality into designing the dosage form.

Generally, if you move right along and don't encounter a lot of problems, it generally requires about six to nine months of effort on somebody's part to arrive at a reasonably good formulation that one could take into the clinic.

Now, this formulation and manufacturing process may not be the final formulation. It may not be a validatable formulation in terms of a manufacturing process, it may not lend itself to scale-up to large production size batches, but at least it is something that can be made with appropriate controls and can be tested in humans in Phase I, and I don't know -- I am pretty familiar with the clinical development scheme of human pharmaceuticals, but I am not very familiar with that in the veterinary. I don't know if you go through the typical Phase I, Phase II, or Phase III that the human testing does. I assume the process probably goes a lot faster in this industry than it does in the human side, but there are others here who are much more knowledgeable about that than I am.

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The formulation is then developed. Again, perhaps the initial goal is to get something that can be taken into the clinic. There is a definition of a qualitative or quantitative composition of the formulation, there is some definition of the manufacturing process. There is generation of stability data of that formulation.

Like I say, it typically takes six to nine to twelve months to get from beginning, the lefthand portion of that slide, the left margin of that slide, at least to a Phase I clinical formulation.

Clinical development then, at least in the human industry, takes on average I guess another five to seven years, and so the formulations people have lots of time to develop that formulation more fully, more rigorously, build more quality into it, scale it up to larger batch sizes, decide whether or not they feel that the manufacturing process is validatable.

They are generating a lot of data, a lot of scientific data, so when the inspector or the reviewer asks questions about that formulation, they have got lots of data to provide to respond to those questions.

One of the favorite responses that FDA gives to the statements that people in industry make is yeah, you have got a good point, but show us the data. If you have

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got the data to show them, you have good science behind what you are doing. If you don't have the data to show them, you are kind of left holding the bag.

You have to remember -- I guess this comment is addressed to industry, because I have been there -- you have to remember that an FDA reviewer or an FDA investigator, for that matter, has never seen your particular drug before, has never seen your particular formulation before, has never seen your particular manufacturing process before, so it is all new to them, and the more you can tell them about it, the more science you have, the more data you have, the more you know about it, the better off you will be.

I am kind of in the same position in what I do at the University of Iowa. We do contract work, we manufacture formulations for companies, and we are kind of in the same position that the FDA is in. We have never seen that company's drug before, we have never seen their formulation before, we have never seen their manufacturing process before, so they have got to tell us very clearly how this works and how it is to be done, so I can empathize with the Food and Drug in that respect.

Finally, then, once we find a formulation that is manufacturable, stable, bioavailable, and all those other good things, we can move on into commercial production once

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the New Drug Application has been approved by Food and Drug Administration.

Like I say, on the human side, there are several years involved in this process and lots of opportunity to do experiments with formulations, with manufacturing processes, with scale-up, and so on. I tend to think, but nobody has ever said this to me directly, that things probably move through the clinic, so to speak, a little faster in this industry than in the human side, but I may be wrong in that.

[Slide.]

How does one arrive at a formulation? This is a formulation selection decision tree. It is not mine, somebody gave it to me. I never worked where they had an SOP that defined this, or that they used something like this, but this is kind of what you do unconsciously I guess and we are assuming here that we are talking about a drug that we want to formulate as a solution, as a sterile solution, although the sterility part of it is left out here, basically want a sterile solution of a drug at a certain concentration.

We kind of start at the upper lefthand corner where it says adequate aqueous solubility of pH 3 to 10. That is about the pH range you can actually formulate human pharmaceuticals in and not cause too many adverse effects.

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So, it is yes or no all the way through this. So, if you have adequate solubility, then, you ask yourself do we have adequate stability either at refrigeration temperature, or at room temperature in this pH range. If we do have adequate solubility and we have adequate stability, then, we just go to some sort of a simple or perhaps somewhat more complex solution.

If the answer is no to the first question, we ask the question can we form a salt either in situ or can we have the chemist form a salt. Actually, there is an arrow left out there. There should be an arrow going from salt formation possible over to adequate stability.

If we don't, if we can't form a salt, then, maybe we start adding things to help the solubility either a surfactant, perhaps some sort of a cosolvent, such as glycerine or alcohol or something like that.

If we really get desperate, we might start looking at cyclodextrins or other types of complexing agents. If we really get desperate beyond that -- and these are all solubility issues, as you can see, going down the right side of the page, then, we may go to some oil system or some very novel delivery system, such as a liposome, a protein complexation or some such thing as that.

The two questions that the formulator has to keep

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in the back of his or her mind when they are doing all this is we want to keep this as simple as possible, but as we get into increasing levels of complexity, you have to keep asking yourself the question can we scale this up. I mean it's all right to make 100 cc's in the lab, but can we scale this up to a large batch size, and can we make it sterile, and if you ever want to trip up a graduate student giving a seminar on some wonderful liposome formulation that they discovered, just ask them those two questions, how do you sterilize this formulation and can you scale it up to 100 liters, and you will see a lot of blank looks when you ask those questions, but that is something that a formulator has to keep in front of him or her, can we scale this up if we get into some esoteric formulation and can we sterilize it with some degree of assurance that it will be sterile every time, and we haven't impacted on the stability of the formulation as we go through.

So this is kind of how, again, a brief overview of how one might approach a formulation problem of a sterile solution or a sterile formulation I should say.

[Slide.]

This slide is not next in your packet. It is later in your packet. I am going to use it twice. If you go back, I don't know, six or eight slides, you will find

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it. It is basically a certificate of analysis of a batch of a formulation

This is a certificate of analysis for a clinical batch of a sterile solution that was produced in our shop. I have tried to censor it. It's all confidential information as to what the drug is and what company it was made for, and so on, so I have tried to censor this appropriately, so you don't know what it is. It probably wouldn't tell you much if you did know what it is, because the compound at this point only had a number.

The reason I brought this slide forward at this point is to talk a little bit about some of the formulation problems that were involved in this particular product.

The compound is an interesting compound. It is not very soluble in aqueous solutions. It is more soluble in alkaline solutions than it is in acid solutions which presents a problem in its own.

It tends to precipitate out of solution if you add any strong electrolytes. For example, if you add sodium chloride to it or any sodium ions to it, for some reason it falls out of solution.

The formulation that we received had a weak base in it which was there to solubilize the compound. It had some dextrose in it which was in there to make it isotonic.

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They tried sodium chloride, but that didn't work. As I say, it precipitated rather quickly, so they used a non-electrolyte compound dextrose to make it isotonic, and it had another surfactant in it, and I am not sure why. They never did give me a good reason for that.

We found out fairly quickly that there was a serious stability problem with this formulation. We made a batch of it, put it on stability test, looked at it at elevated temperatures 50 degrees at one month.

The solution which had started out a nice clear yellow solution wound up as sort of an orange solution and it had a fairly heavy white precipitate in it, not acceptable, and had an assay of around 75 percent rather than 100 percent that it started out at, so we said, folks, you have a stability problem here, you had better reformulate this.

Based on my experience, I said it might be a good idea to take the dextrose out of here, I think the dextrose, being a reducing sugar, is oxidizing this compound. Let's take the dextrose out of here, let's take that other surfactant out of here because I don't know what it is doing anyway, and let's make it simple.

I guess that is a concept we try and follow in formulating dosage forms, keep it -- what's the old -- keep

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it simple, son, or keep it simple, stupid -- so let's take these things out and see if that will work, and things got a lot better stability-wise when we did that.

But we still have this thing here, that you are probably not aware of, and I am going to tell you why it is a problem, we still have an alkaline solution. In order to get this drug into solution at any concentration, and we only have 2.5 mg/ml -- the company would like to have had this formulated at about 8 or 10 mg/ml, but you just couldn't get that in water or in an alkaline solution. So, they said, well, we will go into Phase I with this lower concentration and see what happens, we are not sure what the dose is going to be eventually anyway.

So, we have got a solubility problem right off the bat. As you look on the last line there, the last test parameter is pH. The specification for pH is 8.3 to 9.7. This particular batch came out at 8.9, which is fine. We certainly met the specification.

However, an alkaline pH is problematic, can be problematic in a sterile solution, and the reason is that alkaline solutions tend to attack glass, and if the glass attack becomes too great or too serious, pieces of glass tend to flake off the inside of the vial and now you have got visible particulates in your product, and that certainly

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is not something you want to inject into somebody's veins. You would probably have a hard time getting it into your syringe anyway, because the glass is probably going to clog up your needle.

So, formulating intravenous or sterile injectable solutions at alkaline pH is something that you should try and avoid if at all possible.

So, we have a potential stability problem already. As it turned out, I guess we were borderline in terms of the alkaline pH because this particular formulation over about two years at room temperature storage did not generate particulates. The USP small volume particulate test was passed each time we tested the formulation, but everybody was holding their breath and keeping their fingers crossed, believe me.

However, it leads to another issue. There has been discussion in this particular panel or by industry people, I guess, about terminal sterilization versus aseptic processing.

There is a body of data in the literature that points out that whenever you autoclave or terminally sterilize a dosage form, that process tends to generate particulate matter. Now, this particulate matter is not visible, it is very small, nonetheless, it does form. It

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forms even if you put water in glass vials. You can see an increase in particulate matter if you run it through a high agroyco [ph] or some other type of particle size analyzer.

Once you start particulate formation, it tends to increase over time. Also, in the literature, it has been shown that as you increase the pH above 7, from let's say 7.0 to 7.5 to 8.0 to 8.5, as you increase the pH of an aqueous solution and then autoclave it, you generate more particulates. The higher the pH, the more particulate you generate.

This particular formulation was not terminally sterilized. I think we were afraid to. We did try the experiment, but I think we were afraid to. So, while terminal sterilization does give greater assurance of stability than does aseptic processing, it can in some cases pose another problem in that it will lead to a physical instability due to the generation of particulates mainly due to glass attack, so terminal sterilization is not the end-all and be-all of sterile product manufacturing, although like I say, from a microbiological point of view, it is the way to go. From a physical point of view, it may not be the way to go.

Of course, the other down side of terminal sterilization is you may degrade the drug. We did do an

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experiment with this formulation -- let me back up. We did an experiment or somebody did an experiment with the original formulation that had the dextrose in, and they autoclaved it, and that caused the same problem as we saw it on our stability test. The solution went from clear yellow to orange with a white precipitate in it, so definitely, even 20 minutes at 121 degrees degraded this drug substantially.

When we took the dextrose out and autoclaved this formulation, we saw a very slight decrease in the assay, less than 1 percent, so what this company decided to do was continue to make the product at least for clinical studies by aseptic processing.

They addressed the issue in their IND and promised that they would look at this issue as time went on and as this advanced through the clinic and as the formulation development effort increased, and indeed they have. This product or this drug, as it turned out, required much larger doses than they had anticipated, and because of the limited solubility, they actually had to go to a large volume parenteral.

Now, if you know anything about large-volume parenterals, you know that it is a requirement that large-volume parenterals have to be terminally sterilized,

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small-volume ones do not. So, now they are in a situation of having to terminally sterilize this.

One way to get around the alkalinity and the glass attack is they are going to put this in plastic bags, which poses a whole new set of problems, because you have to ask what are you extracting out of the bag into the formulation, but at this point, that's not my concern fortunately.

Anyway, we will come back to this slide a little later. That is my 10 minutes or whatever it has been on formulation development, and if we could move on to the next slide, I will say a few words about the actual manufacturing process.

[Slide.]

As you proceed through development, you scale-up these formulations. Typically, minimum batch sizes of sterile products in the pharmaceutical industry can be on the order of 20- to 30- to 40,000 units.

This particular batch that I just showed you, which was Lot 214.I0895, I think was about 1,000 vials. So there would need to be considerable scale-up of that to reach a manufacturing level.

[Slide.]

The next several slides show flow charts which are really oversimplifications of manufacturing processes for

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three different kinds of dosage forms. One of them, the first one, is an oral liquid.

The points I want to make on all three of these are that these are all multi-step processes. It is step 1, step 2, step 3. There are different operations, different processes going on in each of these.

These processes, even though these flow charts that I am giving you are somewhat generalized, manufacturing processes are very specific for each formulation, and the third point I want to make about these is that there is usually some in-process testing that takes place as one proceeds through a manufacturing process.

The first one of these you see before you, the manufacture on oral liquid, there are some specifics in here, but if you absolutely looked at a batch manufacturing record, it would be a lot more specific than this, but this gives you an idea of how these things are put together.

It starts out just by weighing or measuring out some water, heating it up, add one of the ingredients which happens to be hydroxypropyl methylcellulose, cool that to a certain temperature, add the remaining ingredients except the drug, and I guess the drug is somewhat heat-labile, so they wanted to add that at a cooler temperature, mix those ingredients in, and here is an in-process.

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Check the pH and adjust it if necessary to something between 3.5 and 4.5, so there is something about the pH that is critical to this formulation. It is either a stability issue or a solubility issue, I don't know which. Then, we add the drug while continuing to mix. Finally, add sufficient amount of water to bring it to volume, again verify the pH, and do a filtration.

So, you can see that there is a heating step, a charge-in of ingredient, a cooling step, charge-in of additional ingredients, a mixing step, charge-in of the drug, and finally another measuring step, so to speak, q.s., or add sufficient quantity of water to get up to the final volume.

It is a multi-step process. There are in-process tests, a couple of in-process tests as one goes through this. Again, obviously, if you were actually following a batch manufacturing record, it would tell you to record these temperatures. It would tell you what type of mixer to use. It would tell you what speed this mixer should be running at. It would tell you how long you should mix at each of these points in the process.

[Slide.]

This slide again is an overview. It is more specific than the previous one. It is for a compressed

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tablet. We haven't talked much about compressed tablets in this group. It again is a series of steps.

I have sort of whited out the name of the drug, which would have been in the upper left corner there under or just above where it says 10,000 grams.

So, basically, it says to sieve each of these three ingredients, the drug, the mannitol, the corn starch, blend them together, granulate them. It's a wet granulation procedure where we add some water. We are trying to densify and actually enlarge the particle size to make it more free-flowing when we compress these tablets, and so there is a wet granulation step which consists of methylcellulose dissolved in water.

So, we have a granulation step. It gives operating parameters for the granulating equipment. There is a drying step. There is then an in-process that you see about halfway down the page, which consists of a loss on drying, in other words, we want to dry this granulation to a certain moisture level.

It has been found in tablet production that if your powder mix is too dry, you often have compression problems. If it is too wet, in many cases you will have compression problems. So, as part of the formulation development process, you try and optimize the moisture

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content of the granulation.

Just to give you a ballpark range, usually, we are talking about moisture content between, let's say, 2 and 10 percent. It is not obviously wet, it is not obviously moist, it is not obviously damp, but there is some water in there.

After the loss on drying in-process step is completed, there is a milling of size reduction, uniformity of size, additional blending of the lubricant, which is the hydrogenated oil, another in-process control.

Here, there is a loss on drying, as well as an assay of the active, so we take samples of this blend and make sure that we have got the right amount of drug and the right distribution of drug throughout this mass of powder. It usually involves an overnight analytical procedure.

If all of these parameters are met, then, we go to tablet compression on a rotary tablet press. Here, we are given the punch size, we are given the weight of the tablet, we are given the thickness of the tablet, and the speed of the tablet press.

Again, there is an in-process control during compression, and you can see a series of tests are conducted on samples taken during the compression process, weight variation test, tablet size, hardness, disintegration, loss

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on drying, and actual chemical assay to active, so we are looking for uniformity of drug in the tablets, as well as accuracy of the right quantity of drug.

This process then went on. This was a coated tablet. I am going to stop at this point. There were probably two or three more pages of this kind of detail that told how to actually apply the coating to the tablet, and I am going to omit that. I have hopefully made my points.

[Slide.]

This slide gives a flow chart for an injectable solution, manufacturing process for an injectable.

Oh, one more. This one is a lot more simple. This one is written in a more simple way, it doesn't necessarily mean it is a more simple process.

Basically, dissolve the drug in the excipients of water, adjust the pH, sterile filter it. Those steps are done outside the aseptic processing area, and I have drawn a box around the portions of the manufacturing process.

This is what we would call aseptic processing or sterile filling. We fill the vials in an aseptic environment in an aseptic way, put the stoppers in, seal them.

The next step, autoclaving, that is terminal sterilization. If you leave the autoclave step out of that,

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you have basically made a product under aseptic condition or aseptic processing. If you add the autoclave, the terminal sterilization step, that is where this idea of terminal sterilization comes into play. So, it is something done at the end, hence, the word terminal.

Finally, you inspect and label these vials.

[Slide.]

The next series of slides -- and really, that was the first of the series -- goes from a simple overview to increasing levels of detail in describing a manufacturing process.

The next two slides represent documentation that was submitted by this company as part of their IND, so this is an IND write-up. This is what the reviewing chemist in Rockville would see as part of the IND, a fairly detailed description of the manufacturing process, but not nearly as detailed as one would find in the actual batch manufacturing record, which are going to be the slides following these.

So, the first four steps here describe the washing and sterilization of the vial stoppers and seals. This is component preparation. As I have said earlier, you can't have a high-quality product if you don't have high-quality components and ingredients, so you have to have written procedures for washing these components and sterilizing

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these components, and that is described, not in great detail, but it basically says that it is done.

Down in step 7 starts the actual compounding of the formulation. Here, it is basically weigh out a quantity of water, add a weak base material to the formulation to get the pH up, bring it up to volume, then heat the solution, add the drug.

The solution was heated to help increase the rate of dissolution of the drug. So, we add the drug then in step 11 to the warm solution, mix it for at least 10 minutes, then, we record the pH of the solution on the next slide, which is step 12.

[Slide.]

Cool it. Bring it up to volume, test the pH again, pull a couple of in-process samples. Here is some in-process testing under step 16. You can see the tests that are done. Finally, in step 19, we sterile filter the solution through a 0.22 micron nylon filter, fill the vials at step 22, push the stoppers into the vials, step 23, put the seals on, and crimp them.

Those steps are all done in a very clean environment, what is called a Class 100 environment, to minimize the possibility of contamination of the product. Then, the vials, we do a batch accounting, inspect.

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We do 100 percent inspection of all vials to make sure the fill volumes are correct, there are no cracked vials, the color is right, the fill volume is right, there are no particulates, and so on, so inspect the vials and then finally label them.

So, these pages actually went into an IND and gave the reviewing chemist sufficient information to convince himself or herself that this product was being made properly and under sufficient control.

[Slide.]

The next page, actually, the next three I guess, are pages out of the actual batch manufacturing record. Again, I have tried to censor this, so you don't know the name of the drug or the name of the company, or very much about the ingredients and the formulation other than the water.

So, here are a few noteworthy comments on this batch record. You will notice on those next three pages in your handout, the name of the product and the lot number are at the top of every page to help avoid any mix-ups in the documentation.

We have recorded the lot number of each raw material. We have recorded the number of the balance used to weigh each of those ingredients. Every step in the

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process has been executed or carried out by a person who initials this case "weighed by," and checked by a second person, so we have got double signatures. This is part of the how, I think -- maybe it's part of the what -- but everything is double-signed and dated.

If you don't do it properly, you can get tripped up. I have seen people get tripped up in putting the wrong dates and the wrong times in batch records. So, it is a very detailed level of documentation.

[Slide.]

The next page, what we call page 7, I am not showing you every page in this batch record. Again, we have got the name of the product and the lot number at the top. This simply describes the components of the vials, the stoppers, and seals that were used, the lot number, our raw material lot number verified by and checked by, again, the double sign-off, and the date.

[Slide.]

The next page, which we call page 10 in our batch manufacturing record, describes some of the actual processing that occurred during the preparation of this particular formulation.

Again, the product name, the lot number at the top of the page, step 8. It says add 36.13 grams of something

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to the solution, mix for a minimum of 10 minutes until dissolved. Well, we put in the start time and the end time for the mixing. They let this one go for almost an hour, but that's okay. It says mix for a minimum of 10 minutes, it doesn't say anything about the maximum, so we followed that instruction. Again, the double sign-off and the date.

Cool the solution to between 15 and 30. We recorded the temperature. It happened to be 28 degrees. Then, it said to q.s. to about 15 liters of sterile water for injection, mix for a minimum of 10 minutes. We put in the start time and the end time. It looks to me like it was about a 12-minute mix. Again, that complies with the instruction, and so on down the page.

There were several pages of these very detailed steps in the manufacturing process. Again, double signatures or double initials, and dates on every step. So, this is the ultimate, I guess, in complexity of the documentation that goes into the production of a batch of a pharmaceutical dosage form.

[Slide.]

Now, if we can come back to that slide that we showed earlier. This is a certificate of analysis for that batch that we just described, and you can see the test parameters that we looked at, that we evaluated. You can

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see the specifications that were in place for this particular formulation at that time, and you can see the results of our testing.

Interesting to look at the test parameters. We have got a chemical assay. We want to make sure that we have got the right amount in there. We have got a broad range to hit, 90.0 to 110.0, and we got right in the middle. We formulated this to 100 percent, so within the limits of our ability to manufacture and within the limits of the ability of the analyst to analyze, 98.7 is pretty doggone good.

The company was concerned about a couple of related substances in this formulation, so we are picking those up on the HPLC assay. One had a relative retention time of 0.78. That one tends to represent a degradation product. We don't know what it is at this point. So, they placed a limit on that and asked us to follow that as a function of stability. You can see it's a pretty low level, 0.05 percent, and then the sum of all others is about 0.7 percent.

These materials, these related substances are actually carried over from the drug substance. These were not introduced as part of the manufacturing process. The process did not create these.

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We did a USP sterility test on this batch. There has been a lot of talk about sterility, sterile products, and endotoxins in this group. There are actually two tests, two separate tests.

You can have a sterile product or a product that is sterile, but it can be loaded with endotoxins. I am not sure if you can have the reverse, but nonetheless, there are two tests that are carried out, one for sterility and one for endotoxins.

Sterility is an all or none, it's an absolute. With all due apologies to the women here, it is sort of like pregnancy, you either are or you aren't. Your formulation is either sterile or it is not within the limitations of the test.

There is a USP small volume particulate test that is carried out or was carried out for this particular formulation. These are allowable quantities of particulates, basically sub-visible, you can't see them with the naked eye, but there are limits on the sub-visible particulates that are allowable, and you are allowed to have some particulates in a dosage form of this type, and this particular batch met that criteria.

We did an endotoxin test, and that has really been a hot topic in this group. You can see the specification is

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less than 5 endotoxin units per ml, which I guess says you can have 4. There is people I know in this group who are tossing around the term endotoxin-free and pyrogen-free.

Based on the limits of our ability to measure endotoxin, I am not sure -- when somebody says endotoxin-free, to me, that means zero -- within the limits of the test methodology, I don't think you can convincingly say that a formulation or a solution has zero endotoxins in it.

Usually, the results are expressed as less than something. If you look up the definition of or the monograph for sterile water for injection USP, the cleanest water you can define, there is a limit, there is an endotoxin limit of not more than 0.25 endotoxin units per ml. It doesn't say zero.

Like I say, this specification, and basically the way the results were reported by the laboratory doing the work, were just as we read in there, less than 5. I guess that should say less than 5 EU. I wrote less than 5 E.

Appearance, a clear yellow solution and the pH you can see. This issue of endotoxins has got me interested. I helped the company I guess work out the specifications of less than 5 endotoxin units per ml, and I don't profess -- I am not a microbiologist -- I don't profess to know much

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about endotoxins. I have tried to define what endotoxins are in that page of definitions that I gave you, but I was curious about allowable endotoxin levels in pharmaceutical products.

So, I got out my USP 23 and I kind of went leafing through that and looked under the monograph, specific monograph for individual sterile injectable dosage forms. These are products that have been on the market for years.

I was quite amazed -- well, not quite amazed -- I was amazed at one of these, but not all of them. I photocopied -- I hope some lawyer here will defend me if someone sues me for copyright violation -- I photocopied about four pages out of the USP of individual monographs. I was curious as to what the bacterial endotoxin level was for each of these.

I am going to read these to you. They are not very long. Diazepam. Diazepam is valium, one of America's favorite drugs. There is an injectable dosage form of diazepam that is used in certain I guess surgical and presurgical procedures.

The USP monograph for diazepam says that it contains not more than 11.6 USP endotoxin units per milligram of diazepam. I guess you are allowed to have some endotoxins in your diazepam.

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Digoxin. I was interested in digoxin because I used to work with a company that makes digoxin, and did some work on the stability of digoxin injection, and so on, over the years. This one did amaze me.

It contains not more than 200 USP endotoxin units per milligram of digoxin -- per milligram of digoxin. I think the digitalizing dose for digoxin is about a milligram in humans, so that means you could get -- you could get up to 200 endotoxin units when you are being digitalized.

This kind of tells me that humans can tolerate low levels of endotoxin, and I don't know, I can't relate to 200 or even 10 endotoxin units. I don't know how much that is.

Fluorouracil, an anticancer drug. It contains not more than 0.33 USP endotoxin units. That is a pretty low level, but keep in mind that people get intravenous injections of 5 FU of about 800 milligrams, so if you have got 0.1 endotoxin unit per milligram, and you get 800, you could get a pretty good dose. Maybe it's the numbers that are scary here even though the numbers are very small, represent very small quantities, I don't know.

The final one, ranitidine, I think is Zantac, bacterial endotoxin unit for ranitidine and sodium chloride injection is not more than 7 USP endotoxin units.

There is an interesting discussion group on the

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Internet called PharmTech. It is sponsored by the PDA. There has been a discussion raging -- not raging -- but there has been a discussion recently of endotoxin units and is there a correlation between bacterial loads and endotoxin concentrations, and there is one school of thought that says there is no correlation, and there is another school of thought that says, yeah, you can calculate how many bacteria it takes to give you an endotoxin unit.

I don't know who is right and who is wrong, but the conclusion I drew from reading all this was it takes a whopping bacterial load to deliver a couple of endotoxin units, so if your endotoxin units are high, you have probably got some other problems.

If they are relatively high, you have probably got some other problems anyway. You may fail the sterility test, because these endotoxins actually come from gram-negative bacteria, and they are chemicals is what they are, they are lipopolysaccharides, and they give a response. Of course, all of our drugs are chemicals and they give a response, pharmacological response. These endotoxins are chemicals, and they give a response. Basically, they cause fevers, but if you give them in large enough doses, they cause a lot more serious kinds of effects.

MR. GUIDOS: We have a break scheduled for now.

