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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

FDA PUBLIC MEETING

DRAFT GUIDANCE FOR INDUSTRY

DEVELOPING MEDICAL IMAGING

DRUGS AND BIOLOGICS

Friday, March 26, 1999

8:37 a.m.

Room 1066

MILLER REPORTING COMPANY, INC.
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P A R T I C I P A N T S

MICAA

Len Baum, Advanced Magnetics (Blinded Reads)
Gordon Brandt, M.D., Sonus
Mark Carvlin, Bracco Diagnostics
Robert Morgan, DuPont Pharmaceuticals
Richard White, Alpine Group

CORAR

Alan Kirschenbaum, Hymen Phelps
Robert Morgan, DuPont Pharmaceuticals
Adrian Nunn, Bracco Research

Marty Rosenberg, M.D., DuPont Pharmaceuticals
Robert Siegler, DuPont Pharmaceuticals, American Society of Nuclear Cardiology
Richard White, Alpine Group

CBER

Sharon Risso
Rebecca Devine
George Mills
Mark Brunswick
Steve Falter
Bette Goldman
Betty Shaw

CDER

Jane Axelrad
Patricia Love
Victor Raczkowski
Brian Pendleton
Robert K. Leedham

CDRH

Don Thompson

OC

David Horowtiz

Joseph DeGeorge, Ph.D.

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David Lee, Ph.D.

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P R O C E E D I N G S

DR. LOVE: Good morning. My name is Patricia Love, Director, Division of Medical Imaging, Radiopharmaceutical Drug Products, as I suspect most everyone knows since I recognize a number of persons in the audience. I'd like to welcome you to today's meeting. This is our second working meeting on the draft guidance for industry on developing medical imaging drugs and biologics.

As you know, we had a first meeting with CORAR, Council of Radionuclides and Radiopharmaceuticals in January of this year, and now this meeting is a working mg with representatives of CORAR and MICAA, the Medical Imaging Contrast Agent Association. I would like to welcome you here.

Just a couple of words on logistics for those who are in the audience observing. This is considered a working meeting, and we're allowed to do this in a public forum based on the public announcement on the Web site. We will be working with the representatives as selected by the two organizations, but there will be other opportunities for persons to come to the microphone and present other issues as the day goes on, and we would welcome that, and that will be fine.

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Also, other logistical issues. There are restrooms and a vending machine across the hallway, and telephones, and if anyone has any questions, please see Betty Shaw. She is sitting at the sign-in table, and she will be able to assist you in any way.

Also, as a working meeting, we're still in the process. I'll make a few other comments later on when we get to the beginning of our agenda topics, but this is an ongoing process of dialogue to determine what's going to be the final conclusions on the guidance itself, and the comment period is still open at this point until April 14th. So this is a process step.

At that point, I'd like to perhaps suggest that we go around the table just to introduce ourselves, and then we can have other opening comments from CORAR and MICAA. Thank you.

MS. AXELRAD: Jane Axelrad, Associate Director for Policy in the Center for Drug Evaluation and Research.

DR. RACZKOWSKI: I'm Victor Raczkowski, Deputy Director in Office of Drug Evaluation III.

DR. MILLS: George Mills from the Center for Biologics.

MR. BRUNSWICK: Mark Brunswick, Center for Biologics.

MR. CARPENTER: Alan Carpenter from DuPont Medical Imaging R&D.

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MR. SIEGLER: Bob Siegler from DuPont Medical Imaging R&D.

MR. NUNN: Adrian Nunn from Bracco Research.

MR. MORGAN: Bob Morgan from DuPont Pharmaceuticals, representing CORAR.

MR. CARVLIN: Good morning. I'm Mark Carvlin, representing the Medical Imaging Contrast Agent Association.

MR. KIRSCHENBAUM: Alan Kirschenbaum with Hymen, Phelps and McNamara. We're outside counsel to CORAR.

MR. WHITE: Richard White with the Alpine Group, consultant to CORAR and MICAA.

DR. LOVE: Thank you. Please, go ahead.

MR. MORGAN: Again, Bob Morgan from CORAR. On behalf of CORAR, I want to take this opportunity to thank the FDA for the opportunity to have this public meeting and continue our work on something that started, at least for CORAR, about four years ago. We've made some tremendous strides forward in getting to this point, and we think it's commendable the way that industry and FDA has worked together. And I just wanted to take this opportunity to express our gratitude for being involved in this process.

Also, just for a point of clarification, CORAR representation today is from the Subcommittee on Health Care, which is made up of Nycomed Amersham, Melancrot(ph),

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Bracco, MDS Norian (ph), and DuPont Pharmaceuticals. So the comments that you will hear coming from CORAR are coming from this subcommittee, and our comments represent a general consensus statement, though there will be particular points in our comments where individual companies may disagree somewhat or