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DR. POUST: I can stop now and run into the discussion or I can just stop, period.

MR. GUIDOS: How much longer will it take?

DR. POUST: I can get through this validation quickly. Then, I have got some slides of pharmaceutical manufacturing. I could skip the validation part and do that in probably 10 or 15 minutes.

MR. GUIDOS: Why don't we take a break now.

DR. POUST: That is fine.

[Recess.]

DR. POUST: Let's pick up on validation and I will try and keep this fairly brief.

[Slide.]

Validation started about 1976 in the human large volume parenteral industry as a result of several outbreaks of septicemia between 1970 and 1976. A group of FDA people went around and started inspecting some of the facilities and found many serious problems in lack of written procedures, lack of knowing what was going on with their equipment, and so on, and so forth.

The concept of validation began about that time.

[Slide.]

This slide is really the FDA definition of validation, and it is a definition of what you call process

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validation intended to cover mainly the validation of a manufacturing process. You can read as well as I what that says.

It kind of gets back to as we will see, validation kind of gets back to what we said earlier about why we have GMPs and the assurance of product quality.

[Slide.]

This slide asks the question of what should be validated and in a word, the answer is everything - manufacturing equipment, laboratory instrumentation, equipment cleaning procedures, operating systems, manufacturing processes, processes common to products, many products, such as high-quality water systems, and so on, everything that needs to be validated these days.

[Slide.]

This slide is titled "Need for Validation," and basically, it is rehash of what I said earlier, why do we have GMPs, kind of the same reasons. This is the reason we need to have validation. Again, I am not going to read these bulleted items, but you will recognize some of the words and phrases hopefully.

[Slide.]

The final slide talks about the different types of validation, and generally, the most accepted and most

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effective type of validation is what we call prospective validation. These terms, prospective, concurrent, and retrospective, are not unique to validation.

People involved in clinical research do prospective clinical studies, they do retrospective clinical studies, and you can gather from the words what is meant here, but a prospective validation is generally the most accepted, the most effective, you have preplanned protocols, they are approved by Food and Drug, implemented before your manufacturing process begins, generally used for a new facility, a new process, or a new product.

Concurrent is kind of validated as you go. At the last meeting, there was a presentation by somebody here in the audience about a wildlife product where only one small batch a year is used and how do you validate if you have to do three consecutive batches, and the shelf life of that product wasn't very long.

Maybe concurrent validation is the answer here. I mean in a validation experiment, one develops a protocol which involves fairly extensive testing, more extensive testing, in-process testing and final product testing, than you would normally use in routine production.

You get that approved by Food and Drug. It makes sense to me that if you make batch No. 1 and it passes all

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of that rigorous testing, why not be able to go out and sell that batch in a special case where it is a year's supply, otherwise, you are going to be throwing it away.

In order to get your three consecutive, obviously, the first one has to pass, as does the second one, as does the third one. If the first one doesn't work out, you throw it away and you figure out what went wrong and you start all over again.

So, why not allow concurrent validation or something for a special situation where you make very few batches and you have a fairly short shelf life on the product to begin with. If the second one then -- you know, you make the first one, if it passes your testing, you sell it, you make the second one a year later, it passes, or maybe it doesn't pass.

If it doesn't pass, you go back and figure out why, and you ask yourself does this have some negative impact on the first batch that passed. Well, probably not given the extensive testing that is normally done in a validation experiment.

Maybe this is something that could be considered for a special situation where we have got low-volume products.

Finally, retrospective validation is basically

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historical data going back, if you had a product that you have been making for the last 10 or 15 years, and doing it successfully, you have got lots of data on that product, you can probably conclude, if you have a high success rate of passing batches rather than rejecting, you can probably conclude that you validated that process.

Retrospective validation was allowed by FDA in human industry for a long time. I think they have gotten to the point now where they are not accepting it anymore. I guess companies have had long enough to use that approach for their products, but maybe that is something that ought to be considered here, extending that grace period, so to speak, in this industry since the enforcement standards have been ratcheted up, I guess, in the last seven years.

That is the end of the overheads. What I would like to do now is what Dr. Sundlof called the virtual tour, kind of gets back to the old saying if you can't bring Mohammed to the mountain, you try to bring the mountain to Mohammed.

At the University of Iowa, we have a very small GMP compliant manufacturing operation which has the capability of producing small batches of clinical supplies for the pharmaceutical industry and for various government agencies.

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We have the ability to produce sterile products, solid oral dosage forms, topicals, oral solutions. I hope this doesn't sound like an advertisement for what we are doing, it is not intended to be. It is intended to kind of give you a flavor of what a pharmaceutical manufacturing operation would look like.

The thing you have to understand is that it is done -- it is rather labor-intensive -- and it is done on a much smaller scale than you would find if you went to a commercial operation.

[Slide.]

It starts with sampling raw materials. We bring raw materials into the facility, we sample them. The sampling room is basically an empty room, it is kept clean. There is a logbook for it. We bring materials in here one at a time, pulling the sample for QC testing. We avoid cross-contamination by bringing them in one at a time.

We take them out, clean the room, and bring the next one in. So, even at this point in time, we are trying to avoid cross-contamination.

[Slide.]

This fellow is simply logging raw materials into a recordkeeping program where we record the name of the material, the quantity, the manufacturer, the manufacturer's

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lot number, our lot number, date received, and so on, and so we can recall this data when it becomes necessary.

[Slide.]

This is the quarantine area. Materials go into quarantine before they are released by QC. It is isolated. There are various ways of isolating quarantined materials. This gets into the how. The what tells you, you have to do it. It doesn't tell you how to do it.

[Slide.]

Pharmaceutical manufacturing especially sterile products start with clean air and clean water. This is a still that we use to produce water for injection USP, very high quality water. We have a hot loop system. This still puts out 150 gallons of water for injection per hour. Feedwater is -- FDA has become concerned about feedwater recently -- feedwater in this case is deionized water.

I shudder to think what would happen to that still if we put Iowa city water into it. We would be buying a new still every couple years. Iowa city water is pretty raunchy just to drink.

Anyway, we produce high-quality water. It is all stainless steel piping. We have got two stainless steel holding tanks. We test the water daily for chemical attributes, as well as microbiological attributes. This

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water is used for cleaning glassware, producing clean steam for our autoclave, producing clean steam to sterilize our freeze dryer, and a variety of other uses.

[Slide.]

Just a bigger view of the still.

[Slide.]

This is what is called a metromatic vial washer. You see that white piping at the bottom there. That is the WFI that feeds this vial washer. So, we clean glass vials and ampules that are going to be used in sterile processing.

The cleaning operation has been validated. We have got protocols, we have got documentation to demonstrate that.

[Slide.]

This is a larger washer that we can do larger vials and larger bottles, quarter-liter bottles, half-liter bottles, and 1-liter glass bottles, and it has been validated.

[Slide.]

This is a pass-through dry heat oven. Once the glassware is washed, it is put into a dry heat oven which will destroy pyrogens or endotoxins, if there are any -- and there shouldn't be any -- but if there are any, it will destroy them. It will sterilize the glassware, as well.

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[Slide.]

The glassware that goes in here is put in stainless trays that are sealed and taken out the back end of this, which you see here, into a clean, fairly clean corridor air-qualitywise.

[Slide.]

This is a stopper/washer used to wash rubber stoppers. Again, it has been validated. The usual way of doing that is you take certain known quantities of endotoxin, dry them on preidentified stoppers, wash them, and then test those stoppers for residual endotoxins. We are proving that we can wash endotoxin off of rubber stoppers.

So, this is a washing process, as well as a depyrogenation process for the stoppers.

[Slide.]

Just another view. You can see that this person is dumping a bag of stoppers into the washer, into the top, and then they come out the bottom once the wash cycle has been completed. The water for that washer also comes from the water from the injection system.

[Slide.]

This is the front end of the pass-through autoclave. The stoppers then are sanitized or sterilized by

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passing them through this validated autoclave. There is the back side where they come out. They go in the front and come out the back.

[Slide.]

This is a sterile operation. This is really I guess what we call a semi-automated filling operation. You can see the gowning and the big thing in sterile filling is the biggest source of contamination in a clean room is people.

You can see we have covered the people up with sterile gowns, gloves, masks, goggles, head coverings. These suits are all presterilized. They go through a two-stage gowning area before they come into the clean room.

The filling area where there is open product, which is where they are operating, is called a Class 100. There is HEPA-filtered air, and that is where the clean air comes in that I mentioned earlier.

HEPA-filtered air from the ceiling washes down over the operation. So, we have got a person filling, we have got a person stoppering, and then there will be somebody on the other side that will be putting caps or seals on there and crimping those.

You can see the bulk solution there in the middle, that kind of milky-looking material.

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[Slide.]

This is another filling operation. Over on the left, about the center of the screen, you can see a very dark red liquid in a flask. That is the product. We are filling that into vials and then putting it into a freeze dryer, which is hard to see, but that is what the person standing on the right is putting a tray of vials into a freeze dryer, so this formulation has to be freeze-dried because the compound is not sufficiently stable in solution.

It is freeze-dried, we remove the water, and then it is reconstituted prior to use, prior to administration to the patient. Again, this was a Phase I clinical supply batch of an anticancer drug.

[Slide.]

There is a better view of the freeze dryer. If you see it with the door shut, it looks like a big bank vault. It is stainless, computer-controlled, self-sterilizing.

[Slide.]

This is a West capper. It is small capping device. We put the seals on and it actually crimps the seals over the stopper and actually seals the vial. The reason the photography is a little hazy there, it was shot from outside the room, the photo was shot from outside the

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room, and the windows have reinforced glass with this wire meshing, so the interference in the photo is just from the wire mesh in the glass, which hopefully gives the FDA people assurance that we didn't put a photographer in the clean room. We couldn't figure out how to autoclave his camera, so we wouldn't let him in there.

[Slide.]

We do monitoring, environmental monitoring during the filling, and I guess I should back up a little bit. You see what looks like a black hose coming down from the ceiling in that photo, and you see two of them there, actually three of them.

Those hoses draw air up through them and they go into a particle counting device, looking for nonviable particulates. We also put out plates, rodac plates for settling, for viable materials that might happen to be in the room, as well, and those are incubated and speciated if necessary.

[Slide.]

This is the other end of those black hoses. This is the particle counter and the printer, so we create a lot of documentation during the process, not only the batch manufacturing record which you saw a few pages of, but printouts from this particulate monitoring that goes on

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during the filling process.

[Slide.]

We do 100 percent inspection of all vials. I think that is pretty much a rule. That is one of the "hows," and you can do it manually, I guess, if you want to call it that, or there are automated inspection stations that the industry uses for larger batches.

We tend to employ a number of sharp-eyed 18- and 19-year-old college students, and they can see things that I can't see, most of us can't see, so we have some real eagle-eyed people. We train them, tell them what they should be looking for, and put them to work.

We classify our rejects as to whether there is white particulates, dark particulates, cracks in the vials, and so on, and we can establish trends then in our manufacturing operation to see if we have got a problem or if we just have isolated problems.

[Slide.]

The next few slides show some of our solids processing equipment going from sterile processing now to the production of tablets and capsules. These are examples of milling, mills that we use to reduce particle size of powdered materials to make it uniform and of an appropriate or desirable particle size. A lot of the shots you see here

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will not have people in them.

[Slide.]

These are typical V blenders used to blend powdered materials. Basically, they rotate on an axis. You put two or three and four ingredients in the one end of those and then close it up and turn the machine on to blend for 10 or 15 minutes. It basically rotates on an axis and the tumbling action is very efficient in mixing in a uniform manner several different ingredients.

[Slide.]

This is what is known as a PDA capsule filler. This capsule filler can put out roughly 4- to 5,000 -- you can fill 4- to 5,000 capsules per hour on this machine. High-speed production machines -- well, I should high-speed pilot scaled machines can fill roughly 25,000 capsules an hour. I guess even higher speed production machines can produce more than that.

Typical batch sizes of tablets and capsules in the pharmaceutical industry, at least on the human side, are generally 1 to 3 million in size. We make a lot of batches of capsules and tablets of 5- to 10,000.

[Slide.]

This is a different type of capsule filler. It is called a Zinazzi and it operates on a different principle

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than the PDA equipment and there you can see an operator making an adjustment on that capsule filler.

[Slide.]

This is a small-scale rotary, I guess this is our beta press, 16-station rotary tablet press. We can produce on the order of, oh, 70- to 100,000 tablets in a six- to seven-hour shift.

[Slide.]

This is a Stokes again rotary tablet press, just a different brand that operates on the same principle.

[Slide.]

This is what is known as a tablet and capsule sorter. This is a computerized device which will weigh individual tablets and capsules. You program into the computer the desired weight and range that you want, and it weighs each tablet or capsule individually and then there is a little lever that flips it either into the "accept" -- you see the two barrels there -- either into the "accept" barrel or the "reject" barrel depending on the preprogrammed parameters and the actual weight of the dosage form.

So, this is a good check if you have got variability, and often in Phase I, the first batches you make with a not very rigorous formulation, you often can get some variability in tablet and capsule weight. So, this is

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a good way to sort out the good ones from the bad ones.

[Slide.]

This is a small coating pan for applying polymer coating to tablet surfaces. Tablets are typically coated for a number of reasons, one, for stability reasons, a second would be to affect or control the release of drug in the body. Another reason might be to cover up an unpleasant taste or I had an experience this summer where we had a tablet that a very unpleasant odor, which is unusual, and we actually had to double-coat that one.

This coating pan operates sort of like your clothes dryer at home. There is a rotating drum inside. You put the tablets in there, you spray a solution of a polymer. The drum rotates much like a clothes dryer does, you spray the solution of polymer in there, pour some hot in there to dry the solvent, and then the residue is the coating that is on the surface of the tablet. If you get all the parameters set up properly, you get a nice uniform, elegant coating on the surface of your tablet.

Some people have tried to coat capsules. That is a challenge.

[Slide.]

We also have a special containment facility for highly potent and cytotoxic type drugs that might be harmful

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to the employees. Part of GMPs is you are trying to do two things. You are trying to protect the product from the people and sometimes you are trying to protect the people from the product.

So, it is a safety issue here. We are trying to protect the people from the product, and if you have a dusty operation where you have got a very highly potent drug, we are trying to protect the people from the product. So, this fellow has on a full-body suit, air-tight. He has got a breathing hose that kind of goes up the back and feeds into the back of the helmet, and that breathing air comes from outside the room.

It also partially inflates the suit, so there is kind of a positive pressure in the suit in that the air flow, if there is a leak in the suit, the air flow will be from inside the suit to outside the suit, so he is not potentially drawing drug inside the suit.

[Slide.]

This gives you an idea of how we monitor that room. There is usually an operator or two in there. We always have a spotter on the outside. They all have wireless radios, and so they are in constant communication with one another, so if the person inside the room needs something or gets in trouble, the person on the outside can

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provide assistance.

[Slide.]

We have a QC lab. Of course, we talked quite a bit about in-process testing, final product testing, and so in a manufacturing facility, you need to have a quality control lab for testing raw materials, for doing in-process testing, for doing final product release testing, and for doing stability testing. So, this is just a few shots from our QC lab.

[Slide.]

HPLC is the workhorse instrument of the pharmaceutical industry and we have got several of those in our facility, so it is a typical laboratory. This is hopefully not too unfamiliar to a number of people.

[Slide.]

Dissolution test apparatus for testing dissolution rates of tablets and capsules.

[Slide.]

Stability chambers, storage chambers set at controlled room temperature, elevated temperatures, such as 40 degrees, 75 percent relative humidity, a variety of other conditions for trying to get an early readout on the stability of a formulation.

[Slide.]

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This is another shot of those chambers.

I guess that is it. Mr. Chairman, I have come to the end.

MR. GUIDOS: Thank you, Dr. Poust, for that excellent presentation. I know that I have learned a lot more about the drug manufacturing process, which wouldn't be hard to do. In just a minute we will allow the panel members to ask any questions they may have to fill in some of the gaps in their minds.

Before we start that, though, I would like to go around the room and introduce -- now that my brain is functioning after drinking some coffee, I remembered that I probably should have some introductions. So, if we could start with Dr. Wolf.

DR. WOLF: Alice Wolf. I am a professor of small animal medicine and surgery at Texas A & M University and I am the companion animal representative.

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

DR. KOONG: Kelvin Koong, Associate Dean, Oregon State University.

DR. FLETCHER: Oscar Fletcher, Dean of the College of Veterinary Medicine at NC State. I am representing avian

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medicine.

DR. CLELAND: Janis Cleland. I am the editor of the Journal of the American Animal Hospital Association, and I am a consultant representing small animal practice.

DR. LEIN: Don Lein, Director of the Diagnostic Lab at Cornell University, representing Microbiology and Chair of the Advisory Committee.

DR. FRANCIS-FLOYD: Ruth Francis-Floyd. I am an Associate Professor and Extension Veterinarian for Aquaculture at the University of Florida. I am a consultant for aquatic sciences.

DR. STERNER: I am Keith Sterner, professional meeting attender and occasional private veterinary practitioner. I do food animal medicine, primarily dairy practice, Ionia, Michigan.

DR. BARKER: Steven Barker, Louisiana State University, Professor in the Department of Physiology, Pharmacology, and Toxicology, representing the analytical chemistry specialty.

MS. HUDSON-DURAN: I am Sue Duran. I am a large animal clinic pharmacist and I am the Consumer Affairs representative.

DR. RAVIS: I am Bill Ravis from Auburn University, Department of Pharmacal Sciences, Professor in

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Pharmaceutics.

DR. GERKEN: Diane Gerken, College of Veterinary Medicine, Ohio State University. I am representing the toxicology discipline.

DR. COOPER: I am George Cooper, U.S. Department of Agriculture. I am representing animal science.

DR. KEMP: I am Douglas Kemp, University of Georgia, representing veterinary pharmacy.

MR. GUIDOS: Dr. Nancy Jaax will be joining us tomorrow, is our expert in Pathology. She is from the Department of the Army.

We would also like to go down the line of the industry representatives and CVM.

MS. DUNNAVAN: Hi. I am Gloria Dunnavan, Director, Division of Compliance, Center for Vet Medicine.

MR. GARZA: I am Manuel Garza, investigator at the Kansas City District Office. I also manage the Preapproval Inspection Program for the District.

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

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

DR. SUNDLOF: I am Steve Sundlof, Director of CVM.

DR. LIVINGSTON: Robert Livingston, Director of

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the Office of New Animal Drug Evaluation.

DR. BEAULIEU: Andrew Beaulieu. I am a Deputy Director in CVM's Office of New Animal Drug Evaluation.

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

DR. LEINBACH: Patricia Leinbach. I am an Acting Team Leader in the Division of Manufacturing Technologies.

DR. NEWKIRK: David Newkirk, Division of Manufacturing Technologies.

MR. GUIDOS: I know there are a few other CVM representatives here, a few who will be speaking later on. I think Chuck Eirkson is one of them.

Is there anyone here from AHI or representing AHI?

MR. STANK: I am Ken Stank with Elanco Animal Health, representing the Animal Health Institute along with --

MR. INCORVIA: I am Gary Incorvia from Monsanto Protiva also representing AHI.

MR. GUIDOS: Thank you.

I don't know what I have done wrong, but I am already 15 minutes behind schedule.

Q and A for Dr. Poust on his presentation or any questions about the CGMPs? Dr. Wolf.

DR. WOLF: One of the things we have concerns

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about in small animal medicine is that we often need to break tablets in order to get the appropriate dose size for our patients. There has always been concern I think in many of our minds that perhaps the drug active ingredient is not adequately distributed throughout the tablet and we may be getting some improper dosages by breaking those tablets up.

Is this a real concern or are the manufacturing processes so good that it is quite well distributed?

DR. POUST: I think the goal really is to get the right amount of drug in the dosage form, but within a dosage form I don't think there are any requirements to have that uniform of a distribution. So, there is a risk obviously. I don't know if anybody has any data on that or not, but there is a good chance that it is somewhat uneven within a given dosage unit.

I think if you start holding the industry to that standard, you will hear howls of protest.

MR. GUIDOS: Dr. Koritz.

DR. KORITZ: The question pertains to the statistics of, let's say, terminal testing of a solution in vials. Are certain confidence intervals or statistical criteria set that there is a certain acceptable failure rate of a product at terminal testing?

What I am trying to get at, are statistics applied

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to such an extent that you can look at numbers and thus remove the emotions of making some of these decisions?

DR. POUST: I guess I am not that familiar with that aspect of it. I think there are some statistical considerations given and there may be data available in the literature. I couldn't tell you what the numbers are.

For example, I know that when one is doing media fills, I think the magic number is you do a fill of about 3,000 vials and there is a certain allowable failure rate at 3,000, and I think you are only allowed one failure out of 3,000 vials.

If you were doing a smaller batch, I don't think any failures would be tolerated. If you are doing a much larger batch, the number of failing vials I think is maybe a little higher, allowable failures would be a little higher, but other than that, I can't help too much. Manuel may be able to shed some more light on this, I don't know.

MR. GARZA: Are we referring to just the efficacy of the sterility cycle or are you talking about the assay of the product itself?

DR. KORITZ: I am talking about the final decision to actually be able to release the product. You have a number of tests throughout this whole process.

MR. GARZA: The final decision is based on a

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number of variables including sterility, endotoxin, the assay, the pH, the monograph, the control of the cycle during this production, the testing of active/inactive materials, the container closure systems, the integrity of the systems.

If any of these links in this chain are weak or found unacceptable, and there is reason to cast doubt on the end product testing, the endotoxin and sterility tests may be adequate, but those are based on a very small sample of the entire batch, and if that is the case, then, you have to assess whether you are going to release that and face the potential of releasing some product that may be either super or subpotent or perhaps questionable sterility or endotoxin content, so it's not just based on the end product test results.

DR. POUST: To add to that a little bit, if you go back to that slide that I showed with the certificate of analysis, there were seven or eight different test parameters, all of those must be met. You can't fail one and pass the others, all have to pass, and if one doesn't, then, yes, you launch into an investigation of that, and if you are convinced it's really the product that is a problem, you reject the batch.

DR. LEIN: Isn't that checked off in process,

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though? I mean a lot of these things are happening as the process is going on, so you really would have a disruption earlier on in the product because they really are going through a series of different check points.

DR. POUST: That is true for certain tests that can be done quickly, such as a pH measurement or even a chemical assay, but a sterility test takes about two weeks to do.

DR. LEIN: Right, that's the end product.

DR. POUST: You don't want to hold your -- because now you are introducing another element, another risk into the process, you hold your batch exposed, let's say, for two weeks.

DR. LEIN: I understand. This is dynamics. I mean you are not coming to the end and saying, by God, we invalidate that piece of equipment back there.

DR. POUST: And that's why we validate all these processes, to begin with, to reduce the risk of that happening.

MR. GUIDOS: I think we have an industry response to the question raised earlier by Dr. Wolf.

MR. STANK: Ken Stank with Elanco Animal Health representing AHI.

Concerning splitting the tablet and scoring on the

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scored tablet, I think you can rest assured that there will be uniformity throughout that tablet. That is one reason why the tablet is scored to allow you to do that. I think there is more risk in the actual breaking of the tablet than there is worrying about whether there is an even distribution of the drug.

I think that speaks to the use of animal drugs for animals rather than using human drugs for animals, because a lot of times the animal drugs are dosed more accurately to facilitate dosing, small doses for animals.

Thank you.

MR. GUIDOS: Are there any follow-ups to Dr. Koritz's question? Dr. Gloyd.

DR. GLOYD: I am probably getting ahead of myself, but there is a statement in here by the Animal Health Institute saying that the current sterility assurance level of 10^{-3} is appropriate, and then someplace else in this small book, it has an FDA criteria of 10^{-6} . That is obviously three orders of magnitude in difference. I am curious, is that an issue? Is that the end result?

DR. POUST: I am not too sure what the answer to that is. I think there is a continuing discussion of that. It may be resolved in some people's minds, but maybe not in other people's minds, which is not a good answer obviously,

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but maybe somebody has a better one.

MR. GUIDOS: Dr. Leinbach, do you have a response?

DR. LEINBACH: Yes. Aseptic processing is acceptable for animal sterile products, and 10^{-3} is the SAL that is associated with it. I didn't see the 10^{-6} in here. I would like to know where it is.

DR. POUST: It is in there. I put 10^{-6} in a definition, but it was a probability of sterility I guess following terminal sterilization. We may be talking about two different things here, too.

MR. STRIBLING: 10^{-6} appears in the FDA's proposed regulation to require terminal sterilization for animal drugs, as well as human drugs, and it is contrasted there with aseptic processing where 10^{-3} is listed by the agency.

DR. STERNER: I think my question to Dr. Poust asks for his opinion and it relates to Question No. 2, which this panel has been asked to answer or address.

When CVM decides whether to adopt a particular drug quality standard, should it weigh the benefits against the costs of adopting, or of not adopting, the standard, my question relates specifically to the question of terminal sterilization and your experience with it, and speaking as a food animal practitioner, I see many things that great efforts are made to ensure a quality product that gets to

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the field, and it gets thwarted very rapidly under field conditions of use, i.e., in a sterile injectable product being put through an inch and a half of armor plating in the middle of the winter on some cattle that come through for injections.

I am curious to know if you think that adoption of higher level CGMPs requiring terminal sterilization will, in fact, assure me, as a practitioner, or others, that, number one, product will somehow be better, and, number two, do you have any opinion about what it might have with regard to availability of drugs for me as a practitioner in the field.

DR. POUST: I think you have to go with the science first, but you have to go with the common sense, as well, and maybe there is a tradeoff there, I don't know, depending on usage in the field.

I don't know that much about this industry, so I don't want to comment on what happens in the field. Most drug manufacturers will tell you they really can't control what happens to a product when it goes in the field.

On the other hand, they ought to make it their business to know what goes on in the field, so they can design their products or their formulations in such a way that they will withstand the rigors of testing in the field.

A good example might be if you have a formulation,

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let's say, that is only stable when kept in the refrigerator, but that product is such that it is going to be riding around in the trunk of a veterinarian's car for six months, maybe you ought to do a better job at formulating that, so it will withstand that rigor. Does that make sense?

DR. STERNER: If there is such a product.

DR. POUST: I am sure there is. When I was in the human industry, this question always came up with regard to physician samples.

I mean it is one thing to store products in a pharmacy or in a wholesaler where you know what the temperature is or can pretty well guess what it is, but what happens when the sales reps carry samples, physician samples around in the trunks of their cars in Arizona in the middle of the summer, do we have a different stability profile here, and the answer is in many cases we do, and we were charged, we who were in the stability testing program for the company, were charged with coming up with guidelines for our sales reps as to what to do and what not to do with respect to those kind of physician samples.

So, I am aware of those kinds of issues and it kind of gets back, you know, it is kind of a dialogue between the company and the practitioners. The company

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ought to know, I think should know, should be responsible to know how these products are used in the field and take appropriate precautions in terms of formulation, and it is a bigger challenge to the formulator.

DR. STERNER: Well, that is precisely the point in answering this question and making a recommendation that paints with a very broad brush about very specific instances.

There is a theoretical consideration which I am very sympathetic to with regard to terminal sterilization. There is the reality of the day-to-day usage of these products and the stability of the product that you alluded to is one that, in my particular endeavor in food animal practice, there is a product which is not particularly heat stable, and yet requires refrigeration, and yet the industry seems to have been fairly successful in utilizing it even with the refrigeration requirement.

My real question is, is will the considerations in terms of manufacturing with regard to terminal sterilization result in some quantifiable improvement in terms of product that is available to me as a practitioner, and I am asking your opinion here.

DR. POUST: Probably not if they have been making it in an aseptic process environment and have validated that

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they can produce a quality product time after time after time. It doesn't make a whole lot of sense at some point in time to go to a terminal sterilization process.

If they have a poor track record, maybe it does make sense to go, but on the other hand, if the product is that heat labile, it may be that the terminal sterilization process will cause an unacceptable degradation of the product in the first place, and that then is a scientific reason not to do it.

DR. STERNER: Well, your presentation very eloquently described good science, as well as common sense, and that is what I think this panel is trying to come up with in terms of recommendations in answering these questions, and it is a very real one representing, you know, my parochial interests on this panel.

DR. POUST: It is my understanding that the FDA has kind of backed away from that terminal sterilization requirement. On the other hand, it makes good sense to me, common sense to me, that you can do a simple experiment in your formulation development activities and determine whether or not your drug will stand the rigors of terminal sterilization. If it won't, fine, you have got the data. If it will, maybe there is a good reason to do it.

DR. STERNER: But as part of the CGMPs, if it

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becomes a pan industry requirement, I may not have products available to me because they can't meet the rigors of that CGMP.

DR. POUST: Right, and that is where you have got to take a look at that. I think that is an important factor.

MR. GUIDOS: Other questions? No.

I would like to now introduce Dr. Stephen Sundlof, Director of the Center for Veterinary Medicine, to discuss issues and overview relating to the manufacture of animal drugs. In his presentation, Dr. Sundlof is going to go over the five questions for the panel to consider over the next two days and to make recommendations.

We are looking for definitive recommendations, but we are not looking for a vote on these issues, just specific recommendations.

Animal Drug Manufacturing Issues Overview

DR. SUNDLOF: Thank you, Bob.

The first part of my talk is going to be without slides, so if we could have the lights back up for the beginning.

I want to start off by again welcoming everybody and especially giving thanks to Dr. Poust for that excellent presentation and the tour through his facility, and by the

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way, Dr. Poust, Manuel Garza indicated that there was about seven GMP violations that he picked up.

[Laughter.]

DR. SUNDLOF: Actually, I am kidding, of course, there was only three. But that was very enlightening for me and I am sure a number of the other people here.

Well, this is kind of a unique undertaking and it is unique that we are having two meetings within six months to get the issues on the table, and that is just an indication of just how complex the issues are that we are dealing with.

It is significant because of the pivotal role of drug quality issues in the mission of the Center for Veterinary Medicine, that is part of our mission. So, I want to acknowledge the contributions of all who have been involved in this intense effort and I want to thank the members of the Veterinary Medicine Advisory Committee and its consultants for your interest in the subject and for your active participation in the May meeting and for your preparation for this meeting, which included reading in a big, thick book of information.

Our appreciation also goes out to the Animal Drug Alliance, the Animal Health Institute, and the American Veterinary Medical Association. These organizations not

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only participated extensively in the May meeting, but also submitted materials for discussion and provided other assistance as we prepared for this meeting.

I want to also make sure and acknowledge others from the industry, such as Bill Lance from Wildlife Laboratories, and Gene Lloyd, who I don't think is here, I didn't see Gene, but whose comments in the May meeting have contributed to the issues for discussion at this meeting and beyond.

I also want to thank and acknowledge the contributions from those people in CVM and other offices in FDA who have been participating in this process especially the Office of Regulatory Affairs. They have really worked to put together the extensive background material that you have received for this meeting.

In addition, they have worked to pull together information and material that responds to the questions raised by VMAC at the May meeting, and these people from CVM and elsewhere in the agency are dedicated, they are experts in their area of work, but they also share my conviction that we cannot do this alone, that it really takes a lot of input from a lot of different people.

We realize there are times when we need the contributions of an independent group of experts, such as

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VMAC and the benefit of participation by the animal drug industry, and by those who use animal drugs and by the public at large in coming to the right decision. It serves the best interests of the public and the profession.

So, I want to invite all of you who are in the audience today, as well as the members of the panel, and the consultants, that we want a lot of active participation in the discussions that will be held today and tomorrow.

Now it is time for you to express your opinions, elaborate on your views, and clarify your positions. We, in CVM, have not made any decisions on the questions that we are presenting to you at the VMAC meeting and we are approaching these questions with a very open mind.

If some of our background papers and comments of our staff may appear in some instances to state our positions, please consider that the statements are made for discussion purposes only, and more than that, we are also willing to reconsider positions stated during the May meeting. So, please, don't feel that we have already made any firm decisions. We really want your best thoughts on this.

To VMAC and its consultants, we are asking for your views on several substantive issues, as well as issues involving process or procedures that might be followed to

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better enable us to make the appropriate decisions regarding drug quality.

You will also have the opportunity tomorrow afternoon to comment on issues raised at the May meeting, but not specifically included in the five questions that you will be asked to deliberate on today and tomorrow.

The point is that we want your forthright advice, as well as your comments and questions on matters that go to the substance of quality standards that we apply, as well as the processes by which we adopt, communicate, and apply those standards.

I am well aware that some of the examples that were presented in the May meeting go beyond the technical expertise for most of the people on the panel, but I also believe firmly that there are matters of scientific policy which you are very well qualified to comment on.

The point of making those statements is that we want you, at the end of the meeting, to say more than just turn it over to a group of technical experts. We really want your expert opinion on these.

This is not to denigrate the contribution of technical experts, but instead to acknowledge the critical role of independent review in an area that has been characterized by controversy for a number of years.

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To talk a little bit about our future plans and what we intend to do with the information that we gather from this meeting, we will take VMAC's advice very seriously and the entire record of this meeting and the May meeting into consideration as we make decisions.

In doing so, we will likely need to consider limitations of the current law and agencywide policy guidance, but VMAC should not be constrained at this point by legal limits and policies of the agency including policies of the Center for Drug Evaluation and Research or CDER.

What I am trying to indicate is that at the last meeting, there was some discussion that we are constrained because of another center, the Center for Drugs, human drugs. There are certain constraints from policy decisions that are made throughout the agency, but we don't want you to be constrained by those. Give us your best advice and we will take it from there.

The outcome of our future deliberations within the Center and the agency could include changes in policy, new guidance documents, new partnership arrangements with industry, positions on proposed legislative changes, and the like. So, we are looking at all avenues of making these changes.

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Our underlying objective is to make decisions that support and improve human and animal health. We intend to respond as fully as we can to significant drug manufacturing issues that the animal industry has raised in recent years.

We want to eliminate or at least reduce the areas of controversy that have affected all of us in the recent years. Dialogue with industry, veterinarians, and the public interest groups will continue to be extremely important to us.

One or more new mechanisms for communication could be an outcome of this meeting. However, I cannot emphasize too much our goal to bring as many matters as possible to closure within the new few weeks and months following this meeting. We intend to act expeditiously on the recommendations.

Thus, I say again to those in this audience this is the time for all of you to offer your views.

Now, I want to talk a little bit about human versus animal drug standards and where there can be differences.

We are mindful of the statement in the September 1995 report from the Senate Committee on Appropriations that the committee expects FDA to exercise the authority it has to establish, where appropriate, Current Good Manufacturing

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Practice requirements for animal drugs that are separate from the requirements applicable to drugs used for human use.

As you know, there was considerable discussion during the May meeting as to whether and when different standards for animal drugs are appropriate and when they should apply.

We have not specifically asked VMAC for advice on the extent to which standards for animal drug manufacturing should differ from those of human drugs. Instead, we have asked the committee to focus primarily on what we believe the first and fundamental question to be, and that is what standards should be applied to animal drugs. We are not looking to identify the differences, we are trying to ask the question what are the proper standards.

To the extent that those standards need to differ in any significant respect from those of human drugs, then, it will be necessary to have the discussion within the agency that I referred to earlier.

The scientific and policy basis for animal drug quality standards is critical in such discussions. Thus, we believe that VMAC's advice, even if not directed specifically to the animal versus human drug question, will be helpful to us in determining whether and where divergence

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in the requirements are appropriate.

I also want to emphasize what we said in May, that we are willing to consider recommendations for standards that are different from those of human drugs. This is in addition to the differences that already exist and that we described during the May meeting.

Let me just give you one illustration that has emerged since the May meeting. CVM has advocated on an international scale appropriate quality requirements for veterinary pharmaceuticals.

This has occurred in the context of the international cooperation on harmonization of technical requirements for the registration of veterinary medicinal products. That is the actual name of a committee, but we have abbreviated it VICH, so I will be referring to VICH, and that is a program again that is intended to harmonize standards across Europe, Japan, and the United States for the requirements for drug approval for animal drugs.

The members have created a working group charged with reviewing the quality requirements elaborated by the International Conference on Harmonization for Human Pharmaceuticals, abbreviated ICH, to determine whether these requirements are applicable for veterinary drugs.

CVM's advocacy has resulted in the working group's

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agreement to recommend to VICH modification from the ICH in certain areas. One example is related to stability, is the allowance of stability testing of drug product in smaller packaging simulating actual market packaging.

A second example is the provision that long-term drug product stability testing for six months rather than 12 months as is in the ICH guideline is acceptable at the time of submission of a registration application.

Although the working group's recommendations have not been formally adopted through the VICH process, we believe that these are examples of appropriate differences between animal and human drug standards.

There were some issues raised at the May meeting, and I will try and respond to some of those issues that were raised that we were not able to fully answer in the May meeting. We thought it would be useful to review a list of the significant issues that were raised at the May meeting, and I will do this in just a few minutes and we will go to the slides then.

We are bringing some of these issues to VMAC in the form of questions to be answered at this meeting, and I will also explain as fully as possible how we are responding to these and other issues.

Although we want you to focus primarily on the

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five questions that I will show at the end of this presentation, we realize that some of you may want to comment on other issues that were raised at the May meeting, and we have allowed time at the end of the meeting tomorrow for you to raise those issues.

I would like to begin with the slides. I apologize for some of the dark print on the dark slides, but the title of that, I think it says May 1997 VMAC Questions.

[Slide.]

The first question we asked was should FDA make any changes in its quality standards for the manufacture of animal drugs or in the administrative and inspectional procedure by which these standards are implemented.

If the answer to that was yes, then, what changes should the agency make (a) in general, and (b) with regard to the following aspects, and those are all the processes you can read there - sterility, process validation, clinical supplies, facilities, components, analytical testing, and other issues.

After careful review of the transcript, we came up with a list of five questions that more precisely focused, yet incorporated a significant portion of the May discussion. The questions which we believe are both appropriate in content for VMAC and manageable in number,

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and there were a lot of questions that we could have addressed. We think we have boiled it down basically to five questions that will address those issues of greatest need for the industry.

In general, we are asking VMAC to focus more on issues that involve prospective changes in standards and policies than on retrospective review of existing standards and policies, this, in part, in response to the priorities expressed by the Animal Drug Alliance, which are the subject of the correspondence between Jess Stribling and me, and copies of those issues are in your notebooks.

I recognize the virtual impossibility of discussing prospective changes without considering the current standards, but I would like to ask the committee to focus as much as possible on the future.

[Slide.]

Some of the issues from the May 1997 meeting. We had some substantive issues, some procedural issues, and then some communication issues, so these are the main questions from the May 1997 meeting.

The substantive issues are characterized by, number one, should FDA make any changes in quality standards for the manufacture of animal drugs. Next is procedural changes. Should FDA change the procedures it follows in

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establishing, communicating, and applying quality standards, and the third is, is there a need for further study by groups other than VMAC regarding the quality standards and procedures.

[Slide.]

I am going to go through these substantive issues. As an introduction to the substantive issues, let me remind you that drug manufacturing quality regulation by FDA generally concerns two subject areas.

The first is chemistry manufacturing and control, which involves drug quality information that is reviewed in an application for approval of a new animal drug. The second is Current Good Manufacturing Practices, regulations and policies, which are pertinent both prior to the approval of the drug, but also become significant after the approval of the drug as firms are inspected.

As you will recall, at the May meeting, there was little opposition to the CGMP regulations per se, but the major concern focused on how these regulations are being implemented.

There was also considerable discussion of the CMC or Chemistry Manufacturing Control standards. The substantive category has three parts to it.

[Slide.]

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First, should the agency make any changes in the criteria for establishing acceptable quality. The first question under that is should human and animal safety as affected by the availability of approved animal drugs be a criterion.

On the other hand, taking the other side of that, should safety concerns be limited to those related to the manufacture of the product in question. We will talk more about that later. Should we be taking into account what would happen if we don't approve a drug, will animals suffer, will other unapproved drugs be used.

You will recall that these issues were raised in the May meeting by Jess Stribling and Joe Gloyd and several VMAC members, and some of the points were manufacturing concerns related to safety should take into consideration the environment in which the drugs are used. I think Dr. Sterner just brought that up.

For instance, the unapproved products that will be used if approved products are not available at a reasonable cost, and FDA needs to base its drug manufacturing CMC or chemistry manufacturing control, and CGMP decisions on scientifically sound premises.

[Slide.]

The second issue under substantial issues is

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should the effect of specific requirements on the cost of manufacturing animal drugs be considered, in other words, should there be a cost/benefit decision made in terms of the quality standards that are applied to animal drugs.

[Slide.]

The third issue is should risk assessment principles be involved. Several members asserted that risk assessment should be applied to drug manufacturing decisions, taking into consideration real hazards and the economics of animal drug use.

All three of these issues are essentially incorporated into one of the questions that we are posing to the committee and I will review that later.

[Slide.]

The second category of substantive issues raised in May has to do with specific factors the agency could consider in deciding whether or not to change its criteria. These includes, number one, can any of the current requirements be reduced or eliminated without reducing the quality, a difficult question to answer, is the agency currently requiring a higher level of statistical assurance than is actually needed for acceptable quality.

Jess Stribling and others raised these issues during the May meeting, and several speakers who advocated

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change in CVM standards emphasized that changes could be made without decreasing drug quality. They argued against what they called the theoretical levels of statistical assurance that may not enhance drug quality.

This issue also is relevant to one of the questions for VMAC, but we have changed the focus more to a prospective one, and we will discuss those a little later.

[Slide.]

Next, the second question under specific factors which could be considered, has the application of current requirements resulted in decreased availability of needed approved animal drugs, would the reduction or elimination of any specific requirements result in increased availability of animal drugs. On the other hand, has the application of current standards improved drug product quality.

These issues were raised by Dr. Gloyd and committee members and others, and you may recall that Dr. Gloyd presented lists of drugs which he contended were removed from the market due to the application of increased and presumably unnecessary Current Good Manufacturing requirements.

On the other hand, little evidence was provided that a change in the manufacturing requirements would significantly increase the number of approved drugs, and

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several practitioners noted an increase in drug quality in recent years.

CVM described its medically necessary veterinary products policy, which is designed to address impending or actual shortages.

We asked our Division of Compliance to research the reasons for the disappearance from the market of the drugs that were mentioned at the last meeting by Dr. Gloyd. Although several appeared to have been withdrawn from the market because of Good Manufacturing Practice difficulties, others were removed for purely business reasons, and in most cases we believe that acceptable substitutes were available.

We believe that it is important to provide a level playing field for those firms who are able to comply with Current Good Manufacturing Practices subject to the provisions of the medically necessary veterinary products policy.

Drug availability, the issues too are generally related to one of the questions that we are going to be asking the committee, but again we have changed the emphasis to more of a proactive one.

[Slide.]

There was also some international implications that were raised if we changed the standards. International

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implications were prominent in the May meeting discussions and they yield the following questions: Would the reduction or elimination of any specific manufacturing requirements serve as a barrier for international sales of U.S. firms?

This issue was raised by the Animal Health Institute and others. Several speakers argued that the changes to FDA's quality standards for animal drugs could jeopardize access to foreign markets.

The basis for their statements was the contention that some foreign countries apply the same standard to animal drugs as they apply to human drugs, and that the human drug standards are the same as those in the United States for human drugs.

On the other hand, several speakers suggested that international standards for animal drug manufacturing should differ in some respects from those of human drugs, and several speakers questioned whether the European standard for human drugs are as strict as those in the United States.

As I mentioned earlier, CVM has advocated some differences between animal and human drug manufacturing standards in the international arena. We have not identified this as a specific question for VMAC, but it is an underlying factor the committee might consider in responding to several of the questions, and those will be

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Questions 2 and 4.

[Slide.]

Fourth, under the specific factors the agency can consider, would changes in the quality standards limit extra-label drug use under AMDUCA or cause any new safety concerns, should sponsors be expected to do extra work to maintain the current level of opportunity for extra-label drug use under AMDUCA.

This issue was raised by the committee members and CVM staff, and I support the statement made by Dr. Blackwell at the meeting, and that is that we do not expect sponsors to do extra research to maintain the current level of opportunity for extra-label use under AMDUCA if changes in the manufacturing standards would tend to reduce the circumstances under which extra-label drug uses could be made.

We recognize that extra-label use will be attempted and found not to work in some situations and that this may be a barrier to extra-label use in some circumstances.

In keeping with my earlier statement, however, we do not consider the matter closed and we will consider your comments.

[Slide.]

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Finally, should the agency permit fewer unapproved drugs to be on the market if it reduces or eliminates some of the specific manufacturing standards.

This point was raised by CVM staff, recognizing that we allow through enforcement discretion some unapproved products to be on the market on the condition that the manufacturers comply with Current Good Manufacturing Practices, however, we believe after further consideration, that it is not a concern because any changes that would be acceptable in the preapproval context would also be acceptable when applied in the enforcement discretion situation.

[Slide.]

A third group of issues had to do with changes that might be considered in specific areas for specific situations. This would include, number one, should the agency make exception for low-volume products, i.e., those that are used for minor uses in minor species and if so, where should the agency draw the line.

This issue was raised by Dr. Lance and several other members of the committee, and we have made this an issue, Issue 1 of the questions for the committee, so we will address this question specifically.

[Slide.]

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Another area of change is suggested in the following question. Should the agency reduce the requirements for in-process controls and finished product testing where validation is acceptable? What percentage assurance is required?

This issue was raised by Jess Stribling and other committee members and can be elaborated as follows. When FDA implemented its process validation requirements, it stated that when a sponsor implemented process validation, the requirement for in-process controls and finished product testing might be reduced, however, the Center has not reduced those requirements even when a manufacturer has validated its process.

We have not included this as part of VMAC questions in part because Jess Stribling has indicated that this is of lower priority for the Animal Drug Alliance with respect to this meeting.

He also asks that the Center for Drug Evaluation and Research, CDER, consider whether it would reduce some of the requirements for in-process controls and finished product tests on the belief that if CDER changes its standards, CVM would also be able to do so, and we have asked CDER to keep us informed of its response to this request.

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[Slide.]

Another specific change suggested is as follows.
Can sterile process validation and specific sterility requirements be lessened without increased risk of higher levels of endotoxin and other biocontaminants?

This issue was raised by Jess Stribling and other committee members, and we have made this into a question for the committee.

[Slide.]

Another specific question that was raised was how can the agency encourage firms to upgrade their facilities while assessing the continued quality of their products.

You will recall a case study presented by Dr. Lloyd involving an approved prednisolone tablet. His firm decided to move the manufacturing of the drug into a new upgraded facility, however, according to Dr. Lloyd, it took 15 months to obtain FDA approval for the supplement application to manufacture in the new facility, and in the meantime, his firm was unable to sell over \$100,000 worth of tablets manufactured in the old facility, had over 1,600 assays conducted to validate the new facility, and has been unable to obtain both prednisolone because the manufacturer's drug master file is not current.

I have asked my staff especially to investigate

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and to evaluate whether there is a perceived or actual impediment to these types of supplemental applications and recommend the appropriate action.

The investigation has not been completed, however, I want to make it clear that I am concerned if there is a potential disincentive for manufacturers to upgrade their facility.

Dr. Lloyd indicated in his remarks that CVM's current procedures make the supplemental application process for site transfers so onerous that many manufacturers decide not to make improvements in their facilities rather than raise the issue with CVM.

I certainly do not want CVM to be seen as an impediment to desired upgrades to manufacturing facilities. This doesn't serve the industry well, it doesn't serve the agency very well, and it doesn't serve the public very well.

I also mentioned that included in the so-called FDA reform legislation that Congress passed just Sunday night, late Sunday night, was a provision intended to minimize delays in drug manufacturing that might be caused by FDA action on certain kinds of manufacturing changes, and we will be studying the legislation to determine its possible impact on this issue.

[Slide.]

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I want to move on to some of the procedural issues. Those are the substantive issues, and those are the largest category of issues. Moving on now to procedural issues, and that was should FDA change the procedures it follows in establishing, communicating, and apply quality standards.

The issues raised in this area included one administrative process, and this is it. Should FDA establish an administrative process for examining new requirements before they are imposed?

This issue was raised by Jess Stribling and we have included this as a question for VMAC.

[Slide.]

Another procedural issue had to do with internal communications. Is improvement in communication within FDA needed to improve consistency between headquarters and the field, and within headquarters, for example, earlier involvement of CVM in the development of agencywide policy?

These issues were raised by AHI and others. With regard to consistency between headquarters and the field, some expressed concern about what they perceived as unequal CGMP and interpretations in enforcement practices from one FDA district to another, and the lack of coordination between investigators.

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On the other hand, FDA personnel pointed out that the adoption of preapproval compliance program has improved interaction between CVM and the field, that there have been specific efforts to improve internal communications, that there is in fact more consistency than is acknowledged and that the problem sometimes is being simply that the firm disagrees with FDA's action.

Nevertheless, I recognize that internal communication is an ongoing problem, and I intend to take steps in the future that will be intended to bring about improvement in this regard.

As for communication within FDA headquarters, much of the discussion in May concerned the 1991 proposed change to the CGMP regulations and particularly the proposal to require terminal sterilization, a proposal which CVM opposed.

I am told that there are no present plans for adopting a final rule, so this particular issue may well be moot. However, as I said in May, and have been saying it at FDA, I have found that the administration may be very responsive to the needs of individual centers, and if there is a proposed regulation that impacts CVM, we would have full opportunity to comment.

We are full members at the table, and so policy

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changes that occur at the agency level do always have the participation of CVM, and we may not always get the answer that we want, but I think we are treated in a very equitable manner compared to the other centers.

[Slide.]

Still another issue had to do with communication between the agency and the industry, and the question is, is improvement in communication between FDA headquarters and the field and the drug industry needed to improve consistency? Is there a greater need for mediation and arbitration?

These issues were raised by several speakers and there have been, and continue to be, complaints that the industry needs are not being heard or are not being considered early enough, and that the industry is surprised too often, particularly in post-approval inspections.

I trust that all will agree that CVM and the agency have been attempting to respond to these concerns through guidance documents, workshops, formal meetings, and other meetings. There is, as you know, a concerted effort to change the culture in FDA from a "gotcha" approach to one of education and assistance in meeting the requirements.

The implication of Good Guidance Practices, which will be discussed this afternoon, will also help, and that

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is a new policy by the agency, that any new guidance has to go through a formal process before it can be released or implemented.

We are all well aware that this part of our regulatory world is not perfect and we will continue to work on it, but I remind our partners in industry that the communications is not a one-way street. My staff tells me that we still find communication problems that could have been resolved had the firm communicated with us, and the solution to this may be simple, just come and talk with us, we are always available.

Mediation and arbitration are formal procedures. We see no need to seek authority to invoke those procedures at this time, but would welcome comment on that point.

Improvement in communication between FDA and the industry is also part of Question No. 5, and will be discussed in just a few minutes.

[Slide.]

Study issues. The third general area of discussion in May had to do with further studies - is there a need for further study by groups other than VMAC regarding quality standards and FDA procedures.

This category included these issues. A. Should manufacturing requirements be addressed on a

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requirement-by-requirement basis involving representatives of the regulatory industry and FDA? That was one question.

B. Should FDA conduct a review of every in-process control and finished product test with the assistance of consultants and in dialogue with the regulated industry?

These two questions were raised by Jess Stribling and we have not included them in the questions because they are considered to be of lower priority to the Animal Drug Alliance and they have a retrospective focus. So, we are not including these issues for discussion at this meeting although they can be brought up tomorrow.

[Slide.]

The final issue from May had to do with the formation of a working group. Should a working group be formed comprised of representatives from the animal health industry and its regulators to clarify the interpretation of CGMPs in the form of guidelines, policy documents, and inspectional findings which interpret CGMP regulations?

This issue was raised by AHI and we have made this into a question for VMAC, so you will see this.

Now, let's get right to the questions for this meeting.

[Slide.]

Question 1. Should CVM change its administrative

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review process for adopting new drug quality standards to provide for review by the Center Director? That is Question 1.

[Slide.]

Question 2 has two parts. When CVM decides whether to adopt a particular drug quality standard, should it weigh the benefits against the costs of adopting, or of not adopting, the standard? If so, how should such benefits and costs be assessed? How do you measure those?

What factors should be considered? For example, should CVM consider the availability of approved animal drugs which improve human and animal health safety? If so, what guidelines should CVM follow in doing so?

I would like to make two comments on Question 2. First, we asked the animal drug industry in the May meeting for information on cost consequences of manufacturing requirements that CVM has applied in the past, and we have not yet received good cost estimate data on that, and this is one reason we decided to place more emphasis on prospective changes rather than going backward and looking at some of the things we have done in the past.

Second, I want to reiterate the importance CVM places on the availability of approved animal drugs to meet the needs of veterinary medicine. At the same time, we are

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very conscious of the need to meet statutory standards for drug quality and we really look forward to your comments on balancing these concerns. This is the difficult part.

[Slide.]

The third question that you will be asked to answer or to address is: Should CVM tailor its interpretation and application of quality standards in the regulation of drugs for minor uses and minor species? If so, what are the factors that most directly impact on the decision as to how to tailor the interpretation or application?

[Slide.]

Question 4. Can sterility validation be reduced without increasing the risk of microbial contamination?

[Slide.]

The final question is: Should a process be developed that would involve representatives from the animal health industry and its regulators to review and identify inconsistencies in the application and interpretation of quality standards for animal drug manufacturing and to prioritize the identified issues? Or are the current mechanisms that we have in place sufficient to meet the need for communications between FDA and the industry?

In conclusion, I trust that this review has been

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somewhat helpful, if not lengthy, to you as you prepare to provide your advice and comments during the rest of this meeting. You will have ample opportunity to provide your advice and comments this afternoon and tomorrow, however, I am sure that you may have questions on some of the things that I have said this morning, so at this time I encourage any questions and again thank you for your participation in this important undertaking.

I will turn it back over to the chairman.

DR. LEIN: Any questions from at least the committee at this time for Dr. Sundlof?

MR. GUIDOS: Keep in mind that Dr. Sundlof will not be here tomorrow, so if you have any questions, it may be best to ask them now.

DR. LEIN: Dr. Wolf.

DR. WOLF: This may sound like sort of an off-the-wall question, but in the animal food industry, certain standards are maintained because unfortunately, there are people who eat animal foods.

Is there any concern that if we change drug standards for animal drugs, that some of the animal drugs might get diverted for human use?

DR. SUNDLOF: That is a concern, and some animal drugs are used for human use, we are aware of that. I think

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the question that this committee needs to address is should we be setting our standards on how drugs may potentially be used as opposed to how they are intended to be used, and again it is not a simple question to answer, but we welcome your feedback on that.

We deal with this issue in other areas, for instance, should we require that companies develop analytical methods for drug residues in species for which there is no label indication, do we penalize companies for how drugs might be abused. In some cases we do, and in some cases we don't, and you have to walk that fine line. You have to I think base it on what the actual public health implications are for those decisions.

DR. LEIN: Other members? Yes.

MS. HUDSON-DURAN: Well, of course, my favorite problem I guess I addressed in May is again it seems over and over again we really don't know how to identify whether endotoxins are a problem or not, but at least with the human USP standards, we were read earlier that different drugs have the EU values.

For example, diazepam, which had a high EU value, causes a tremendous amount of problems when given I.V. It causes phlebitis, it causes infection at injection sites, and as a pharmacist or as a veterinarian, at least we know

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that information and I can know. I need to filter that product.

So, again, labeling to me is something that we are missing. I can accept standards, but we need to be able to make a judgment call as professionals to say okay, this is what we have as a product, for the amount of money that is needed to produce this product economically and to sell it economically to veterinarians, this is the best we can do, but at least let us know what we have in that product.

If it is made from sterile water, and whether it is 10^{-3} to start with, or 10^{-6} to start with, I think that is a minute point, but the finished product, whatever it be, I just want to know what that is, and then we can make the judgment call.

DR. LEIN: Do we know always whether that is really endotoxin, a pyrogen, or product itself, because product itself can also be caustic.

DR. POUST: Diazepam, I think has a pH of about 10 or 11, which will cause a lot of problems. It is also not completely aqueous. It has got what propylene glycol -- so I don't think that is endotoxin. I think that is some other bad actors. But that is the best we could do with a very insoluble compound.

I don't know how much of this is done in the human

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industry. If you look in the PDR, and look up any injectable dosage form, you will find the ingredients that are in there. Everything that is in there is required to be put on the label and made part of the labeling. That is how I know it is pH 11 and it has got propylene glycol in it. I don't have any inside information here except I own a PDR.

I don't know, with animal health products, whether that is a requirement or not.

DR. LEIN: Yes.

DR. POUST: It is. So, at least in sterile products, every ingredient is listed on the label. Is that right? So you do know what it is.

DR. LEIN: Other questions? I have one just on the international part again. That still comes back. If we are in a situation of looking at standardization globally, what is that level today? Is it something less than what we are talking about with CVM, FDA, or is it something more, or is that unknown?

DR. SUNDLOF: Right now, because there is not harmonization, different countries have different standards, and we are attempting to harmonize those standards right now, so that GMP requirements for approval of a drug in Europe would be the same. They would just submit one package of information.

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Whether those are more restrictive or less restrictive than some of the issues that we are talking about today, I can't answer. Sharon Thompson is our expert and also Bill Marnane has been dealing with the international aspects of that.

But the good thing is that we are still in the process of trying to come to grips with what those standards are, and that is why this committee is very timely because if we can get the opinion of this committee, it is in time to -- and we decide to make those changes -- it is in time to have those changes enshrined in some international policy.

You know, we are in the process of participating and trying to develop consensus, so good thinking that comes out of this committee can be used, may have tremendous impact on setting international standards.

DR. LEIN: With regard to international standards, there is one which is conspicuous by its absence, which we have not definitely been asked to consider, and that is the financial impact, the economic implications of pharmaceutical approvals, and I think RBST is a classic example of that in the fact that it does not enjoy international harmonization with regard to approvals.

DR. SUNDLOF: Yes. Well, that is a particular

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example of a drug that was the subject of issues that went far beyond the manufacturing standards. I think most people would agree that the manufacturing standards were not an issue that has impacted its registration on the worldwide market.

DR. LEIN: And continue to be.

DR. SUNDLOF: And continue, right. But the purpose of the international harmonization effort is to set the ground rules for the requirements for drugs and then leave it up to the individual authorities as to whether or not they plan on approving that in their country.

As you can imagine, it gets into issues that go far beyond the science. It goes into other factors, political factors, socioeconomic issues, and a number of other areas that I don't think this committee wants to be dealing with at this time. But if you do, let me know, I will give you a job.

DR. LEIN: It's good to put that to the end because we all have a flight to make, you know.

DR. KEMP: I would kind of like to get back to what Sue Duran was asking about. She has very well demonstrated how complex it is, these pharmaceutical dosage forms and on the human side, I think we have discussed this in the past we have an Orange Book we go to, to determine

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the bioequivalence of the products. On the veterinary side, back in my hospital, I have no such data to look on what is bioequivalent. I would like to know why we don't have that.

I also kind of pose the possibility that if we had that information, maybe the market itself would sort out the manufacturing processes that may be there.

DR. SUNDLOF: That question could come up in some of our communications efforts that is addressed in the question about the agency communicating with the industry and that might be a suggestion that you would like to make, that we put in place something similar to what occurs for human medicine.

I think Sue Duran's question was more if we have standards for, for instance, endotoxin for individual products, if we are going to make changes and allow various standards for various products, then, all that information should be contained in the label, so that the professional can use his or her judgment in determining whether or not they want to accept any additional risk that might be posed by that.

Did I capture your question correctly?

MS. HUDSON-DURAN: Right, and to answer your question, yes, I know that valium has a pH of about 10, it probably eats some of the glass off, maybe some of those

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chemicals are glass, I don't know, but again, at least if I look at that and I know that that number is high -- and I don't know where these numbers are coming from, because I am sitting here thinking should I be worried if I am at 200, should it be a problem, you know, if we have got an animal that weighs 50 grams, is that going to be a problem.

I don't know the answer to that, and those are guidelines we haven't even addressed, and there is not a lot of information out there to say when endotoxins become a problem with pharmaceuticals. We can't even begin to look clinically until at least we have some kind of guidelines to know what we have in those products.

So, at least we can say, okay, we know that product is hard to manufacture, it has got other ingredients in it, so maybe we need to filter that if we want to use that drug. My colleague over here elected, since he had such problems with it, he was never going to have any free anesthetics again, so, you know, that is a bad experience, and those are problems that you have to deal with all the time.

But again, at least we know that that is a difficult drug to manufacture.

DR. STERNER: Dr. Sundlof, I think what we are all talking about here, as practitioners or whatever discipline

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we bring to the table, is making an informed therapeutic decision, and the same level of risk assessment that Dr. Wolf might use in her therapeutic decision process for a companion animal might be vastly different than I would employ as a food animal practitioner under field conditions.

I alluded to this earlier. I hope I made clear the concerns that I have with regard to drug availability under the realities of practice that each of us have to function under and the ramifications that Current Good Manufacturing Practice policies and particularly enforcement may have on an industry, that might be of great concern to Dr. Wolf's practice or the equine practitioner, that may be of little or no concern to me as a food animal practitioner.

DR. LEIN: Other questions? We are nearing the lunch hour.

MR. GARZA: I just want to make one small comment. A question has come up on the endotoxin issue and whether you would want to filter that to remove some of this.

What you have at your disposal at your end may remove some microbiological aspects of it, endotoxin will not be filtered out. Just to clarify the issue. If it was, sterile filtered drugs would be endotoxin-free. Endotoxin is achieved by a different method, its removal.

It is either removed by washing or inactivated by

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heat, but filtration at least what may be available to you at your disposal will not eliminate that.

DR. LEIN: Other questions? Hearing none, we can move on to lunch. Thank you very much, Dr. Sundlof.

[Whereupon, at 12:00 noon, the proceedings were recessed, to be resumed at 1:00 p.m.]

AFTERNOON PROCEEDINGS

[1:00 p.m.]

DR. LEIN: Dr. Sundlof has some presentations of certificates for outgoing members.

Presentation of Certificates for Outgoing Members

DR. SUNDLOF: This is the time when I have the pleasure of recognizing members of the committee for outstanding work that they have done on the committee. Also, it is somewhat of a sad time because our members will be no longer members anymore, but they will be always welcome to come back and spend time with us at these meetings.

I would like to recognize the following people for having served so well on this committee for three years. It doesn't seem that long, it seems like I was just welcoming them onto the committee.

I would like to recognize those three individuals at this time. There is a fourth one, Dr. Jaax, who is not here today, and, Dr. Lein, I would like to prevail on you to award Dr. Nancy Jaax her certificate tomorrow.

DR. LEIN: I would be happy to do that.

DR. SUNDLOF: Thank you.

Let me first call up Gary Koritz. In recognition of outstanding service, thank you very much. It is signed

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by the Commissioner Michael Friedman and myself. Again, thanks for all your help.

DR. KORITZ: Thank you.

[Applause.]

DR. SUNDLOF: The next award of recognition goes to Sue Duran. Sue. Thank you for your contribution as our consumer representative and also because you bring your expertise in pharmacy and your input in medicine.

MS. HUDSON-DURAN: Thank you.

[Applause.]

DR. SUNDLOF: Finally, Dr. Alice Wolf. Again, thank you for all your assistance.

DR. WOLF: Thank you. It has been an education.

[Applause.]

DR. SUNDLOF: Mr. Chairman, I turn the floor back over to you.

DR. LEIN: Thank you very much and thanks to all the members that are leaving us, and those that are staying also.

Next, will be a presentation on Question 1. Keep in mind Question 1: Should CVM change its administrative review process for adopting new drug quality standards to provide for review by the Center Director? That is the question.

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The first one to do a presentation is Dr. Dave Newkirk.

Discussion of Question 1

DR. NEWKIRK: Thank you. I only have a few comments really to make on this question.

[Slide.]

The first, as our background paper on this question illustrates, the fact that previously, CVM attempted to alert drug sponsors of evolving new manufacturing standards through policy letters or response letters to drug applications.

At that time, we believed that this approach would be helpful. We recognize that this approach could be seen to be a disadvantage to some and thus we no longer notify industry in this manner. CVM now adopts standards through the process outlined in the Good Guidance Practices document, published in the Federal Register in February of this year.

Under the GGP concept, nine government groups, such as trade organizations, industry, consumer groups, et cetera, will be able to provide us input in the development of new guidance. Through this process, the public including the regulated industry has more of an opportunity than ever to participate in the development of new drug product

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quality standards before they become finalized.

It should also be noted that the GGP process provides for appropriate agency review and sign-off before the new guidance is published.

Level 1 documents, for example, which include complex and controversial issues, as well as new drug quality standards, require sign-off by at least the Office Director level, if not higher.

Thus, while automatic review by the Center Director is not required, it can be employed at his or her discretion.

In conclusion, we believe there have been significant changes to CVM's administrative process since concerns were first raised.

[Slide.]

First, CVM no longer makes policy through policy letters. Second, our latest reorganization consolidated all manufacturing issues into one division, the Division of Manufacturing Technologies.

Finally the Good Guidance Practice document provides CVM a more flexible way of developing new quality standards while communicating the agency's current thinking.

While CVM has come a long way in just the past year, we certainly welcome any suggestions for further

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development.

Thank you.

DR. LEIN: Thank you.

Any questions at this time for CVM?

DR. CLELAND: Since this policy, the GGPs came out in February of '97, has it been implemented and what is the response from industry?

DR. NEWKIRK: As of now, we have had interests come up that have actually utilized this process. The fact it is there gives us a tool which before usually required formal rulemaking, a very lengthy process.

DR. SUNDLOF: In the context of manufacturing chemistry and good manufacturing processes, that is true, we have used the Good Guidance Practices to publish other documents, and so we are already using that.

DR. LEIN: Other questions?

DR. POUST: The GGP is being used in the human pharmaceutical industry in the development of a number of guidance documents. I happened to attend a small symposium at the AAPS meeting last week where there was some discussion of how effective this was or is, and I think the general response of industry is that they like the process, but I guess they do have a few concerns and it is easy, could be easy.

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The generic people, for example, kind of berated Roger Williams for leaving them out of the process on one of these guidance documents, but it sounds like it is a good system if everybody puts forth their best effort to maximize communication, I think is what I was hearing from the industry. They would like a little more of outcomes-based guidance documents, and they are still seeing some fairly rigid interpretation of what comes out of these guidance documents.

The big project right now is the SUPAC concept. SUPAC stands for Scale-Up and Post-Approval Changes, and it is going to be a series of guidance documents related to specific dosage forms. There is one already out, SUPAC-IR. There is a SUPAC-SS, which I think is about to come out or has come out, which stands for Semi-Solid dosage forms.

There is a SUPAC-SAS, that I think Dr. Leinbach is on that group, as I recall from her mentioning last time. There is dialogue, I know, in the development of these things, and in principle, it sounds like a very good idea and as long as people put forth their best efforts, both on the FDA side and the industry side, to get the issues out and get them discussed and get them agreed on, I think it will work is kind of what I have heard.

DR. LEIN: Other questions?

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DR. KOONG: In the document provided to us, there was a response from AVMA, and I would like to hear clarification from AVMA. The answer basically on this question provided by AVMA was that they think it is appropriate for the Center Director to review the new drug quality requirements before they are finalized.

The next sentence specifically pointed to the present Center Director has the depth and scope of experience in understanding -- I think that is a compliment to Steve. But would your position change if we have a different director or a new director?

DR. GLOYD: What is the next question?

DR. KOONG: My point is that when we formulate policy or recommendation, I don't think that should be individually specific. We are setting up a system here.

DR. LEIN: Other questions from industry?

MR. STRIBLING: May I make three comments on behalf of the Animal Drug Alliance, all of them brief?

DR. LEIN: Please do.

MR. STRIBLING: Number one, in response to the past question, I had asked Dick Geyer or at least told Dick Geyer that while we had said Center Director, it would probably make more sense to have some superior level supervisor, and not the Center Director, because the top

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person any organization does not have time to deal with everything, but it seemed to us that it was important to have some review at a higher level than the level adopting the criterion.

A second comment is that if the Good Guidance Documents mean what we think and hope they mean, they are very, very good and this is a very good procedure. As I understand it, this means that if an investigator writes an observation on a 483 that appears very strange and arcane to the company, the company can call the district director and say I have not seen any Good Guidance Document on this, and the district director will say wipe it out, and ditto if something comes up in an incomplete letter that has never been out before, the company can call the Center Director and say I have never seen this before, and the Center Director will say, gee, this is something new, we do plan to come out with it, but we haven't yet, so wipe it out, it's not necessary to approval.

That is very, very good if that is what it means, because it responds to concerns that the prior management, Drs. Guest and Teski, and those who are still there, Dr. Livingston and Mr. Marnane will remember was the first concern of the Animal Drug Alliance, which was new requirements being imposed for the first time and in

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complete letters, and what the Good Guidance Document policy does is to enable everybody to be notified at the same time and to be notified prospectively, and that is very good.

The third comment is that we affirm, assuming we know what this means, the Good Guidance Document is very good, it doesn't answer the whole question that we asked at the May meeting or that we have been asking since 1991, which was a question, not only of having industry participation and being notified prospectively before requirements are made, but the way the requirements are proposed, originate, and rise up out of the Center, and this document, the GGD simply doesn't address that.

What we had asked was that there be some -- and we believe is very necessary -- that there be some level above whatever division is making a suggested change and new requirement, that would look at it, and to go back to Dr. Poust's statement this morning as he talked to industry and said, you know, you need documentation, well, I am a lawyer and I say, yeah, I would like to hear some data, so that when a new requirement comes up, there is someone somewhere who says, gee, what is the problem that leads you to think that we need this additional requirement, what problem are we going to solve.

Number two, how often has that problem arisen, has

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it arisen once every 30 years, and do you suppose if it is just arisen now and not arisen since 30 years ago, we won't see it again the year 2020 or 2025, and in that case, do we really need it, some kind of analysis, and again, I don't think that this policy addresses that.

Pat Leinbach and I were talking about this this morning, and she assured me that there is sign-off review, and I know that when I was in the General Counsel's Office, I used to sign off and review, too, but sign-off is one thing, careful, thoughtful review, prodding questions, really examining requirements to see if they are necessary is also we think an important part of it.

DR. LEIN: I think it is back to risk assessment that we were talking about early on.

MR. STRIBLING: Precisely, yes, sir.

DR. GLOYD: Just to elaborate on my facetious answer to Dr. Koong, I think it is important to whatever it is, the identified authority review those policies or regulations before they are, in fact, put out in the field, because, you know, the fact that the Director may be blind-sided otherwise if they don't have that opportunity to review. It makes perfect sense to me.

MR. STRIBLING: May I make one other personal comment?

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DR. LEIN: Please.

MR. STRIBLING: I am speaking against interest, because a lawyer makes money when new things come out under PPG and he is engaged to help a client or an association respond, but if it turns out that the agency internally looks at some things and kills them before they get out, it is cutting out some matters that lawyers would be happy, hard to work on.

DR. LEIN: Did you want that in the record or not?

MR. STRIBLING: Thank you. I don't care.

DR. LEIN: Any other comments?

MR. GARZA: Just a clarification with respect to inspectional findings. The findings that we list following inspection are deficiencies that the investigator in his or her opinion sees, and not a statement that something should be done, as Mr. Stribling has alluded to.

If the review of that report finds that that deficiency, as identified by the investigator, has limited or no impact on it, the firm is not obligated to make -- the only obligation the firm has is to justify if they do agree that it is a deficiency, what plans, if any, they have for correcting it, and if they disagree with that, their justification for disagreeing with that because either the management has more information that was either not made

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available or was not understood by the investigator, that would cause that deficiency to be invalid, and it is not as simple as Jess has alluded.

So, it is not an issue of I list something on the 483, and you must act. It is various levels of review that come into play.

MR. STRIBLING: Manuel is absolutely right. I didn't mean to simplify that much, but it does mean that an adequate response for a company, when it responds to each item on the 483, would be that is something that has never appeared in a Good Guidance Document, it is new, and on that basis, as I understand this policy, the head of Compliance would say yes, it is not new, we won't enforce it yet on this company.

MR. GARZA: And that is correct, and a 483 is not a Good Guidance Document. It is not establishing policy, it is just listing that at the time of discussion of the deficiencies, management is requested to comment on that, and as I happen to be at an occasion, I have removed deficiencies because I was shown to be in error in listing that.

If that is the case, then, management is obligated to respond to that, and the investigator is obligated to carry that response back to our office to show that in our

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report, we list what we believe was a deficiency, and in the response that management offered, at times management will not respond and say we will respond in writing, but they do have that option, and that can be addressed at the site before the inspection, individual or team, leaves that site.

DR. LEIN: Any other questions? Any from the audience and the committee?

Shall we at least go forward with Question 1, and see what the committee's concerns may be. I would like to do this, if I could, by each one of the members, if they have got a statement they would like to say about Question 1. Again, remember what we are being asked. Should CVM change its administrative review process for adopting new drug quality standards to provide for review by the Center Director?

DR. KORITZ: While I find that the Good Guidance Practice document is indeed a major step forward, it addresses a major problem which is that of a mechanism to improve communications, and I believe that as far as sign-off and review, that it should not be mandatory for the Center Director to do so, but it is adequate at the office level.

DR. LEIN: Do we want to go down the line here? Maybe we could start at the end and come up. Dr. Poust.

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DR. POUST: Could I ask Dr. Leinbach -- because she is involved in one of these, the development of one of these guidances -- to describe for us what FDA-industry interactions there have been in your particular experience in terms of I guess numbers of industry-FDA meetings and the kinds of people from industry that sit in on this. I assume it is a task force?

DR. LEINBACH: Yes, it's an FDA task force. It is across the agency. There is about, oh, maybe a dozen FDA staff members. In August we had a -- well, when we first met, we decided it was such a tremendous undertaking that we wanted to be sure that we addressed the concerns of industry, because some of these issues are going to be fairly difficult to deal with even though we have limited it to sterile aqueous solutions.

So, we went to PDA who set up an open forum for industry to come and address their issues to us, their concerns, and there were five or six categories. We had kind of a round-robin organization, so that each person could attend at least five out of six sessions, and they could -- the representatives from the companies could voice what the concerns are.

So, now what we have done is we have taken all those into consideration and we have six groups that are

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working individually on the six different categories and hopefully, these will come together very soon in a document. We hope to have the first draft in about six months for internal review, and then it will go out for outside review.

DR. POUST: So, it sounds like there is quite a bit of industry involvement here, and these open fora might be the place to address Mr. Stribling's concern about do we actually need this or not, and I would assume that in these forums, if there was widespread feeling on the part of the industry that perhaps something is not needed, it would be stated there, if not done earlier with some other mechanisms.

I support the concept with the proviso I guess that there be plenty of opportunity for industry involvement and dialogue in developing these guidance documents.

DR. LEIN: Dr. Wolf.

DR. WOLF: I guess I am pretty flexible on this issue. I can see both sides of this. It seems to me that while I am sure the Center Director has many more things to do than he or maybe she at some point can reasonably accomplish, that it is probably a good idea for the Director to know all of the different things that are coming through the Center, and it doesn't say that the Center Director is required to approve the changes, just that they are to

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review the changes and that to me seems to be a good idea.

DR. LEIN: Dr. Koong.

DR. KOONG: I guess I am in agreement with Dr. Wolf on this question, but I would just like to add basically when the CVM adopt new drug quality standards, the question to me is where the buck stops, and if the buck stops at the Director's level, then, he should have the right to review it only if he wants to, and the staff, you hire good people that make you look good, and they should be allowed to be making decisions in a delegated way, but that is only delegation. If authority is delegated, you can always take it back.

So, I like the flexibility in your organization, but keep in mind the buck stops on your desk.

DR. LEIN: That means if there is a problem, he is going to answer, right? Dr. Fletcher.

DR. FLETCHER: It seems to me that since we met last spring, the GGPs were coming out about that time, I guess, or maybe a little bit before, so it seems to me like some of the issues that we were addressing may really have been dealt with to some extent.

I think it is a little bit unclear to me, although it seems to me from what I am hearing, that there is careful and thoughtful review or at least a mechanism within the

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current GGP process to have that careful and thoughtful review. I think that is where the issue comes.

I think it is important enough to have that discussion at the Director's office. That might not be right and I don't know how we might want to speak to it. Some of these issues might not be deemed within CVM of being important enough to have that discussion at the Director's level, others might be, and I would hope that within the process of coming up with the GGPs, there would be some mechanism to have that discussion in some anticipation of what the issues would be and perhaps even some process that says we are contemplating doing this, how do we get the feedback maybe even before we did it. I don't know if that is appropriate.

What I am reading and what I am hearing about that, we are making an effort to standardize a process by which we put information out in terms of what the policy is going to be. We are not doing it piecemeal for various kinds of policy "letters," and everybody then across the whole industry catches this at the same time and has an opportunity to respond to it.

DR. LEIN: Thank you. Dr. Cleland.

DR. CLELAND: I agree with Dr. Fletcher. I think from what I read on the GGPs, it seemed like they were

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really a good step forward, and it also seemed like since it is now a "validated" -- I use that in quotes -- now a "validated" process, that perhaps some of the question may be somewhat moot because obviously, if the FDA is going to go to the point of having a document for some guideline, somebody is going to look at it. It is not just going to be a piecemeal type of thing. So, it may be somewhat of an issue that may no longer be an issue due to the development of the GGPs.

As far as the Center Director or some level reviewing the things, I would support that, but again I don't know that we necessarily need to say that the Center Director needs to review every single one, but that there is some review, so we make sure that everybody is on a level playing field.

DR. LEIN: Thank you. Dr. Floyd.

DR. FRANCIS-FLOYD: I certainly support the GGP concept and the views expressed by members of the panel. I think that this step is very positive because, number one, I don't think the Center Director should have to review everything. If he has good staff, they should be able to do some of that, but it should facilitate communication at the highest levels if there is the requirement or the understanding that there is senior responsibility. So, I

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think Dr. Koong's comments were very appropriate.

DR. LEIN: Dr. Sterner.

DR. STERNER: If I read the CVM commentary behind Question 1, it provides for a Level 1 and a Level 2 review, is that correct? Okay. In that case, somebody within the agency will not a priori come up with rules and regulations, but it is signed off on by a responsible party and ultimately the Director has the opportunity for review should that happen.

If my understanding is correct -- and I guess I am asking the question rhetorically -- then, I certainly would be very much in favor of it.

DR. LEIN: Dr. Barker.

DR. BARKER: The mechanisms that CVM already uses to involve the participation of private industry and private citizens is I think fairly adequate. The GGPs add another level of input from all persons involved in the industry and regulatory concerns and in private industry.

Anytime we can increase dialogue and so that everything is more fully understood, it is an advance. As Mr. Garza pointed out, 483s do not set new policy. New policy must come through a open discussion with the advances in technology, the need, which in part I guess what we are here for, to employ some of these new technologies.

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The regulatory component of CVM represents the people of the United States. Private industry represents private industry. We are here to try to discuss what possible conflicts may arise between those two in providing what the public would expect from both of these groups.

For the particular question, review by the Center Director seems a part to be handled by the GGP and that any Director of a Center, such as this, if it were major policy changes, would probably have reviewed this anyway.

The review processes I think are more than adequate already, and whether or not the Center Director needs to be specifically stated as being involved in that process, it probably gets down to a little bit too much detail.

DR. LEIN: Ms. Duran.

MS. HUDSON-DURAN: I certainly believe in quality control, but also, the more guidelines, the more time it takes, more people to review, so I just want to remind everybody that we want a quality product, but also from industry's standpoint, particularly if we want to promote people making products, we can't take excessive numbers of years to approve drugs.

So again, if you could even set some timely frames to review these, and of course, if the Director is very

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busy, he may not be able to do that. Maybe he could get a report monthly of everything that has been approved or decisions made that aren't major changes, but anything that adds to prolonging approval of drugs, even though these guidelines are good -- and, again, I really believe in quality products -- just do not want to make it be another six months or a year to get something approved.

DR. LEIN: Dr. Ravis.

DR. RAVIS: I think that this provides probably for more practical, realistic review process than having the Center Director be involved in such depth, I guess, with each guidance.

One thing, is there any question would ever arise as to what is a Level 1 or a Level 2, that that would become an issue?

DR. LEIN: So that you would separate these out is what you are saying?

DR. RAVIS: Right. Is there ever a gray area which is a Level 1?

DR. LEIN: Steve, could you make a comment to that?

DR. SUNDLOF: Yes. Most of the time there is a gray area, and we generally defer it to our chief counsel at the FDA and our Office of Policy, and they look at the

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document that we are proposing, and they will tell us in their opinion whether that is a Level 1 or a Level 2, and if it is a Level 2, they would say, well, you know, it's kind of a gray area, but I think you ought to err on the conservative side, and then we declare them Level 2's and we ask for comments.

DR. LEIN: Dr. Gerken.

DR. GERKEN: Well, this is the hazard of being on this end of the table when you start on that side, but I am not advocating you start the other way with the next question.

DR. LEIN: That will happen.

DR. GERKEN: I figured it would.

So, when everybody has said it all, what else is there to say? I agree, as long as CVM has enough opportunity to have their input and an equal contribution around the table of the really big FDA, then, as long as you are convinced that is true, then, I think this is fine.

DR. LEIN: Dr. Cooper.

DR. COOPER: Looking at the Good Guidance Document, I think FDA has demonstrated that it does listen to concerns that are being expressed, and in looking at this process, I think they have developed a prospective notification process that is open for comment.

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FDA, like any other organization, is not perfect, and I think in this process, it shows a willingness, if wrong, to correct any wrong that has been made, so I think that is positive.

In looking at the involvement of the Director, I don't think it is necessary. I think at this particular point, with the reorganization of the CVM, the staff that have been employed, we give them assignments to act for efficiency sake. I would have to believe that Dr. Sundlof meets with his staff on a regular basis, and through these meetings, there is an understanding of what the real sensitive issues are for CVM.

I think with these discussions, there will be an awareness and understanding on the part of the Director as to what issues need his personal attention. Otherwise, I think that the prospective review and the fact that it involves input from a number of different interests in the drugs that are being approved, I think can probably handle it without direct involvement of the Center Director, realizing that if there are any appeals or activities that don't go the way they should, that he can in fact be contacted.

One of the questions I would have when we look at the approval of these documents for the Center is the person

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who signs approval, the person who is often contacted for resolution, you know, the disagreements or concerns about development.

DR. LEIN: Dr. Kemp.

DR. KEMP: It appears to me that the GGP is adequate and functional, and I think CVM has made a great effort to communicate with industry, and I see absolutely no reason for the Director, who is more administrative, that it might actually slow down the process in what needs to be done.

DR. LEIN: Steve, you could answer this question or anyone else from your group.

What are the number of policies that would come across than this sort of a description at an annual basis, is it burdensome?

DR. SUNDLOF: Yes, but that's my job. With the GGP concept, if are going to propose a new change, something that it doesn't just clarify something that we have always done, but an actual change to the way that we regulate -- and that would mean any change to the requirements for Good Manufacturing or Chemistry Manufacturing Control changes -- that would be a Level 2 document, that would have to go out for public comment -- I am sorry, Level 1, would have to go out for public comment, and I always see those and sign off

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on those.

Generally, the way things work, if there is policy changes, I don't sit down and meticulously read the entire huge document with all its attending, you know, regulations that it refers to, but I will generally ask the people that put the document together, that constructed the document, to come in and explain it to me, and then I -- and these guys will attest to this -- and I ask them questions until I understand what it is that we are asking and why that is important, and I will continue to ask those questions until I can explain it back to them, and if I can't explain why we are doing something, then, it just doesn't go.

So, I think that GGP process is going to be very instrumental in making sure that -- and I think in many cases, changes, what are considered to be policy changes that are done by incomplete letter or by speech or whatever, many cases were never intended to set new policy, but it just kind of comes out that way through no ill intention of anybody doing it. They said I have a great idea, and then all of a sudden we have some policy.

This is going to force us all to start really looking at those kinds of things that may be the most intelligent thing you could imagine and why didn't we think of this sooner, and somebody has thought of it, and they

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would like to implement it, but you can't do that anymore, you have got to go through this process. That is the way it works.

The agency isn't going to allow us to do it any different way. I will look at all those documents, and I will ask the questions, and we think, you know, we are really hopeful that this will provide a lot more input by the regulated industry.

It should help considerably in addressing the issues of policy by incomplete letter, by speech, and people that don't do that will have to explain why they did what they did.

Again, I think nobody does it on purpose, it is just you get caught up in the moment, and that is the way things work out.

DR. LEIN: So it sounds like exactly that is happening and it is really briefing, which make sense, and that you get your people that have started with this, that are explaining it and why they have done it and gone forward.

It sounds like the committee really backs the GGPs as the real avenue to go forward and that the way it is done today sounds reasonable and hopefully would be of great value to us as we go forward looking at drug availability

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and the work that goes with it.

One thing I wanted to bring out a little bit further was something that Mr. Stribling brought forward or Jess brought forward is really this risk assessment, and if it is changed just for the sake of change, new technology that may cost a lot more, but really is not going to improve anything in the drug, but would make the drug cost more or take longer for approval, that that become part of the decisionmaking basically, as you sit with industry, and we know that there certainly is technology that can get us to a finer point, but if there is not need for that, and it is going to cost more, that we at least take that into deliberation before that becomes a new approved way of doing something.

I think that would help us basically with cost to drugs and moving more rapidly in availability.

Any other statements from anyone as we have reconsidered on the committee?

DR. STERNER: Do you need a motion from the committee?

DR. LEIN: I don't think so. I think all we are looking for is at least a basis of consensus.

MR. GUIDOS: Just to let you know, I think Dick Geyer wanted to clarify this, as well. As we go through the

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five questions, you may get clarification on one of the preceding questions. It may give you some additional information, and so we are allowing some time tomorrow, towards the end, to re-evaluate and reconsider some of the recommendations in case you want to make some clarifications.

DR. LEIN: Seeing that we are ahead of time, we will dive right into the next topic, which is discussion of Question 2, and Question 2 is: When CVM decides whether to adopt a particular drug quality standard, should it weigh the benefits against the costs of adopting, or of not adopting, the standard? If so, how should such benefits and costs be assessed? How do you measure those?

What factors should be considered? For example, should CVM consider the availability of approved animal drugs which improve human and animal health safety? If so, what guidelines should CVM follow in doing so?

To present for CVM, Mr. Charles Eirkson.

Discussion of Question 2

MR. EIRKSON: Good afternoon.

[Slide.]

I guess since the last meeting of the VMAC, the Center has been considering the questions that were

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presented, that is, should we weigh the benefits against the cost of adopting or not adopting new quality standards, if so, how should we weigh those benefits, and also what factors should we consider when we do weigh those benefits.

[Slide.]

The first question, that is, should we weigh the benefits against the cost of adopting or not adopting the standard, in looking back over this issue, I think we found that FDA does, in fact, do some formal cost-benefit analysis for certain actions, and those types of actions are ones which the government, I think in a much broader sense than just FDA, has to find the thing significant enough to warrant us doing cost-benefit analysis on it.

When we do do cost-benefit analysis -- and when I say "we," I mean the Center for Veterinary Medicine -- we often and always rely on the bigger resources that are given to FDA for doing the cost-benefit analysis. We employ the FDA economists, as well as the legal staff, there.

The point I am trying to make here basically is that the Center for Veterinary Medicine, in fact, FDA does not routinely do a formal cost-benefit analysis at this time, predominantly because the resources that are required to do that are fairly intensive.

For that reason, we would say that the prospects

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of us doing routine cost-benefit or informal cost-benefit analysis on each new drug standard is somewhat limited.

[Slide.]

Again, I would get back to the fact that the resources that are required there are fairly high, and with CVM's competing priorities, their relatively limited resources, and their increasing workload, that that is one side of the idea for really not being able to do a routine type of formal cost-benefit analysis for each of the new drug quality standards.

Of course, those things I think can always be overcome if there is enough initiative to do that. There is another side to the issue, though, as well, that may cause some additional problems. The other side to that is that we have -- "we" being CVM -- have limited access to cost information concerning the manufacturing facilities.

That is because of competitive, as well as the complex, nature of the manufacturing processes. From a competitive perspective, the industry pretty much likes to keep their processes and technologies secret.

From the complex nature of things, each manufacturing process is often somewhat unique, and to gather information on each manufacturer for a particular drug quality standard would be quite an undertaking.

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Add to that, that FDA really has very little authority to request cost information, it makes getting the kind of information that is necessary for that type of an analysis somewhat difficult. I am thinking back, there have been cases where we have asked for that type of information and haven't been able to obtain it, again because of the competitive nature and the idea of keeping that information trade secret.

[Slide.]

That being said then, there is an avenue now that is open with four companies and others, anybody really, to have FDA consider the cost information. The Good Guidance Practices that have already been discussed here quite extensively require now that FDA publish in the Federal Register any new standards that they are going to put in place.

When those publications come out or are announced in the Federal Register, anyone, including the industry, has an opportunity to make comments on that. The comments that could be submitted could include information on the cost of implementing a new quality standard, and whenever FDA looks at implementing that standard in a final way, then, they can consider those types of things.

[Slide.]

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The next question then is if we do do this, how should such benefits and costs be assessed. I think at this point we haven't gotten to a point of being able to say how would we do this on a routine basis. You could say that the industry, whenever they do submit a comment under the GGP, they could actually go ahead and provide us with what their interpretation of a cost-benefit analysis is.

As long as we can verify that information that is being submitted, I think we could probably use that as one avenue to consider cost whenever we implement a new standard. I would say at this point, with regard to the methods that we would use, we are certainly open to any suggestions in terms of the techniques and methods that we could use when we are conducting a cost-benefit analysis at this point.

[Slide.]

The last question that was addressed was what factors should be considered, e.g., including availability when we do cost-benefit analysis, and if so, whether any guidelines should be followed.

The response that we came up with, with that, is that in looking back over the implementation of standards, I think we felt that we already do tailor the interpretation and the application of a lot of the quality standards to

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drugs and to implementing them.

In particular, we will do it on a case-by-case basis every time we implement a new standard or a new supplement or a request under a new supplement, or anything of that nature, I think we try to interpret things in terms of the cost. That is on a case-by-case basis.

In a more general sense, we have guidelines with regard to minor use and minor species and how we will consider certain areas in terms of new standards being implemented.

The factors that we often consider include things like the drug quality relative to target animal safety, to efficacy, as well as to the human food safety. We consider the batch-to-batch size, as well as the frequency of the production. We consider what the labeled species is to be treated, whether the product is for food versus non-food uses, and also the formulation of the product.

With regard to the specific issue on drug availability, minor species I believe was designed predominantly to address that issue, where you have little need for a lot of a product being produced, but there is definitely a need in the industry for that product.

That is taken into consideration, also, the expedited review status and the policies and guidelines

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associated with the expedited review status takes into account drug availability.

Again, there, we are always I think open to any new suggestions for factors that ought to be considered when we are considering a new drug quality standard.

[Slide.]

The one thing that I did want to point out I gather was that we don't really lower the quality standards in any of these processes. What we try to do is modify the means to fulfill the standards that are being tailored for any new drug approval.

I think an example of that would be that in minor species, rather than having a large number of batch testings to demonstrate a particular standard, they might reduce the numbers of testings to be required to demonstrate a standard, and thereby, you are not really reducing the standard, you may be reducing your statistical confidence that the standard is going to be met, but that does reduce cost somewhat, I believe, when you go from three or four batch testings to one or two batch testings. So, that would be an example to that.

That pretty much wraps up the presentation I think in a summary of what is in the handout that you all got. We also did look at the positions that were submitted by AHI

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and by AVMA, and I can provide some response to that.

With regard to the AHI position statement, we agree. We think the Good Guidance Practices does provide a means for addressing those who are interested in us, FDA, considering cost-benefit in making decisions.

We also believe that the GGP addresses regulatory creep as presented as a comment, and we believe that the processes that we use, that CVM does apply the same quality standards for all drugs.

[Slide.]

In response to the AVMA comments, the expedited review process seems to or I believe does address the issues related to the need for a product for use, as well as the effect of the availability of the new drug product.

With regard to questions on how to weigh benefits and risks, the FDA statutory mandate does require that the risks to the public be one of the primary concerns that we have to deal with, but that said, in the evaluation, the risk to consumers including users of drugs, the animals themselves, and the consuming public of producing or consuming unhealthy or unsafe food supply can be weighed in the direct risk to consumers.

Finally, we definitely agree that the existence of a hazard does not necessarily equate with the risk to

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consumers.

Just today, I saw the Food Animal Concerns comments and at this point I don't really have a response to that.

That is all I have got right now.

DR. LEIN: Thank you.

Reply from industry? Animal Health Institute?

MR. STRIBLING: For the Animal Drug Alliance, this is a much simpler issue than the question and the answers that will come up. I don't think there is anything that I disagree with that Mr. Eirkson said.

What I and the Alliance do agree with passionately is Dr. Sundlof's redefinition of the meaning of the word "safety," and he is not even a lawyer. Maybe he is hanging around with too many, but not a lawyer.

Historically, the Food and Drug Administration has looked at safety and approval of quality and approvability entirely in terms of the drug product itself.

What Dr. Sundlof did when he became Center Director, in fact, even in his presentation to the Search Committee, was to say you not only look at the drug product itself, but also the context in which it is used, and the rule of thumb simplified is -- and I believe this, and I hope the Center for Veterinary Medicine does, and FDA does,

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although I am not sure, I know Dr. Sundlof does -- that it is always better to use an FDA-approved product than an unapproved product, or a product that is approved for a different species, but not the species you are going to use it in, or for a condition other than the one that it has been approved for, or that has been illegally imported into the United States, or that has been compounded without approval either in a good compounding facility or in a bathtub, that it is always better to use an approved FDA product.

I believe that and as I understand what I think I am echoing Dr. Sundlof, all that the Alliance is saying, echoing we think Dr. Sundlof, is, hey, when you approve drugs, make darn sure that we are looking at the issue of availability, which is not a cost issue. It is a simple one, you look at the Green Book, which has a list of all approved products.

If there is a species for which a product is lacking and a condition in a species for which it is lacking, then, you have got a need.

It is far better, I believe -- and I think Dr. Sundlof believes -- to use an approved FDA product, which means you make every effort to facilitate approval, although I agree with Mr. Eirkson and everybody else in the Center,

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not to denigrate safety, effectiveness, or quality, but that if there are incremental levels that are nice, but not absolutely necessary, then, by darn, you approve the product and you get it out there because it is better to have practitioners and producers using FDA-approved products.

I agree, none of us is talking about lowering quality. We are certainly talking about whether it is -- again, your risk assessment, Dr. Lein -- whether every single requirement -- I am looking prospectively as this meeting is addressed -- whether every single new requirement is really necessary.

As I say, to us it is very simple and it is not a big thing for FDA to look at. It is not nearly as complicated as all this risk-benefit stuff, but we believe it is very important, but what we heard over and over and over again at the May 13th meeting was FDA will look only at the product, and that is contrary to what CVM's Director is saying, and it is contrary to what I believe is good policy just as a citizen of the country.

I believe in FDA and I believe in FDA-approved products.

DR. LEIN: Other industry comments? AVMA?

DR. GLOYD: Mine is a real short one. I was really pleased to hear Mr. Eirkson say that in its review,

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FDA-CVM does engage in a cost-benefit analysis and I think that is very important.

DR. LEIN: AHI, any comments?

MR. INCORVIA: I really don't have anything to add other than what is in our position paper, and I think everybody already has that.

DR. LEIN: Committee questions?

DR. BARKER: Mr. Eirkson, the GGP is only going to apply to new standards?

MR. EIRKSON: It is my understanding that is what it would be applied to yes, any new standards. Any new standards that would come out would have to go through the GGP process.

DR. BARKER: So cost-benefit ratio studies would only be related to new changes?

MR. EIRKSON: And not on a routine basis at this point, I mean other than if we get information that we could consider in evaluating cost or benefit with regard to the implementation of a new standard, we could consider that information.

DR. BARKER: Is it anticipated that argument will be made about existing standards?

MR. EIRKSON: I don't know at this point.

DR. BEAULIEU: The GGPs, one of the primary

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principles of the GGPs is that industry has an opportunity to raise issues which in their judgment either require new guidance or require existing guidance to be changed, so if the agency accepts a recommendation from industry that it go back and modify one of its guidances, then, that guidance would fall under the GGPs as it was revised, and would have an opportunity to update if it wasn't done before any cost-benefit analysis.

DR. BARKER: So this opens the entire CGMP and approval documents for existing drugs and new drugs to review?

DR. BEAULIEU: Well, the industry has an opportunity to raise issues which in its judgment, the agency ought to deal with. The agency in its judgment may not be able to deal with every issue that the industry raises. Hopefully, there would be a dialogue between the parties and we could prioritize and deal with what we and the industry believe are the most significant issues to deal with. So this is always that opportunity, yes, to retrospectively go back and visit some of our existing policies.

DR. BARKER: Is this also going to be applied to the human drug pharmaceutical market?

DR. BEAULIEU: The GGPs apply across the agency.

DR. LEIN: I didn't ask for additional comments

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from anyone else in the audience. Yes, please.

MR. WOOD: I am Richard Wood with Food Animal Concerns Trust, and our background sheet was handed out this morning at no fault of Richard Geyer. He asked for it a long time ago, but we didn't get it to him very soon.

I would just quickly like to highlight a couple of things in those comments for your information.

DR. LEIN: Please do.

MR. WOOD: FACT does not support a formal CVM benefit-risk assessment for the following reasons, and most of those reasons have already been debated and discussed, so I just want to really quickly list them.

First, we want the Good Guidance Practices to work. The Good Guidance Practices in themselves, as published in February, provide the opportunity for discussion of benefits and risks. So, we want that opportunity within GGPs to work, and that that would be the form then where benefits and risks would be discussed.

We agree also with comments that have been made by CVM most recently, and others here this afternoon, that any assessment of benefits and risks must be broadly defined. We were a little bit concerned about the change in the question from the original draft to the one that was passed out by the committee, but then I was reassured by Mr.

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Eirkson's comments that, in fact, they are not just looking, or this kind of a discussion would not focus solely on financial costs, but would focus on the full range of impact also on animal health and human health, as well.

Third and finally, another tier of steps needlessly encumbers a non-regulatory procedure designed to clarify the CVM guidance process if the GGPs are not used in lieu of a risk assessment.

Section 1 of the GGP document describes how the FDA sought to define "guidance" in terms that allow for clarity regarding this procedure. Numerous suggestions to broaden the definition in that process as it was laid out in the February document were rejected. FACT supports a procedure with minimal specific steps. Such clarity will enable public participation as the public will readily understand the procedure and how best to impact its outcome.

Such clarity will also enable timely agency action as was earlier indicated. The CVM has stated that they neither have the time nor the resources to conduct an assessment. Therefore, to ask the CVM to take such a step is to ask for delay.

As an alternative, the CVM is considering apparently, according to some of the documents that we read, whether or not to ask industry sponsors to provide the cost

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analysis. Such a step would be unacceptable unless CVM is able to verify that analysis.

Thank you.

DR. LEIN: Thank you. Any others from the guests, audience?

Back to the committee then. Questions? Yes, Ms. Duran.

MS. HUDSON-DURAN: I guess maybe I am just asking for clarification. Suppose the industry submits a product, say, a calcium product for food animal that is cost effective, that is not pyrogen-free, not made from sterile water, made from distilled water, and that is accepted, I certainly hope that that will be documented somewhere on the label, so that if we decide there is no other calcium products available and we have to use it extra-label in a horse, we can make a judgment call.

DR. POUST: A comment.

DR. LEIN: Yes.

DR. POUST: I guess to further clarify what Dr. Barker was asking, I think these GGPs provide for periodic review and update of the policies fairly frequently as opposed to some of the guideline documents that are out there now.

For example, the human industry has been working

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with a 1987 guideline on stability testing. I think the Center for Veterinary Medicine has its own guideline. I don't know what the date of that is.

There is supposed to be a new guidance document coming out on stability testing, and the need to address Mr. Stribling's concern, the need for such a guidance is based on the fact that the ICH stability guidelines, which came out in the last couple of years, are rather deficient in a number of areas and there needs to be clarification.

So, these guidance documents, the GGP do provide for periodic review and update, and they do cover or can cover all aspects of GMPs, I guess, or anything else related to New Drug Applications or what have you.

DR. LEIN: Other questions?

One thing I was wondering, does the GGP let industry or veterinary medicine become involved -- maybe it is through the industry route of the pharmacological companies -- concerning maybe withdrawal of a drug or a change in its manufacturing? Is this a process where they could be involved in that as far as the cost-benefit of that or the cost loss?

I should be talking about maybe there isn't a benefit in the cost part of it, and we are really coming down to some of the things that we have lost recently

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because of not meeting sterility or one of those different compliances. Would it open it up for that?

DR. SUNDLOF: Generally, products that are approved through an individual company, those issues are not discussed in the open forum policy areas. Those are made on an individual product-by-product basis, and because a lot of the information that is being assessed is commercial confidential information.

Maybe I ought to let Andy answer that.

DR. BEAULIEU: I just wanted to point out that there is a process that has existed for a long time within the agency for any involved party essentially to petition the agency with respect to what they think our policy ought to be.

Even on a particular product, if it came to the attention of a concerned party that we are in the process of taking an action which they thought would damage them in some way in terms of a product coming off the market, they could send a citizen petition in to the agency to request that we reconsider that decision or whatever, so that process outside of the general policy setting process we have been talking about, that process also exists.

DR. STERNER: If I could just make a couple of comments. It seems to me that many times by the time a

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crisis reaches that point, it is already beyond the crisis point and I think specifically of the injectable iron issue of a few years ago, where the CGMPs apparently impacted the availability of the product, and the notion that nobody could have anticipated, I am not sure whether you call it the domino effect or whatever, where we went from some availability to in effect zero availability.

I am not sure that this additional comment is germane to the discussion, but I will throw it out. I have heard a lot of comments about cost-benefit with regard to the pharmaceutical companies' interests, but speaking further down the food chain as a primary caregiver or more a secondary caregiver now, or adviser to those who treat the animals on the dairies and the farms that I work at, conspicuous by their absence on this advisory committee and sometimes speaking to CVM are the consumer groups themselves whose lack of availability of effective pharmaceuticals is probably a pretty muted voice, and I alluded to Dr. Poust's comments earlier with regard to certain injectables, and so forth, but it seems to me that part of the cost-benefit goes to what is the cost to the producing industry.

I am wearing my food animal practitioner's hat rather than companion animal practitioner's hat when I talk about this, but the food animal industry in this country is

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in a world market, and we want to be competitive with others, and the lack of efficacious products may make us less competitive. That is a concern that I have specifically or bring to this discussion.

I think that issues of human food safety aren't the issue here, but the fact is do we have products that address very real problems from producers' perspective, that address animal well-being issues, and I don't think we have addressed that or it is not alluded to in Question No. 2 specifically. It has looked more from the manufacturers' perspective.

DR. LEIN: Yes, Dr. Koong.

DR. KOONG: Keith, I really agree with your statement there and I, in my position, back home I do work with the producers, I hardly work with any veterinarians. I think that is a very, very important issue, that is, the cost of adopting or not adopting a standard resulting in a drug which is not available.

I want to go back to Jess' comment about FDA-approved drug. So, that is a linkage there if the cost of adopting the new standard or not adopting resulted in a bathtub mixing of whatever available to the rancher, and I think that is more harm to the animal health in general than the FDA-adopted drug.

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DR. LEIN: Dr. Floyd.

DR. FRANCIS-FLOYD: I would like to add to the comments expressed by my colleagues, because I think that this is one of the areas where we really, really need some help, those of us that are in the field.

We have to look at cost-benefit analysis and certainly when we are dealing with production animals, cost is going to be the most important factor in determining whether the animals are going to have access or the producers are going to have access to those products because it is going to determine whether or not a company pursues commercialization of a possible product.

The other thing is I am so grateful for some of the things that Mr. Stribling said and because they reflect Dr. Sundlof's position, that approved products are preferable to unapproved products, and some of us work in industries where we have no approved products, none, and we not only have then an issue of animal health because we don't know if we are delivering efficacious product to the animals, there is also concerns about environmental impact, there is concerns about worker safety because of people handling these products on a daily basis, and it is a real gray zone and it puts you in a position of liability, professional liability and personal concern, and it

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certainly creates risks for the animals.

So, I would hope that we could keep risk assessment in the larger context, that it extends beyond an economic analysis of cost-benefit, that it extends into the reality of what each of us has to deal with on a daily basis in our industries.

DR. LEIN: Other statements, questions? Yes, Dr. Kemp.

DR. KEMP: Is there a post-adoption process for one of these drug quality standards, and if so, is there a mechanism to put the standard on hold while the process is being reviewed or while the statement is being reviewed?

What I am getting at is if you come up and someone from industry says it is awful, terrible, can they go and ask for a review of it, and the actual implementation is put off for a while rather than having the economic damage of not being able to put out product?

DR. BEAULIEU: In theory at least, the GGPs would require a significant change to be put out as a draft or comment before we implement that change. The same, of course, is true of regulations where there is a comment period, where you intend to make the kind of change that requires regulation.

Level 2 changes, which are not supposed to be

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significant changes in policy, and that might reflect something like a minor change to an existing policy, can be put out always subject to comment after we implement them, and that might be kind of the primary distinction between Level 1 and Level 2.

DR. SUNDLOF: I think part of what I thought I heard you say, Doug, was that if we change a standard and then some company who is financially or for other reasons unable to comply with that standard and runs the risk of having FDA shut them down, are there mechanisms, so that that company can come in and work with us, that we don't immediately take that product off the market, that we can try and work with the company to bring them into compliance, and I think the answer to that is yes, and we do that, especially where we consider there to be a need for that drug and if that is the only sponsor that is producing that particular drug, then, we are even more interactive in trying to make sure that the individual comply.

There are some situations, however, in which despite a lot of concerted efforts in trying to work with the sponsors, that for one reason or another they are just unable or will not comply, and in some cases, those may be the only sponsors of the drugs which are needed.

So, we find ourselves in a position where we can't

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continually turn our back on a problem that looks like there is no due diligent effort to resolve, and a lot of those come out as things like -- well, I don't want to use iron dextran as an example -- the iron dextran example is something that we never want to occur again, and we want to make sure that if there are medically necessary drugs out there, that we have policies in place, such that we will do everything in our power within the law to make sure that those products are in some way protected without sending out the wrong message that it's okay to bend the rules.

So, we deal with these issues on a case-by-case basis and if we feel that there is due diligence on the part of the sponsor to try and comply with the standards, we certainly will work with those sponsors.

DR. LEIN: Other questions? Diane.

DR. GERKEN: If I understand this correctly, could you have a GGP or whatever that acronym is, GGP, that is different from the human side, could you institute that, so if there were GGPs that came through that were approved agencywide, that you could then for reasons of maybe economic reasons -- and I am talking about all the different economic reasons -- amend that slightly to fit the veterinary medicine scenarios or veterinary medicine special needs?

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DR. SUNDLOF: Guidance is guidance, and it is not regulation.

DR. GERKEN: So, the flexibility is built into it, so that you can handle it on a case-by-case basis?

DR. SUNDLOF: Well, we would want to handle it on a policy basis, a guidance policy basis, but, for instance, if the agency came out with a Good Guidance Document that CDER had established, and we felt -- first of all, we felt that it didn't apply or that there were some things in there that did not apply to veterinary medicine, we generally would, before that policy actually went out, there usually is some communication, and we would say things like you, you know, you would put in qualifying language that says this does not apply to animal drugs.

If we just missed it, you know, if we didn't anticipate -- which often happens -- a policy may go out and which we didn't anticipate would have a negative impact on veterinary drugs, but it turns out later that in actual practice, the unintended consequences of that were such that it caused our industry a problem, then, we could go out with individual guidance to say that in terms of these particular conditions relating to animal drugs, that other policy documents may not apply and that this is how we would interpret our regulations and laws in order to work with

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that particular industry.

The good thing about policy documents are that they are just that, they don't have the binding effect, legally binding effect of regulation or law.

DR. LEIN: Dr. Fletcher.

DR. FLETCHER: I think, Steve, you have answered this question. I was going to pose it this way. Does the company have the ability to develop and use a Good Manufacturing Practice that might be different from that in the GGP for minor species or to meet an availability issue?

The assumption I am making here is, is that the Good Manufacturing Practice would accommodate the items that are listed in the Center's report, such as drug quality and those kinds of issues, the question here being that if a company demonstrated a Good Manufacturing Practice that met the drug standards, and some of these other of the drug product formulation, that type of thing, and the issue then becomes one of drug availability, they say if we have to do these other five things, this drug is not going to be available.

The answer I am hearing is that yes, there are mechanisms to look at what those Good Manufacturing Practices would be, and if the quality of the product could be assured, then, a variance or an exception to what the

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general standard would be issued for that specific product, is that right?

DR. SUNDLOF: I think, in essence, you are correct, Oscar. We are getting into some areas that maybe I could ask Andy Beaulieu to comment on.

DR. BEAULIEU: The next question, the minor use question probably focuses this issue. It is sort of a subset of what we are talking about now.

DR. LEIN: No. 3.

DR. BEAULIEU: Yes, Question 3.

DR. LEIN: Keith.

DR. STERNER: To add to Andy's comments -- and this is implied I guess by all of this discussion -- is the need for information to be made available to users of products and the need for, in Steve's former life, the FARAD issue and the fact that somewhere along the line, those of us who practice and make recommendations need information still to be made available to us to make intelligent scientific decisions, and the plug has been pulled on that at least in some formal mechanism for a period of time, however temporary that may be.

I guess just for the record, I think that it would be incumbent on this committee to lend its support to a continued support of FARAD for making that information

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available to us.

DR. LEIN: I think that goes ditto, too, for the USP group through the Veterinary Association of Pharmacologists' Therapeutics group, and their scientific review of data basically for extra-label use. That looks like it is running into the same crisis of financing.

Other questions?

DR. GERKEN: I want to ask Dr. Sundlof, in relationship to what Dr. Sterner talked about, about the end users, the economics as far as the end user, is there any kind of model that is available that takes that into consideration at all, because really, I totally agree with him that when I think of economics, that is the part of the economics that I think of, not the pharmaceutical necessarily company economics, and I don't know that I have any solution to that, but that is something that really ought to be somehow considered in this whole equation, because that is really where the availability issue is at.

DR. SUNDLOF: If I could respond to that, well, we certainly agree and I think in the next talk that Dr. Beaulieu is going to give on Question 3 about minor uses, some of that will be taken into account.

From a strict legal perspective, we are not supposed to be taking such things as cost-benefit analysis

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into our decisionmaking process or other societal issues in making our determination as to whether or not a drug should be approved.

We are supposed to be looking strictly at the issues of safety and efficacy, quality. When you hear the next presentation, I think you will understand that some of those changes that we may need to make require changes in the legislation in order to set separate standards for animal drugs where the need is great.

The paradigm that we have used, which assumes that everybody can afford drugs or that we shouldn't be concerned about that, in reality, has led to some of the problems or most of the problems that we are sitting here talking about now, that stimulated the passage of AMDUCA. I mean these are symptoms of a larger problem, and we are struggling to address those, just as we are asking you to struggle to address those.

I would also indicate that we are contemplating adding another member -- and I say contemplating because we have to get approval from higher ups -- to add another member to this committee which would be a representative from minor species, so that we would have somebody like Ruth present at all the meetings that do represent those industries.

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Keith mentioned why aren't the actual producer associations represented on the panel, and we take the position that we would hope that the representatives who represent the commodities, whether it is companion animal or food animal or poultry, do represent their base of constituents who are the producers.

If we haven't made that clear, I apologize, but really we ask you to serve as an advocate for those particular industries, and that is why we felt that there was a need to add a minor species person, because that particular segment, which is a diverse, diffuse segment, but is not represented on this committee.

DR. LEIN: Coming back to your question that you just answered, Steve, and the safety and food safety and safety for the animal down through, I think are major issues, but you also have an issue, though, for at least animal suffering, just like you would have for human suffering, which becomes part of this as we look at that in minor use especially or sometimes in major use, that becomes I think the same issue and that you look at, too, as another priority. Is that right?

DR. SUNDLOF: Right. We basically do a couple of things. We evaluate drugs like you would for human. We balance the risk versus the benefit. You know if the cure

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is worse than the disease, then, it doesn't get approved. If the disease is worse than the cure, then, that forms a basis for an approval, and that is purely a risk-benefit analysis.

Superimposed on all that, of course, is the human food safety, which is not a risk-benefit, which is purely a risk. I mean the standard is reasonable certainty of no harm, it is not the harm that the drug might do versus the good that the drug might do.

That is the law, that is where we have to draw the line, and you can be -- you know, it can be the most needed drug in the world and would prevent all kinds of animal suffering, but if it didn't meet the food safety requirements, we would not be able legally to approve that.

So, we are constrained to a certain extent even though we, as caring, feeling individuals, want to do what is in the best interests of the animals, and we will try, you know, and we will try and be as flexible with the law as possible without breaking the law in order to address the need to prevent animal pain and suffering.

DR. LEIN: Other questions?

DR. STERNER: I have just one minor comment I guess to Dr. Sundlof's comments if I might, and it seems to me that with regard to human food safety, the reviewer, even

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though they have this ironclad standard with regard to human food safety, if one looks at the potential for contamination of human foods derived from animals, from food animal origins, clearly, there are certain categories of compounds which carry a much higher level of concern or risk, i.e., very small levels of penicillins as were referred to in our reference manual, are of much greater concern than, say, if there were some compound that would address Sue Duran's comments about endotoxin, the likelihood of endotoxin carrying over from food animal or a group of food animals, you know, to the human food supply, I believe is reduced if I could treat a particular animal that was in endotoxic shock for a temporary period of time, then, the concern would be over a penicillin beta-lactam family of compounds that might have a carryover which could have very serious health ramifications for a person sensitized.

So, it seems to me some logic still applies in terms of the human food safety issue in cost-benefit analysis or risk-benefit.

DR. SUNDLOF: And we would say that that is balancing one risk against another risk, and you take the lesser of the two, since we are not allowed to do the benefit thing, you know, so we say, well, the risk of approving the drug may be less than the risk of not

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approving the drug and having animals carrying disease to humans or whatever, and we can make those kinds of arguments if they are very clear.

DR. STERNER: The approval process is blind, right?

DR. SUNDLOF: Yes.

DR. LEIN: Any other questions?

We could do two things here. We could finish this up and come back and start in on 3 after we finish this, or does the committee want to think about what their answer is going to be on Question 2, or would you like to start through that at this point? Start through, okay.

I will start over on the left side at this point.
Dr. Kemp.

DR. KEMP: I don't know how to answer this really. Conversations with CVM over the last few years indicates they look at cost and benefit and risk every time they make a decision, so obviously, you need to -- I am just going to kind of pass, I don't know how to answer it. I know that you do consider these things, and you have considered them even on the surface. A lot of times you say cost is not a consideration, but it comes up over and over again.

DR. LEIN: Shall we do all three of these at once instead of coming back and going through each one? Can you

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do that in one fell swoop?

DR. KEMP: I think I did.

DR. LEIN: I think you did, too.

Dr. Cooper.

DR. COOPER: I think there are two parts to this, and I guess I would have the same comments. There seem to be an ability in the approval process to weigh benefits and cost as new standards have been adopted and will be adopted.

Hearing Dr. Sundlof's comment, I think this is perhaps best described in looking at the regulatory role that FDA has. They are concerned with safety, efficacy, and quality, and I think as long as these three issues are not compromised, then, there is I think some way in which cost and benefits can be assessed.

The presentation that was made earlier before this shows that there is some flexibility in terms of how CVM is willing to make this assessment. As long as the assessment is based on good science, and I think where apparently an established process appears to work, I am not very concerned that they may not be perfect as we go through this, but there is at least a concerted effort to look at the cost and benefit to the process.

There is a regulatory rule, which is legal, which takes away the compassion, and I think as long as CVM

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carries out its regulatory role and is open to ongoing comment and discussion with representatives of the industry without compromising the safety and health of animals and the public, then, I think you are probably okay.

Other than saying that allowing CVM to continue to do its job, I don't see a basis for recommending anything different than that at this particular time.

I think in listening to the comments, there is a basis for considering drug availability, and I think there is some flexibility in terms of how you might interact with the drug company particularly if there is a need that is not being met, but as long as it is not compromising health, then, I think we should move ahead with that.

I give that as general comments. I am not giving you maybe a definitive answer, but it seems as if a process is in place that gives assurance needed and a way of assessing of cost and benefit.

DR. LEIN: Dr. Gerken.

DR. GERKEN: Well, we all know that the FDA is not the EPA, and so your charge and regulation is a little different. I guess in some degrees, EPA does take some criticism on their cost-benefit analysis or risk-benefit analysis.

I was a little bit surprised that the comments

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from the industry groups did not include some recommendations on how to do this, because just at first blush, you would think that they would have some comments about how it might be done, and I guess I was kind of surprised and in some respects I guess pleased, but I am glad that CVM has the flexibility to handle these things internally without having a whole bunch of policy things that are constricting them or actual regulations that they have to contend with.

So, at least for this part, I guess I think that it is being handled probably in the best manner. I still do have some concern over what Dr. Sterner alluded to, and if I had a good suggestion, I would give it to you, but I don't have a suggestion just like everybody else in this room, so I don't know.

I guess this is something that we still have to continue to struggle with, but it is a real concern and I do think there should be plans to revisit this somehow in the future. I am not sure that the GGPs have the internal built-in review process where they come up and automatically are reviewed unless somebody brings them to the table, but it is a new process and you have not gone through it before, so you are not exactly sure how it works, so I guess we just have to wait and see how things work out, and if it doesn't

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work, then, we will probably be back considering this all over again.

DR. LEIN: Thank you. Dr. Ravis.

DR. RAVIS: I think that probably different groups would come up with different cost-risk analysis. I think you have the practitioners' concern there is a cost-risk, the public safety, I think, and then the pharmaceutical manufacturers, and I don't think they are all going to be able to come up with the same cost analysis.

I think the Center has apparently tried to be responsive to some of these cost concerns. I think the next question dealing with minor species is probably the way to deal with a group of drugs that has come up in May, and we will discuss again now, as a way to deal with these and provide the availability of these products.

I guess the one thing is that there are many reasons why a pharmaceutical manufacturer may decide not to market a drug, and it isn't always related to GMP concerns.

DR. LEIN: Thank you. Ms. Duran.

MS. HUDSON-DURAN: Well, if I could be assured that if these gentlemen made a guideline for the pharmaceutical companies to make a product, and it could be made for 20 cents, and we are going to get it for a dollar, that would probably be fine, but we don't have any

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guarantee, we don't control cost, the FDA doesn't control cost, so just because we cut back on standards has little impact on what somebody charges for a product.

So, I would like to be trustworthy and think that that system would work, but people like money and that is the way it is. So, again, irregardless of whether we decide to speed up approval, we still have to have a certain standard and we should have learned a lesson from a product that got on the market that didn't work, because it is really hard to get a product off the market that doesn't work when you do not have another product.

So, again, even though cost is important, and I have been there, and I stay poor, I am married to a farmer, so I really relate, so the bottom line is those are two separate issues and I really can't see that making the guidelines a lot less lenient are really going to impact what we are going to pay for a drug.

However, if it is going to be something that costs hundreds of thousands of dollars, yes, I could see we certainly need to curtail that. Again, on meetings past, I really don't know where we have dropped the ball of wax, but we keep talking about we need drugs, you know. You people that need these products need to be sending letters to manufacturers and say, hey, we have a need for this.

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If you have statistics to cite in the fish industry, you know, we are spending a hundred thousand dollars on an unapproved drug, here is an opportunity to make money, then, you know, you could some of those things. I think that would be much more beneficial than trying to figure out a way that we could cut back on quality to get a cheaper product.

DR. LEIN: Dr. Barker.

DR. BARKER: I am kind of, of two minds on this. Being a little schizophrenic is nothing new to people that really know me. It is the difference between I think in part being practical and realizing that the FDA already does something that is not part of their mandate, and that is to consider the cost-benefit analysis, especially when dealing with the availability of a drug to treat a disease for which currently no drug exists, there is an obvious benefit with very little risk given that that disease might be terminal.

At the same time -- and I saw it written somewhere in here -- about giving away the farm, you want to be flexible and give the appearance of bending over backwards, but you just don't simply want to bend over.

The mandate is safety, efficaciousness, and quality. There is probably a good reason why the original mandate did not include considerations for social issues and

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cost-benefit analysis.

That statement by itself covers such a large range of possibilities, the cost of manufacturing the drug versus the benefit of doing certain types of CGMP-required tests, you know, will our arguments degrade into I can make this drug cheaper and I can make more profit, and yes, it is already available and three other companies make it, but the cost-benefit analysis is if you do away with this regulation for my drug, I can make it cheaper.

Hopefully, that won't happen and I don't think that is the intent. Clearly it is necessary to consider cost-benefit analysis in anything we do, and any individual who is asked to make a reasonable decision has to have all the information that is available to them that is scientifically sound, responsible information to make a good decision, you have to consider these things.

It is currently illegal, but you told us not to necessarily pay attention to the rules, so you probably should change that and you should seek legislation to do so, so that it can be clearly and openly considered.

Who should provide that kind of information? That information should probably come from the companies petitioning to manufacture the drug or from interested bodies, such as consumer groups or other groups,

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veterinarians who need a drug or perceive the need for a drug. They should provide the kind of information I think to the CVM, to provide knowledge about what needs to be assessed and how it should be assessed.

What factors should be considered? Again, that is a very large swamp. I am not sure exactly how far you want to go in what you would consider a cost and what you would consider a benefit in trying to make these decisions, but clearly, when CVM decides whether to adopt a particular drug quality standard, there should be reasonable and rational consideration of information that reflects a cost and a benefit in pursuing a particular regulation.

DR. LEIN: Dr. Sterner.

DR. STERNER: Well, I will wear my Cows 'R Us hat for few moments and try and represent the industry just a little bit, and I do have a specific suggestion. I think that mine is an affirmative response to Question No. 2 when CVM decides whether or not to adopt a particular drug quality standard should weigh the benefits against the costs of adopting or not adopting of standards.

I would say emphatically yes, I think they should. One mechanism that I think has not been readily apparent within CVM, and that is the training of its reviewers and the breadth of their experience in the industry that they

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are going to regulate.

I think that while they don't have to be considered a path to the industry, certainly if they have a better breadth and understanding of the impact that their reviews have on an industry, it may in fact then, without necessarily looking at specific cost and benefits of it, at least give them a sensitivity to the need for a product and the potential deleterious impact that the lack of such products being available might have.

So, to that end, one specific mechanism would be that there be an ongoing -- and I am talking wearing my food animal hat here -- dialogue, experience, exposure to the production animal industry in this country by reviewers, so that they understand some of the needs that are there, and that circumvents the concerns that some have over the economics of it.

To address Sue's concerns, I too recognize that we live in a capitalistic society, and I recall one product that was coming out a few years ago for the treatment of bovine respiratory disease, and when one of my practice colleagues asked the particular pharmaceutical manufacturer how it would be priced, they said don't worry, it will be competitively priced. I well recognize that just because lowered costs in manufacture might be there, they are going

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to be recouped, they are going to be amortized as quickly as possible.

I still think it gets back to the availability of products in an industry, and it needs to go beyond just the manufacturer.

That finishes my comments.

DR. LEIN: Dr. Floyd.

DR. FRANCIS-FLOYD: Well, I would agree. As I stated earlier, I think CVM should pursue efforts to normalize, if you will, of inclusion of cost-benefit analysis when it considers potential adoption of particular drug quality standards. I don't think that is something that should be done in a once-in-awhile basis, but I would qualify that by saying that perhaps a formal economic analysis is not exactly what we are talking about here, at least not what I am personally talking about.

I would say that the GGPs represent a step forward and provide a mechanism for establishing dialogue between manufacturers, industry, and the FDA, and are a very positive step.

I personally support the broader context for cost-benefit analysis beyond sheer economic considerations and further support the concept that the availability of FDA-approved drugs are far preferable to the use of

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non-approved drugs.

I think beyond safety, efficacy, and product quality, it is important to consider risks which could be involved with such things as availability of alternative products, animal health and well-being, public or worker safety, and environmental concerns, and mechanisms to accomplish some of this may not currently exist given the present regulatory constraints.

I am going to digress for just a minute because we have used a mechanism in Florida to address this with some of our environmental compounds. When you are dealing with the aquatic industry, you have to deal with products that go in the water, and as soon as something goes into surface water, then, you have the Environmental Protection Agency that you have to deal with.

Well, in the ornamental fish industry, which is my primary group that I work with, the reality is that there are products out there, people are in business, they have access to products, and when you deal with regulators, it is very disconcerting to go to a regulatory group and say, look, they are using this stuff, it is out there.

It took some degree of courage, if you will, to go to Tallahassee and tell our Florida Department of Agriculture and Consumer Services that our farmers are using

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products that they are not allowed to use, but the reality is that they are using it, they buy them in the middle of the night, in the dark, who knows where they come from, who knows what the quality is, but these products are going into surface waters.

We found that we had a tremendous ally in the Florida Department of Agriculture, Division of Pesticides, because they really weren't interested in maintaining the current practice any more than we were.

When you have non-approved products being used by people illicitly, if you will, you have no control over product quality, you have no control over how the product is used, you have no control over how you are going to educate the people that are using the product, because you can't acknowledge that it is being used.

So, I would say that anything FDA can do in the short term or the long run to digress from its historical product safety, product quality, and product efficacy to this broader context is going to be beneficial.

I think that as we work with more and more species and more unusual circumstances, this is going to be very important.

DR. LEIN: Thank you. Dr. Cleland.

DR. CLELAND: I agree with what Ruth said as far

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as the economic situation, but I do feel that I don't see how, even though I know that FDA is not supposed to look at the economics of the situation and the cost and things when they are evaluating products, I don't see how anyone in the real world today can make any decisions without looking at the cost.

I mean realistically, Keith keeps saying, you know, the companion animal side, we don't have to worry about it because the little Fifis, the little daughter of so-and-so, but in reality, we too have to look at the cost of every drug that we prescribe, because people, they will accept a certain cost to a certain level, but they won't accept everything we want to offer them.

I think that in the real world, we have to look at the cost-benefit situation. I know and I am remembering something from several years ago, so I may not be remembering correctly the exact figures, but when the terminal sterilization appeared in the Federal Register -- and Joe may be able to remember the figures better than I do -- the FDA had estimated that the cost to the companies was going to be in like the hundreds of thousands of dollars, and yet when AVMA went to the companies and asked the companies, they said no, it would be much more than that, and maybe somebody from AHI could address that.

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Again, my memory may not be too good at those figures, but again, if we are looking at a major change or a major policy, somebody needs to look at how much it is going to cost, because eventually, it will filter down to our patients and drug availability.

DR. LEIN: Dr. Fletcher.

DR. FLETCHER: I would answer that question yes, the first question yes, and I think there are different levels of benefit-cost analysis. We have basically been talking about that, and I am thinking about it, not at the level of the company making the product.

So, at a very gross level, the first thing that comes to my mind is availability, what effect do regulations have on availability to treat a particular disease or set of diseases, so I would say that that would be something legitimate to look at.

If imposing these regulations means that this product is not going to be available, then, maybe we ought to look at it or at least give the company an opportunity to make a counter proposal with GMPs that would satisfy at least these five things listed in the Center's statement under Question 2, that have to do with drug quality, batch size, labeled species, food use. Steve said it better, safety, efficacy, and quality.

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Those standards ought not to be lowered, and they ought to be, in a pragmatic way, the question would be could they not come up with GMPs which would satisfy those and allow the availability of the product.

That is not the same thing as doing a detailed cost analysis at the company level for what additional cost is imposed by going to a new standard.

So, I would answer that question yes and I would say, how should benefits and costs be assessed, look at availability, and then what factors should be considered, I think the Center has identified the factors that should be considered, and I think what I was hearing was that there are mechanisms for a company to discuss with the Center what GMPs they will use to satisfy those criteria for safety, efficacy, and quality.

DR. LEIN: Thank you. Dr. Koong.

DR. KOONG: There is not a whole lot to add, but basically, my answer to Question No. 2 is yes, and I agree with what Oscar just said, and Ruth, you have put it very nicely and I would say the same thing with what you all said, but I forgot what you said.

But the other way of looking at it, I want to bring up another issue, herd health management in the area of preventive medicine. I think, as a rancher, I would look

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at this as sort of a buying insurance program. If the premium is too high, I am going to take the risk.

DR. LEIN: Good way of looking at it.

Dr. Koritz.

DR. KORITZ: My answer, of course, is yes to this question also, and I think Ruth's response was particularly eloquent. I think from a practical viewpoint, certainly it is FDA's position that quality standards are not lowered, but it is interesting conceptually that confidence and meeting particularly quality standards is, in fact, adjustable. It is a statistical concept that you are accepting a lower level of confidence for a particular standard if it is a minor use product.

DR. WOLF: I definitely agree that cost-benefit analysis should be considered insofar as is possible within the constraints that were discussed by Mr. Eirkson. Apparently, such data is not always made available to the FDA at the time they are considering some of these things, and although it is within the realm of a company to provide that data if they feel it may influence the decision one way or another, I certainly think that the five different points brought out in the FDA summary here are very important in consideration and that I would want, particularly as a small animal practitioner -- no offense to the large animal sector

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-- to be sure that one of the costs of changes is not an increase in the number of adverse reactions or adverse events, whereas, an abscess given to one out of 200 injections in cattle may not be important, it surely would impact my practice.

So, I am in support of that.

DR. POUST: It sounds like the Center is already engaged in this activity of cost-benefit analysis and I think they should continue to do so insofar as possible, realizing that there are limited resources and limited information available to them, and I agree that when FDA comes out with these cost estimates of the cost of changing things, for example, the terminal sterilization issue, they usually take a beating from the industry because the estimates are much lower than the perceptions at least of the industry, but nonetheless, I think it is a good practice to continue.

I think that however this comes out in terms of a recommendation by this committee, I do think that special attention should be given to the issue of availability or lack of availability, however you want to put it, resulting from new quality standards, not only from the pharmaceutical industry point of view, but from the patient point of view.

DR. LEIN: Again, it looks like the committee

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certainly agrees that it is important that we look at cost when we are adopting new standards and that basically, the main thing, number one, is the things that you have pointed out from CVM and that we agree with, that we want at least products that are FDA approved whenever possible and the importance of that, I think that has eloquently come out by members in the committee here, and that quality and safety and food safety issues and efficacy have to be number one, but also that the committee feels that the standards, if the bar is raised higher because of new techniques or, say, terminal sterilization is a good example, if we had products that didn't have this before, that did meet at least safety and efficacy and the quality, that that shouldn't move that product up into terminal sterilization for veterinary medicine.

Again, we could accept the higher standard if that was approved, but if we had companies where this was going to be a problem, and it really didn't make any difference to the outcome of treating that patient, that should be allowed.

So, what we are talking about is really two different CGMPs for veterinary medicine and for human medicine as long as we meet the major things with quality and safety and food safety and efficacy.

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DR. SUNDLOF: Can I ask you a question, Mr. Chairman?

DR. LEIN: Yes.

DR. SUNDLOF: You have raised an interesting concept and I would just like to get your response to a very hypothetical situation.

I have already said that I don't think that terminal sterilization regulations are going to ever become implemented, but let's just take a hypothetical situation where we said, okay, now we are going to require terminal sterilization on all injectable products that we approve from now and here into the future, but in your scenario, we said to the companies, but you have produced this product, we have years of experience to show that there are no adverse reactions due to abscesses or other things which terminal sterilization is intended to resolve.

Again to Sue's concern, what do we do with the labeling? We have two different products, one that is produced using terminal sterilization, another one which is not. Would you suggest labeling one or the other products, you have a choice, you know, you say this product is not produced using terminal sterilization, or you say to the other one, all the new products, all the new products are going to be produced with terminal sterilization, do you

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have them list that on there to get at Sue's question?

DR. LEIN: I think you would list exactly what happens to that product. I don't see a reason why you wouldn't say this has had terminal sterilization, this product has not had terminal sterilization.

DR. SUNDLOF: You would require both?

DR. LEIN: I think you could.

DR. POUST: That is not part of labeling now, is it?

DR. SUNDLOF: In intramammary infusion products it is.

DR. LEIN: Yes.

DR. POUST: Again, I go back to the human industry. There are a lot of injectable dosage forms out there and none of them say this one has been --

DR. LEIN: What they do with the processing.

DR. POUST: Yes, and I don't know that that is an issue.

DR. LEIN: Dr. Cleland.

DR. CLELAND: If you got to that point, Steve, and I know this is hypothetical, but the thing to do would be not to say this is not terminally sterilized, because that sounds like a very negative thing, just say aseptic filled. The veterinarian should be able to identify the difference

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between the two. Whatever the process were, the no-terminally sterilized product was handled by, just identify that process. I don't think you need to put that it was not terminally sterilized.

DR. LEIN: One other thing that could be thought of is that you haven't really changed the requirement for veterinary medicine in that. You have just raised the bar for the human medicine part. I mean they could do either basically without concern.

DR. SUNDLOF: My hypothetical scenario was what if CVM said, okay, from today forward, through regulations, you now have to terminally sterilize all injectable products, meaning that some products that are for veterinary use wouldn't by virtue of being grandfathered in would not have to.

DR. LEIN: I am looking at it another way, too, that for that class of products, say, X company comes in today that is not grandfathered, but wants to make that product, but doesn't want to go through terminal sterilization, would want to do it, yet under the regulation that was there before, that they be given that ability to go forward with it.

So, it is a different level for veterinary medicine from human medicine. I will take it back to the

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diagnostic world where we have a new test that may become sanctioned by NVSL or by OIE as the test, and what we are trying to get there is that we have more than one test that is sanctioned. There is other ways of doing this, and basically, we may end up with three or four sanctioned tests that you could do this by.

I think that becomes important because there is different levels that you want to be looking at. As long as you are getting the accepted benefit, that it is not causing a health hazard or safety problem or efficacy problem or a food safety situation, all you have done is raised the bar or given them a different way of getting to the endpoint.

I think it lets maybe the little guy stay in business a little better.

DR. STERNER: This theoretical XYZ pharmaceutical compound, I will put a better focus on it perhaps, let's say it's in the tetracycline family, and Dr. Wolf can find some use in her feline practice for a tetracycline compound, perhaps Haemobartonella -- I don't know if that is still in vogue -- and myself, as a dairy practitioner, might find that posterior digital dermatitis only responds in particular herds to tetracycline.

Do you think that application of tetracycline compounds topically to the heel of a dairy cow in the

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environment that she walks in, that that terminal sterilization has any impact other than adding to the cost of the drug that I am going to choose to treat her with? It just doesn't make any difference.

The ultimate determinant goes back to that economic choice, okay, knowing that that is the only compound that is going to work theoretically in this case. The bottom line is it is going to be cost. Yet, in Dr. Wolf's consideration, she is very concerned about the sterility of the product and its potential to cause abscesses in her practice, correct? Two entirely different rationales for utilization of the product, but, you see, you impact me negatively if the product is not available.

DR. LEIN: Of course, he is using it extra-labelly.

DR. STERNER: Which I can legally do.

DR. WOLF: And I probably would be, too.

DR. LEIN: Yes, that's true.

Dr. Fletcher.

DR. FLETCHER: One thing, I wanted to be sure that our comments relative to this Question 2, while may be transferable over to the minor species, in this context we are not talking about minor species use, we are talking about major species use.

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I just want to be sure that we understand that is what we are talking about, because we have said several times minor species, but I am thinking about several conditions in poultry, for example, for which drug availability is an issue, and that is why I think the availability of the product gets at a cost-benefit at a level beyond the company.

DR. STERNER: And by making it legally available, you have created at least some sort of a paper trail that if there is, in fact, the human safety problem, it is a lot easier to follow than the truck in the middle of the night dropping stuff off at who knows where.

DR. LEIN: One of the problems with minor species, the next day they may be major species.

DR. GERKEN: Dr. Lein, I think there is one issue, though, that again we are talking about availability, and the two different uses is a good example, but that goes back to putting things on the label, so that the person knows who is choosing to use it, it is their choice to choose to use it, that they know what it is, you know, how it has been processed or that it is at a different standard that it was produced under.

I think that that is not probably something we discuss very much is this labeling other than Sue is

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continually talking about labeling.

DR. LEIN: Some of that may come back to use of FARAD and the USP, if that can continue, because that gives you more in depth than what you may be able to put on the label, too, comfortably.

DR. GERKEN: Well if that is true, then, there needs to be something on the package insert or something that says where that can be found, but I think that realistically, the person using the product has to have access to that information, it has to be relatively handy for them to use.

DR. LEIN: I think today almost every practitioner, especially in the food animal industry, knows how to get to FARAD or if it is going to be available.

DR. STERNER: They used to answer the phone.

DR. LEIN: But I mean basically they were utilizing that heavily.

DR. GERKEN: But they are not going to know whether it's sterile in-processing or whether it is a different process. I mean FARAD is set up to deal with other issues. I mean you could have FARAD if we can ever get it in vogue.

DR. LEIN: Sue.

MS. HUDSON-DURAN: Again, you know, you buy all

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these products and you think you know what you have, and after the meeting in May I went home and actually Dr. Rodell and I went through a lot of labels in the pharmacy, and you know, you can really learn a lot when you read, and you read the details, and there would be products that were pyrogen-free, that said they were made from sterile water for injection, that is all it said, and then there would be products that were not pyrogen tested, particularly, we were looking at calcium products, that would say "q.s. with distilled water."

Now, again, I know the difference and there are some pharmaceutical people, and you have all learned the difference here, but the average person is not going to look to see. Again, if that just said basically what the end product is, I think that is the way to go.

Again, we use the cheaper calcium products in the cow, it doesn't seem to be a problem, and we use the product in a horse, but again, when I run out, this year, there was a discontinuation of a product of calcium that was pyrogen-free, so we had to choose to use the non-pyrogen-free product, which again I could say to my practitioner, okay, this is the only product we have, but be aware it is not pyrogen-free.

So, that is all I think that a decision can be

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made. At least we know that.

DR. STERNER: But, Sue, aren't you reassured by the fact that the formaldehyde is used as a preservative in that calcium?

MS. HUDSON-DURAN: But formaldehyde is in such a little-bitty amount.

DR. STERNER: See, you are willing to accept that risk, but others may say that zero is the only acceptable level.

MS. HUDSON-DURAN: Well, not for \$2.00.

DR. LEIN: We have probably come to our endpoint. We have adequately filled everything up over 3 o'clock, but we have answered Question 2, which we were supposed to come back and go further with.

I think we can take 15 minutes easily enough, maybe 20, and maybe there will be a few public comments yet to come forward, and then we will get into Question 3.

Thank you.

[Recess.]

DR. LEIN: I would like to open the floor for any comments on Question 2 from the guests and audience on Question 2.

Hearing none, we will move on to Question 3 or the discussion of Question 3, which is: Should CVM tailor its

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interpretation and application of quality standards in the regulation of drugs for minor uses and minor species? If so, what are the factors that most directly impact on the decision as to how to tailor the interpretation or application?

A presentation for CVM on Question 3 is Dr. Beaulieu.

Discussion of Question 3

DR. BEAULIEU: Thank you and good afternoon.

[Slide.]

My remarks are going to be relatively brief. I think this issue is, to some extent, a subset of the question we just talked about, but I, and I am sure others here, will be happy to follow up on any points that we don't touch on or I don't touch on in my presentation.

It may be important for you to know that I am not a chemist, much less a manufacturing chemist, I am not, in fact, the first choice of presenter for this information here today. I am standing in today for one of our manufacturing chemists, Dr. Dennis Bensley, who is heavily involved in the review of drug products intended for minor use and minor species.

For those of you wondering why me particularly, the simple answer is because I was the one who was late to

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the meeting where the decision was made as to who was going to take Dr. Bensley's place. That is true.

However, there is I think some logic to the decision to have me up here, and I do want to say that I am very happy to have an opportunity to talk to you here today. Dr. Bensley could not be here today because he is involved in an extern program in which CVM reviewers spend time with animal drug sponsors learning more about the practical aspects of supporting drug approval. Our hope is that such programs will further improve the level of communication between CVM reviewers and drug sponsors.

Dennis and I are both part of the task force that the agency formed in response to Congress' directive under the Animal Drug Availability Act, sometimes called the ADAA, to propose ways to facilitate the approval of drugs for minor use and minor species.

Following the receipt of public comment on that issue, the process of drafting those proposals is well along their way, and I can assure you that Dr. Bensley representing the manufacturing chemists of CVM has played a very active part in this process.

The ADAA did not direct the agency to lower its standards for the approval of new animal drugs, but it clearly gave the agency, and consequently animal drug

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sponsors, greater flexibility with respect to how to meet those standards.

Personally, I believe that CVM was moving down this path well before the passage of the ADAA, and therefore the Act basically affirmed the direction in which CVM was already headed and removed several impediments to the Center's progress.

The following remarks, which are directed specifically to the application of quality standards to drug products intended for minor use or minor species, were prepared primarily by Dr. Bensley.

CVM believes that it does modify its interpretation and application of quality standards, that is, manufacturing methods, facilities, and controls, in the regulation of all animal drug products.

Quality standards are not lowered, but the means of meeting those standards are tailored on a case-by-case basis to fit particular new animal drug products including those for minor use for minor species.

A number of factors impact on our assessment of quality standards for drugs for minor use in minor species including the quality of the drug product used in the clinical studies, that is, the quality of the product that was used to establish target animal safety and

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effectiveness, batch sizes, and frequency of production, for example, minor use in minor species, drug products manufactured infrequently do not need three lots to be manufactured upfront for process validation.

The labeled species, for example, the data addressing the quality standards for a minor use in a major species would typically be more extensive than for a similar product for a minor species.

Food versus non-food species. For example, certain aspects of quality standards are considered more significant for food animals, such as impurity levels that may affect human food safety.

Lastly, drug product formulations. For example, sterile injectable products need more stringent quality control than aquaculture drugs intended to be added to the water, that is, essentially to be added to the animal's environment.

Most of the currently approved or pending drug products for minor use in minor species, that are not also approved for a major species, are either sterile injectables or aquaculture products.

We have reviewed and accepted alternative means to address quality standards for the chemistry manufacturing and control sections of the new animal drug applications for

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these minor use in minor species products.

In essence, we have tailored our interpretation of the regulations and guidance documents regarding filing recommendations and CGMPs to facilitate the approval of these minor use/minor species products.

Through close communications with CVM, the FDA field offices are generally aware of the unique nature of these minor use/minor species drug products and typically conduct their inspections accordingly.

I believe the letter from Dr. Lance, under Tab 3 of your notebooks, attests in part to this better working relationship between FDA inspectors and animal drug sponsors.

To ensure that the review process for minor use in minor species products is conducted consistently, a limited number of reviewers are assigned to review the chemistry manufacturing, and control of such products, and Dr. Bensley is probably the premier reviewer in that regard.

I am going to stop there in terms of the prepared comments and let the discussion go where it will, and be happy to respond to questions now or later.

DR. LEIN: Thank you.

Any statements from industry? Dr. Lance.

DR. LANCE: Good afternoon. I am Bill Lance,

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Wildlife Pharmaceuticals in Fort Collins. I am speaking from the perspective of my firm, and I think I represent the ADA's stance on this issue.

As a leading statement, I want to affirm or confirm what Dr. Beaulieu just said, is that I believe that the Center has been proactive in addressing these issues. If you take his statements, I agree with everything that is written 100 percent with one exception, and by my own letter I have already testified against myself, but I still want to follow up with these statements.

Where I have found the breakdown has been in the communication between the Center and the field. The Center has been very proactive in setting new policies, precedents, to make these minor species, minor use drugs available. What generally and typically has not happened is that in the field, when the field inspector comes into a facility, they are working from almost an absolute zero base of information on doing their inspections.

The times in my experience where the field investigators have taken an appropriate view of their on-site inspection, there has been a tremendous proactive dialogue from the Center to the field, not from the field to the Center, about what this inspection is about, what are the appropriate guidances in making their interpretations of

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GMPs.

If I have a further challenge in this area to expand from what comments have been made to this point, following Dr. Sundlof's continuing thread, as I listened to Dr. Sundlof's presentation this morning, which I thought was just absolutely wonderful, the thread that I see through there is communicate, communicate, communicate between industry and the Center.

Well, I would challenge the Center even further to communicate with the field offices in what this process is all about. In this room, we could all agree, the FDA Center for Veterinary Medicine could agree, VMAC could agree, and we could affirm that from this day forward, all tigers will be vegetarians, but somebody has got to go out there and convey that message to the tiger before I am going to feed him a carrot.

That is what we are into. So, with that, I am sure, much to the astonishment of some people in this room, I affirm what has been said by the Center, that they have and are breaking new ground in this area, but somebody needs to tell the tiger.

Thank you.

DR. LEIN: I like that.

Other statements? Joe?

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DR. GLOYD: Well, as long as Andy mentioned the word "aquaculture," I have to give my annual reminder that there have been no drugs approved for aquaculture in the last four or five years, maybe longer.

Going on to something else, following up on Dr. Lance's issue with communication, I had a call from George Holzer, who I think provided you all with an outline of his saga with FSH. Somebody said that sounded like the script for a 60 Minutes broadcast, but Dr. Holzer was telling me this noon that a colleague of his, who was doing investigational new drug work on a foreign product that is an FSH-approved product outside the U.S., is doing some work here, and subsequent to the last May meeting, there was a change in FDA's policy regarding FSH products which allowed veterinarians to import products from other countries for use here.

This particular individual had a two-person inspection team from FDA come to look at his records as far as his investigational clinical studies work on the product, and somehow or another they came to the conclusion that he was also getting product from outside the country, and they wondered how in the world he thought he could get away with doing something like that.

So, obviously, those tigers had not been told

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about the vegetarian issue either, and I think that that just further confirms what needs -- maybe it never can be done, maybe all of FDA's field inspectors will never totally get the word, but it continues to crop up.

DR. LEIN: Other comments? Comments from the committee?

DR. FRANCIS-FLOYD: I would like to address a question either to members of CVM or to members of industry that are here. A couple of the comments I have heard just in the last couple hours, as they pertain to minor use drug approvals, is that you have got to work with industry sponsors, and I guess maybe I am still in the dark about this, but I have yet to find someone who feels that the market, at least in the ornamental fish industry, which is the third largest aquaculture industry in the U.S., is adequate to pursue a label.

The most recent example I can give, I am trying to figure out the exact numbers, but a product which was a pesticide, not a drug, that we were able to get approved through the Department of Agriculture 24(c) process, this product was Baylucide, which is manufactured by Bayer, and we wanted to purchase -- we figured if every pond in the industry used this product, the most that we would use in a year would be something like 1,000 pounds, and the product

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sold for about \$30 a pound.

The industry, there is no way they are interested in that kind of a market as far as putting funds into developing a label on that kind of a market. So, we were able through the Department of Agriculture and the industry to finance some research, and I think we ended up with about \$28,000, and then worked through the 24(c) process, and eventually did get a label, and the product has had a huge impact on the industry.

We estimated that \$3.5 million in savings the first year it was available to the industry, but the drug sponsor, if we had had to wait for them to move forward and do it, it wouldn't have happened.

So, I guess my question is am I missing something or is this a real perception that drug sponsors are not interested in these minor, minor uses?

DR. BEAULIEU: Speaking for CVM, that is certainly our perception. A number of the proposals that we are working on in response to Congress' request tried to deal with that issue, trying to come up with innovative ways to provide greater incentives than currently exist under the current statute.

It is a very complicated issue. Some of the things we do that people in this room would applaud, serve

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as major disincentives to new product development, AMDUCA, for instance. We have had INADs that were under development, Fish and Wildlife, and other state agencies were using products under the INADs, generating data into those INADs on the basis of which we felt we could support an approval for those products.

At some point, those folks basically said we can no longer justify spending our dollars, spending public money to generate data into these INADs when we can simply use these products in an extra-label manner, and that is a problem. I mean that is one of the most direct examples of where AMDUCA has provided a specific disincentive fairly late in the process.

That was one of the drugs, you know, Joe, we were hoping was going to get approved as an aquaculture drug as a result of this process, and the plug got pulled relatively late in the game because somebody decided they couldn't justify the cost.

I honestly believe that CVM is doing as much as it can to facilitate the process. We have a national aquaculture coordinator. We very much supported that position, we support in part financially, and that person's primary responsibility is to serve as a marriage broker essentially between those people that have needs and those

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people that might be willing to help meet those needs.

Ultimately, even if all the data to support the approval were generated at public expense or otherwise essentially contributed by virtue of producers being involved in the process and being willing to keep the records, and so on, that are necessary to document that data they are collecting, somebody ultimately has to manufacture the product and put a label on it, and in some cases, we can't even get anybody to do that.

Hopefully, we can develop an incentive to some of these proposals, some of which will provide enough of a niche market, so that maybe not the major manufacturers, but folks like Bill Lance and others, may be able to say, okay, now there is a process in place, there is opportunity here that is worthy of investment, so I am going to set up and go into the business of meeting that need.

We got a lot of good comments when we went out for public comment on this proposal, something on the order of 35 to 40 comments, a lot of which were very thoughtful. I mean there is a lot of concerned folks out there, and we have tried to analyze all those and incorporate those into our proposal.

It is going to take -- the deadline on that is April of next year, and the agency is going to try very hard

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to meet that deadline, but I have to say that when Congress asks the agency to do something, almost certainly the Department will want to get involved in whatever the agency's answer to that request is and maybe even Office of Management and Budget.

So, there is going to be a lot of review at higher levels, and possibly some of the proposals that CVM has come up with will be considered too far reaching to satisfy some of the folks in the Department or higher.

We are talking about finally a recognition that certain kinds of products for certain species are simply never going to be approved under the current process. We have got to radically change the way we are doing business to meet that market, and whether we propose things that are too radical for other folks, we will see, but for what it is worth, CVM is trying very hard to be innovative in this area.

DR. FRANCIS-FLOYD: I just wanted to comment, Dr. Beaulieu, and thank you personally and on behalf of the aquaculture industry, and Dr. Sundlof, because CVM has been awesome in what you have stimulated in terms of supporting these minor industries, and it is nice to get some of this out on the table, but you guys really deserve some commendation for what you have done.

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DR. BEAULIEU: Thank you.

DR. LEIN: In that same vein, can industry act as the stimulus without having a pharmaceutical industry involved? Can you do it through a university and industry, that was through a pharmaceutical company, or more like Dr. Lance has done, basically, not directly coming as a pharmaceutical industry?

DR. BEAULIEU: I think all of those things are possible. A lot of the data are being generated now, not at the expense of pharmaceutical sponsors, but at the expense of producers, at the expense of state organizations --

DR. LEIN: I see some of that with the biologics industry certainly has gone that way with USDA licensing, the duck industry runs its own show, and part of the poultry industry does in that part of it. Could they also be the masterminds of really the pharmaceutical part of it?

DR. BEAULIEU: That is a good question. The extent to which some folks that aren't traditionally in the business could get up to speed and become part of the business, I mean in terms of actually manufacturing these products. I don't know. That is a good question.

DR. LEIN: Or taking a product and secondarily trying to license it.

DR. BEAULIEU: Contract manufacturers is always an

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option.

DR. LEIN: Dr. Wolf.

DR. WOLF: I think the biggest question would be the size of the industry, the size of the use of the drug, and the war chest that that particular industry may have. The beef producers may have quite a large number of members and quite a large amount of money with which they can work, whereas, minor species, such as the ornamental fish industry, probably doesn't have the same number of producers in the same numbers.

So, I think the biggest problem would be, one, finding that money to do the research, because it is very, very expensive to do, and the number of animals that are involved, and also then finding someone to manufacture the product when -- this may come as a surprise to everyone -- but the drug manufacturers aren't in it for their health or our health per se -- they are in to make money, and if they feel that it is not a viable money-making project, you may not be able to even find anybody to make it for you.

DR. LEIN: Others? Yes, Kelvin.

DR. KOONG: I just wanted to make a comment, to point out that in the plant science area, and they are far more advanced than we are in the animal area, that is, the pesticide use, obviously, that, because of water quality

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issues, is monitored and regulated by EPA, and in the plant area, there is an established mechanism for monocrop use, pesticide, and actually, that is a defined process and procedure.

As a matter of fact, there is a national project, used to be called IR-4 -- Dr. Cooper, you may help me what it is called now -- basically, the national network tried to get those things to go through EPA and therefore approval for minor use crop for pesticides.

DR. LEIN: These would be compounds already used or developed.

DR. KOONG: Right.

DR. LEIN: That is what I was wondering, if you could do that.

One thing I brought up the last time, and was trying to come back to the human orphan drug situation, and does this apply, is that more where you have got very limited use and probably don't have a pharmaceutical company that is really looking for that, and is more of a clinician or research in a way or pharmacy department within a hospital that becomes involved in that.

DR. BEAULIEU: That is, in fact, a useful model, and I think you can anticipate that some of the proposals that come forward will be based on that model. A lot of

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that is dependent upon creating tax incentives and other incentives for firms willing to get involved in manufacturing those products.

Now, CVM is always going to suffer by virtue of trying to use that model because we cannot, clearly we cannot afford to charge for our drugs what human manufacturers can afford to charge for human drugs. We don't have third party payers, for instance.

So, for these very low-market products, it is possible with some tax incentives, and so on, to sweeten the pot, to actually recover costs on some of those small-market human products that we probably couldn't accomplish that on our side.

So, we think we need options beyond that one, which is clearly one we want to go with, but may not serve all our needs. In fact, on that score, I have to say there is no one model, there is no one system I think we are going to be able to develop that is going to be able to meet all the needs of the minor species. It is just too diverse a population to come up with one system, whether it is the current system or some one system different from the current system that is going to be able to meet all those needs.

I mean you are talking about products for crickets and earthworms, I mean tropical fish, elephants -- I mean

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the diversity is enormous, thousands of species involved, and to think that any one approval process is going to be able to accommodate that diversity is dreaming.

We have clearly established that the one we have now, after using it for 30 years, is a total failure with respect to meeting the needs of the minor species caregivers. It hasn't worked in 30 years, and it won't work in the next 30 years in my humble opinion.

DR. LEIN: Dr. Floyd.

DR. FRANCIS-FLOYD: Along the lines of what Dr. Beaulieu has stated, and some of the ideas like looking at some of the models that exist in the plant world, which has worked for us in Florida on two products, and we have got three more in the process, which as I said are pesticides, not drugs, but the other part of this is that we are dealing with companies in a lot of cases that are not traditional pharmaceutical companies, and it would seem like if we go into nontraditional possibilities as far as getting some drug approvals, then, maybe that would open the door for some nontraditional drug sponsors, if you will, so that we could get some of the products that are maybe already being used, but get them under some sort of system where we do have some level of control over them and then can educate people in their use and can test their safety and efficacy,

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and get good labels, and all this.

DR. LEIN: Other questions? I would just ask whether we really look at safety and quality aspects with these -- which I think you do yet -- and if it was the food animals, certainly, that would become a big problem, too. So, I think it is, but it is, of course, in a minor situation, compared to a major species with a high volume drug. The same things are there, but you might be doing it in test tubes instead of batches.

DR. BEAULIEU: Even with respect to exposure of the human population, I mean by definition that exposure is going to be a whole lot less even for --

DR. LEIN: And you need the analytical chemistry and the ability to test for this within tissues and residues, so all of it is there, but it is done at a different level.

DR. BEAULIEU: But that gives us the ability, as we have done for a number of years, that gives us the ability to extrapolate some of the information from major species to minor species. Where we already have a major species approval, we can spin that off.

Having said that, even there, even where the government through the NRSP-7 program now -- it used to be IR-4 -- where the government has essentially spent all the

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money to conduct the studies necessary to support the approval and announce the availability of all those studies for reference purposes, we still can't get pharmaceutical sponsors sometimes to add that claim to their existing label because they perceive that there might be some liability associated with that, not having generated the data themselves, they are not willing to assume the risk or potential risk of putting that claim on their label.

So, that is another potential incentive that we might work on, if there is some way to protect sponsors from that kind of liability, we are looking at that.

DR. LEIN: Dr. Kemp.

DR. KEMP: Under product liability law, isn't a manufacturer of a drug responsible for any damage that drug caused, regardless of whether or not they knew the final use of the drug? As I understand it, it goes deep pocket, it goes from the distributor all the way to the manufacturer, and all the way back up the chain on liability, so I don't know, do you really escape any liability, I mean do you incur a natural liability?

DR. BEAULIEU: I am not sure that it wouldn't take a special dispensation in the form of an act of Congress to try and protect folks, and whether that would work under all the liability laws, I am not sure.

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DR. LEIN: Jess, can you answer that question?

MR. STRIBLING: The product liability laws go technically to the product, and whether it is actually faulty, et cetera, but in fact, juries are very often willing to look to deep pockets, and so companies need to be worried, not only about the actual status of their product, but also about what a jury might do in the event that a problem was alleged.

The current administration has -- and I am talking about Washington now -- has shot down a number of laws that are designed to soften the potential damage, harmful effects of product liability laws, so it is not at all clear that there is going to be any relief in the immediate future.

DR. LEIN: Dr. Floyd.

DR. FRANCIS-FLOYD: This will be just brief, but again getting back to what Dr. Beaulieu said about product sponsors and labeling, one of the things that we were able to do in Florida with the 24(c) process for the pesticides was that the Florida Tropical Fish Farm Association negotiated with the company that manufactured the product, so the sponsor that has the label, and then I guess the inferred liability, I am not sure about that, but that is the actual, the Fish Farm Association as opposed to the company that manufactured the product.

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DR. LEIN: I think that is what I was saying about groups, if they could afford to do it, could they become responsible.

Yes, Steve.

DR. SUNDLOF: I wanted to just take a minute to address some of the issues that I think Bill Lance and Joe Gloyd raised about communications with the field and how sometimes those handoffs don't work as well as we would like to.

I can tell you that the examples that were given are real examples, and we don't always have the kinds of communications with the field that we would hope to have, where everybody knew what had transpired either between CVM and the company, or the field and the company, so that we are not constantly tripping over one another.

I have asked Dick Geyer to begin proceeding to address this issue. We have had over the past few years very good working relationships with the Kansas City District. Most of our drug companies are located in that district. Now I think we are in a much better position that we know what they are doing and they know what we are doing, and we have had a lot of very good comments that have come back from the industry.

Where we haven't been as good is in some of the

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districts outside of the Kansas City District, and we just have to do something to try and resolve some of the communications issues, and there is nobody at fault, nobody is doing anything that they shouldn't have done that results in some of these miscommunications, it is just a matter of putting the time and effort in and working out procedures, so that we will have an idea when they are going to inspect a facility, and so that we can apprise them of certain waivers from regulations that we may have allowed, for instance, with a plant that is manufacturing less than 1,000 doses per year, and those kinds of things.

It is a very real issue and I didn't want that to get lost in this discussion.

DR. LEIN: Other questions? Yes, Joe.

DR. GLOYD: Going back to something Dr. Fletcher said a moment ago or that had to do with the last question about a drug sponsor being able to create and validate its own Good Manufacturing Practices in a case of a minor use product, I am not sure that really got answered. Maybe I slipped off into dreamland for a minute. Did you get an answer to that, Dr. Fletcher?

DR. FLETCHER: I don't know, Joe. It is related both to non-minor species and minor species, and I didn't get a contradiction to an assumption I was making that it

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was within the realm of the company to negotiate with the agency to do that. So, this would be a good time to maybe say is that assumption valid or not.

I think what is coming up here is a question of there is nobody out there that really wants to step forward and attempt to do any negotiating with the minor species.

DR. BEAULIEU: What was the "this" we were negotiating?

DR. FLETCHER: I had said it would seem to me a scenario in which a company, in the event that new GMPs were being suggested through the Good Guidance Practices format, and in looking at the cost-benefit, at the level of availability, if that company came and said we have got a set of GMPs that we believe will allow us to meet the quality standards, those five items, now, can we use those in lieu of this new proposed standard particularly when the issue is one of availability, would then the agency look at that in a favorable light.

That is what I was seeing was that nodding of heads that said yes, because that gets at the how we are going to achieve a quality standard, and the new proposal might be looking at new technology for assaying something or whatever, but here is a company saying we have got what we think are GMPs that would address the quality issue and also

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allow the availability of the product.

I am hearing the answer that says yes, that is doable.

DR. BEAULIEU: Our minor species guidance document which went out in draft not too long ago, basically encourages sponsors of minor species products to come in and talk to CVM with respect to almost all aspects of the application including the manufacturing controls, not to make any assumptions about what CVM might or might not be willing to accept, come in and sit down and talk to us.

DR. FLETCHER: What I am hearing is that for minor species, there is nobody, in many cases, most cases probably, there is no company out there willing to negotiate that or stepping forward to do that, and then I am hearing that there is a gap sometimes in the communication between what CVM would look at with GMPs, and how in the case of field inspectors, they wouldn't carry out that.

It seems to me that that is doable, I mean that is a problem that can be attacked by improving that level of communication.

DR. LEIN: This was Dr. Lance's concern, too, but that again goes back to that orphan drug thing I was talking about, too, because that also has to bring that together in the human part.

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Any other questions?

MS. HUDSON-DURAN: Again, we talked about it several meetings ago, nothing ventured, nothing gained, but maybe making a list to publicize in AVMA and publicize in the pharmaceutical industry to say these are products we are interested in having formulated.

It may be that there is not a big use, but a lot of these products are economical to make and as long as someone is making a profit, you know, I think again we talk about products that we need, but I really don't think a lot of people are aware of what products that we do need, because if you go to visit pharmaceutical companies, they have got a research and development, but they have pretty well got a protocol for three or four years down the line and they are always asking for new ideas, but at least have something as far as presenting a list of drugs that we feel, maybe prioritized, that we feel that are important.

DR. BEAULIEU: I think that message is starting to get across. We have worked with the aquaculture industry, have been for five or six years, and one of the first things we did was say you have got to clearly articulate what your needs are and you are going to have more needs than we can reasonably accommodate whatever we try to do, so you have got to prioritize those needs, so we can start working on

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the most important ones first.

Now that is a very diverse industry in itself and to get those guys together and decide, you know, which 10 drugs would provide the most bang for the most people was not easy to do, but they did it.

They really made an effort to do that, and it is discouraging -- I agree with Joe -- it is discouraging that having started that process, we haven't seen more come out of it, but there are projects that are moving along the way, and there is a lot of state dollars involved in that. They manage to give millions of dollars, at this point invested in the research for aquaculture by having each state contribute to a pot of money that would go into research.

DR. LEIN: I think the model is Dr. Lance, who is going to talk right now.

DR. LANCE: I want to make a couple of comments. I believe, as a company, that is what you describe is what we do. We are looking to fill those needs. You know, the statement that I live by is I am in veterinary medicine because I love animals and I love what I do.

I am in the pharmaceutical business because that is a route to get to the tools that I need. I am not particularly in love with pharmaceuticals, and so we are constantly, as a company, we are looking at things that need

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to be done.

We want to do the most important things first, and what comes into our equation -- now I am talking as a businessman because we have to make a profit -- so, what is the raw material going to cost, can I get anyone to make the raw material, and if I can get that through, and again I have to come back to CVM and say, okay, we are going need 100 grams of this a year, can we talk about in-process testing on raw material. Generally, they said yes. Okay, we have got that problem solved.

Then, we talk about safety and efficacy studies. Then, we start tacking that cost on, and then at a point we have got to go back and assess the product and say, okay, does the user, does the ultimate user, are they really going to use that much, and are they willing to pay this price, because we can tell them what it is going to cost, and like the list is endless, but what we do is we prioritize things that we think have the most immediate need.

We are off into right now one of our hot issues is reproduction control in pigeons. In the next two or three years, we are going to drive a safety and efficacy group out, they will be leaping off the fourth floor before we get done with it.

But we are looking at those, and this is what we

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do for a living, we do it for fun, too. But those are some of the factors that go into it.

Thank you.

DR. LEIN: Thank you.

MR. SHEPHARD: My name is Mark Shephard. I am with Shotwell & Carr. With regard to the issue of aquaculture drugs, our firm has had limited experience with it, but one of the things we have seen in the realm of that experience is that many of the drugs -- substances, let's put it that way -- that are efficacious for, for example, ornamental fish, are really commodity items, copper sulphate, potassium permanganate, formalin, for example formalin went through I believe there is two approvals for formalin now.

The problem becomes not just the issue of profitability to the company, but it is market protection afterwards, because any level of regulatory requirement on something that is little more than a commodity item, puts it -- I guess the point I am trying to make is where is the incentive to get approval for a commodity item if that raises the price of the product to the point where producers just go out and buy the commodity in place of the approved product. I think that is really the issue that needs to be gotten around, because I think there are some small outfits out there that would be willing to go through the process if

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they could get market protection afterwards.

Thank you.

DR. LEIN: Yes, I think that is a difficult one unless you have got a non-commodity type of a product that you can work with. That is almost where industry has got to be a leader, I think, but it is not an easy one, and I don't know how you get protection. Can you get protection, Dr. Floyd?

DR. FRANCIS-FLOYD: Again, I am going to go back to the pesticide model because the issue raised is extremely important and it has resulted in the loss of labels for at least one product.

One of the mechanisms that is available to us in Florida -- I don't know whether this is national or not -- for pesticides is that they control the pesticides, so that with the two products that we have licensed through the 24(c) process, Baylucide and Baytex, they can only be purchased by producers that have a special license which is issued by the Florida Department of Agriculture, Division of Pesticides, and the products are sold only through one outlet, which is the Florida Tropical Fish Farms Cooperative, so you have control of the product going to the market, control of the product as far as who purchases the product and how much they purchase.

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Therefore, if somebody has product and they are not licensed or they can't account for how they have used it, then, there is potential for enforcement action and also it pretty much -- I don't know how effectively it might have shut down, but there was no black market supply, if you will, for Baylucide, because that was a product that wasn't available to them through the outside market, but for Baytex, I don't really know whether or not they are still trading it in the middle of the night on the dark roads, but I would suspect that for most producers that would not be a wonderful alternative when there is a legal product available now.

DR. LEIN: Yes.

MS. DUNNAVAN: I would just like to quickly comment that that is part of my role in compliance. If there is an approved product out there and people are using an unapproved product for that condition, then, that is where I need to be pursuing enforcement.

I mean you can characterize that as protecting the product. I don't like to quite think of it that way, but certainly there is no incentive for anybody to get approval if, in fact, somebody can use the unapproved product just as easily. So, that is at least one of the roles for compliance.

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DR. LEIN: Could you control a brand, though, for formaldehyde basically, I mean made by several different companies?

MS. DUNNAVAN: If there is an approved formaldehyde and someone is using a commodity formaldehyde for that same approved use, that is illegal, you can't do that, and we could pursue some enforcement action.

DR. LEIN: Or copper sulphate?

MS. DUNNAVAN: Or copper sulphate. If there is an approved product and someone is using the commodity or a concoction that mimics that approved product, then, we can and should be pursuing some enforcement action.

DR. STERNER: But doesn't that get down to the allocation of your resources with regard to enforcement actions?

MS. DUNNAVAN: There is no question about that.

DR. STERNER: I think that is, if I am not mistaken, a national program that people who purchase compounds like Ruth has talked about in terms of registered pesticides have to have application licenses and there is a national licensure form that they have to pass.

I know it is in my state, and I see lots of heads nodding, so that type of product certainly falls under much tighter control than commodity type products. You really

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are skating over thin ice if you think you can make any active enforcement stick in that setting.

DR. LEIN: Other questions?

Seeing none, let's come back to at least answering this No. 3 question: Should CVM tailor its interpretation and application of quality standards in the regulation of drugs for minor uses and minor species? If so, what are the factors that most directly impact on the decision as to how to tailor the interpretation or application?

Why don't we start with Janis and go around this way at this point.

DR. CLELAND: I said off the mike that he was getting mean starting in the middle here.

Well, I think the whole discussion is pointed at the fact that in order to get approval of products for minor uses and minor species, that some interpretation or some tailoring of interpretation in application is definitely necessary.

Unfortunately, the tone of the conversation was even if CVM is very responsive to doing it, and appears to be working very hard to try to accomplish that, if they don't have drug sponsors or groups willing to bring drugs to CVM, they can have as much tailoring as they want to, but it won't matter because nothing will be resolved.

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So, I definitely think the answer to the first part of Question No. 3 is yes, and then as far as factors that most directly impact on the decision as to how to tailor the interpretation or application, I guess the main ones that I would think about are, one, is this a species or use involving a potential food animal for the obvious reasons of food safety; two, how large a population of animals is involved and what is the likely percentage of that population to receive the drug. For example, and this of course is not a minor use, but when Merck looked at Heartgard, they looked at the population of dogs in the United States and saw lots of sales.

So, I think that that needs to be reflected, too, because obviously, if you have something that you are only going to have a very small batch of, then, something needs to be done, so that you don't have to jump through all the hoops compared to a drug that goes to a lot of animals.

DR. LEIN: Thank you. Dr. Fletcher.

DR. FLETCHER: I like what you said, Janis. I would say yes, and I think CVM is, in fact, doing that. The material that Dr. Holzer provided suggested that the emphasis be on the animal and human safety, but I think in the material that CVM gave us, you identified those same five areas which I think to me make some logic that the

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agency, to fulfill its responsibility, I think has got to look at those.

The other issue there needs to be more dialogue is how do you go about establishing the basic data, so a company wouldn't have to do it on safety, for example, and we have talked about a number of models, but I think that dialogue needs to continue, for example, for veterinary colleges, for instance, what is it that we could do. Ruth's example of what is happening in Florida because of that impact or her presence there.

So, I think we have to work with those producers in our states to come up with that basic data, so that is not an added burden on the company, and then we have to know what possible partnerships could we form to get a product manufactured, to maybe get out of some of those traditional ones that have been used that are in fact commodities, because they may not be the best thing to use for the particular diseases.

DR. LEIN: Thank you. Dr. Koong.

DR. KOONG: My answer to Question 3 is yes, but I would like to go even beyond that. The question was should CVM tailor its interpretation and application of quality standards in the regulation of drugs for minor use and minor species.

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What I would like to encourage CVM to do, to make a different statement, I think CVM should develop a different process and a quality standard in the regulation of drugs for minor use and minor species.

There is some conversation about that industry should take the lead, why they are not, because if you look at those industries, they see what is the quality standard, the hoops they are going through, and the potential market, 30,000 or \$100,000, they are not going to take that lead because any lead you take is an investment for their company, so I think I would suggest CVM take a proactive role, take the leadership role, first of all, to find out is there real need out there, and I think basically, my limited interaction with the State Department of Agriculture, at least in the State of Oregon, I think there is other states, too, Florida, I think some kind of an inquiry to the State Department of Agriculture, each state has a state veterinarian, they phase those issues constantly on the ground in terms of minor species.

We have llamas, emus, and all those things. I think they have the first, you know, underground feeling for the real needs out there, and they may have some good suggestion and come back to you for whatever the next steps should be. As far as that input, I think in the vet college

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or state veterinary extension specialists would be also a good source.

DR. LEIN: Thank you. Dr. Koritz.

DR. KORITZ: I agree, too, that certainly there should be a tailoring in the regulation of minor use drugs and for minor species, and so forth. Certainly there should be a consideration of food versus non-food animal. Human safety concerns, food safety concerns are certainly involved in that.

Economic importance to the producer groups certainly are a factor to be taken into consideration. I feel that CVM is in fact trying to do this very hard. Obviously, this is an area that I think it would be very difficult to write clear-cut decision trees as to how to proceed. It is an area where the best approach is simply open communication between the industry, the producer groups, the consumer, and FDA.

DR. LEIN: Thank you. Dr. Wolf.

DR. WOLF: I know this is going to begin to sound like the Department of Redundancy Department, but, yes, I agree that there should be tailoring. My main areas of emphasis, what factors should be considered include animal and human health safety, drug quality and cost to both producers and consumers of the drug, and I echo what the

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last two gentlemen have said about communication of needs from both the producers and the consumer side to work with the CVM on these issues.

DR. POUST: It sounds like the Center is doing a very fine job in working with the industry in tailoring the recent interpretations and I would encourage that that be continued. I think basically I am saying yes then to the first question.

The second question, I think the factors have been identified and I agree it would be difficult to put these in the form of a decision tree or a standard operating procedure with its inherent restrictions just by definition of a standard operating procedure, so I would again encourage the continued dialogue in working with industry in tailoring these interpretations.

As I mentioned this morning, there are many ways to comply with Good Manufacturing Practices. The what is well defined, but the how is not always well defined, and as long as the flexibility and the dialogue is continued, then, I think we will be successful in doing this.

DR. LEIN: Thank you. Dr. Floyd.

DR. FRANCIS-FLOYD: Well, I certainly concur that CVM should tailor its interpretation and application of quality standards and would encourage CVM to continue the

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excellent work that they are doing with the minor use species.

Some of the factors which have been mentioned, which impact the decision -- and that is more of a what than a how -- is availability of alternative approved products, availability of drug sponsors, and continuing to explore mechanisms of bringing new players to the table, availability of generic or commodity type products should be considered because perhaps some of the products would be of lower priority than products that don't have some sort of a generic alternative for a number of the reasons that were discussed.

DR. LEIN: Dr. Sterner.

DR. STERNER: If it ain't broke, don't fix it. It appears to me that, in fact, CVM is making very good progress. We have heard that from Dr. Lance and in the field and everybody here. That is very encouraging.

I think that it gets back to availability is still the issue here and I would say that with one proviso, and that is there needs to be some mechanism with regard to minor use approvals, that they don't wind up being misused under the provisions of AMDUCA.

If they are legally available and approved, the other side of that knife that cuts both ways is the fact I

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recognize there are colleagues who will see it as a license to do whatever they may very well please, and I guess that is where Gloria's office or shop comes into play and starts walking into some clinics and says we would like to take a careful look at your records, folks.

I think you need to be prepared to do that and if you are not, then, maybe you have to pull back on how easily and how quickly you do these approvals. As I said, with AMDUCA, there is a responsibility on our collective shoulders as practitioners, and I take that one very seriously, but I have colleagues who don't necessarily look at those as seriously, and they revolve primarily around the issue again of food animals and human food safety.

You know, I want to be able to use drugs intelligently, but the other side of it is I don't want to be painted with that very black brush when I have colleagues who misuse that AMDUCA license.

DR. LEIN: Dr. Barker.

DR. BARKER: Question 3 is similar to Question 1 and 2, in fact, that CVM is already doing much of what they are asking us to approve of. Certainly, CVM should continue to tailor its interpretation of applications of quality standards and regulation of drugs.

It has worked very well, and for the instances

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where we have minor uses of drugs for minor species, it is absolutely essential in being able to provide the drugs for use in the industry.

As far as what are the factors that most directly impact on the decision, those factors are the same that you use to address all drugs - they have to be safe and they have to be efficacious, they have to be of quality.

It is just that in dealing with the small output of drug, the number of batches that have to be manufactured, and the small number of animals, may actually be tested. You have to decide what are the minimum criteria that address those three major factors.

DR. LEIN: Ms. Duran.

MS. HUDSON-DURAN: Well, again, from what I have seen and heard is that I hear frustration from CVM about getting these products approved, and I was sitting here trying to think.

We are using some products now through sponsors who are veterinarians or some of them are Ph.D.'s and we might could come up with some ideas where we could get some funding or maybe stimulate some of the graduate students because I know we just looked at the Iowa manufacturing process, and I know Auburn University has an extensive amount of equipment, and that might be a possibility if they

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could get an INAD that some graduate students in pharmaceuticals could make 1,000 doses or 5,000 doses and actually do it through an INAD, so that the source is available.

At least we would know that a quality person, someone under supervision and someone who knows the standards are actually making those products. To me, that is much better than a pharmacist trying to compound something from a source that they are not sure when they order it how pure it is.

It may be that AVMA and some of these other organizations could set up some fellowships, because people who work in these graduate positions work very hard for a small amount of money, many of them less than 12- or \$15,000 a year.

I think that might be an avenue we could pursue, and they do have the expertise and the supervision.

DR. LEIN: Good. Dr. Ravis.

DR. RAVIS: I think anytime that you not necessarily have two sets of standards, but modify standards to accommodate a group that you probably have to clearly define what that group will be, will be minor use and probably there is a responsibility, both of the people that are manufacturing it or using these items to monitor its use

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and monitor how much of it is being used, and whether it is being used as intended. But I am in agreement about tailoring the guidelines.

DR. LEIN: Dr. Gerken.

DR. GERKEN: Well, I agree with the question. Again, I am positive for that, that CVM should tailor the quality standards for minor uses and minor species, and, of course, my interest, you know, is in minor use, minor species, the antidotes in many cases don't have a chance in any way, shape, or form, and I am thinking of not drugs, but chemicals that we would like to be able to use and we don't have a prayer in getting them approved unless we come up with some really innovative kinds of things, because even just obtaining the chemical is difficult, let alone going through "manufacturing," which is often just 100 cc's or 300 cc's.

We are talking about really small amounts, and quality control is not a really big issue when you can see that some animals survive and very few animals die from this. This is a matter of life and death with some of these antidotes, the molybdate being one of them.

So, I don't know how you solve that problem unless we can do some really innovative things. I think it is possible, but it is obtaining the chemical and being able to

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use it, and I don't know how to work that out, whether that can be sponsored by, you know, our specialty group and people, just as a labor of love, put their time in. You know, it is something we talk about, but there is really not -- I don't see any answer to that, and it is truly a minor species/minor use.

So, I don't come away from this discussion very happy about where we are going in that particular area.

DR. LEIN: Dr. Cooper.

DR. COOPER: My answer to Question 2 would be yes. I would like to commend CVM for its demonstrated willingness to listen to groups that have alternative uses for drugs in minor species.

In listening to the discussions, I think one of the things that comes to my mind is that CVM and the drug industry cannot be all things to all people, and one of the things that I know is that there is an increasing number of minor species for a number of reasons that are being used, and even though you have regulations that show a great deal of flexibility, I think there are some things that are really beyond your control. There are some things that you just cannot do.

What kind of incentives can we establish, so that there is as greater responsiveness, I think that is the real

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question. The minute the drug companies look at the bottom line, I think there has to be some compassion or willingness to assume some risk.

There has to really be a way of engaging the broader community of minor species, so that priorities can be set and to really communicate the fact that you can't be all things to all people. There will be some issues that you can respond to satisfactorily, there will be some issues that I think the drug companies will show willingness to respond to, but I think now how you go through the process of identifying priorities that really make a difference, it is a real question.

So, I commend you for listening. I recognize that this is a very tough job because you can't do all things and that show that you are responding positively to the questions, but I think over time maybe there is a way that we can respond.

There are certainly opportunities that have been described today of looking at Departments of Agriculture. There may be partnerships that could be formed with other federal agencies that would be sensitive and allow you to expedite the review of the approval process for minor use in minor species.

So, I think you have made a big step forward now

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to show that you are willing to join hands with those individuals who have an interest in minor use and minor species applications, and I commend you for that and recognize, too, that you have a very difficult job ahead because there are some things that go beyond the scope of the agency.

So, I say yes and give you some encouragement realizing it is a difficult job.

DR. LEIN: Dr. Kemp.

DR. KEMP: My answer to Question No. 3 is yes, but strongly encourage you to stay as close to established quality standards as possible. In situations where you have a product that is not up to the general quality that is so indicated on the label or the extension of the label that we call the insert, so we will know it seems to be a recurring theme here.

As far as factors, I include safety as an obvious factor, cost, drug availability. Other factors might be quality standard for the product should be tailored to the approved use of the drug in an "appropriate manner." I don't think that over the years you talked about safety in terms of use. I don't think every use requires the same standard.

In addition to that, as Keith has mentioned, I

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think you also need to consider the potential extra-label use of the drug because we all know it is going to take place, somebody is going to take that cheap, low standard drug and they are going to apply it to some other use, and some of it will be in animals and some of it is going to be in people. That is just a fact of what I see out there.

The Orphan Drug Act is human, human drugs on it, and later has a standard of a potential market of 200,000 human patients in the country, and apply that over to an animal setting is acute, if you are talking in terms of goats. You know, 200,000 goats is a pretty good bit of the goat population. You could have 200,000 catfish in one operation. Try and define that criteria to actually apply this minor use to minor species across the board is going to be very tough.

It seems that everything that is driving this so far has been money, and perhaps the dollar volume, the estimated dollar return on the market might be what you have to look at. How you get ahold of that, I don't know. That is going to be extremely difficult. I suspect you are going to have to go in that direction.

DR. LEIN: Again, it looks like everyone is pretty well in agreement or unanimously in agreement that it is yes to No. 3 question, that certainly we give great applause to

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CVM and what they have done so far with minor use and minor species.

I think all of us agree that the standards should remain high from the standpoint of quality and efficacy and food safety, and all the things we have gone through with the first two questions.

I think there could be some good example setting here, and we ought to do more, whether it is through CVM and through FDA updates and news, whether it is through AVMA, whether it is through other journals of these minor species to bring out the good things that maybe Dr. Lance has done as an example, what Dr. Floyd has talked about, because I think example setting is going to be important for people to get an idea of where to move to, so we ought to be saying more about that.

One of the things that certainly came up with this Partnership with Industry Program that Dr. Lance spoke about in his letter, and that should be promoted, I think, more as something that certainly CVM is doing. So often CVM gets the black note basically, frequently from us, and I think this has a lot of kudos for them for working with industry.

I think the important thing here, too, is that we have these FDA-approved drugs. We said that before for any use. It would be better if we had an approved drug, and

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they are going to be used extra-labelly anyway.

If we don't have approved drugs and know something about mechanism, know something about pharmacodynamics, pharmacokinetics, residue levels, then, we are really working in the dark, and the more science we can get to any of this with approved drugs, the better we are going to be in at least working with these minor species and also using them extralabelly, because we are going to be able to take what we have a knowledge there, and apply it to at least a species that is close to it.

So, I think it benefits all of us if we can get approved drugs in this minor species situation. Again, I think we should continue to look at the Orphan Drug human situation where even with very small quantities, if at least CVM is involved and the data can be collected, it is doing more than not collecting that data.

So, I think that is an important situation that we can utilize it, get benefit, and still collect data in that situation. So, it is something that we ought to be working more with, and certainly universities, ag departments, the species groups themselves, as the Wildlife Group has done, should all be looking at how they could be a major player in this and work with it, and maybe you will even influence some drug companies to become secondary players in this with

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their products.

It certainly appears that Bayer has done that for you in part with insecticides or pesticides.

I think we all agree that should move forward and that we should be giving a lot of credit to CVM for what they have done.

I think that brings us to the end of the program for today. We are going to start at 8:30 tomorrow morning again. It is amazing how we have filled the time allotment. I thought we were going to get done earlier, but give us the time and we will fill it. So, it is like any void, where there is a vacuum we tend to slide into it.

Have a good evening and we will see you tomorrow morning at 8:30.

[Whereupon, at 4:50 p.m., the meeting was recessed, to be resumed at 8:30 a.m., Thursday, November 13, 1997.]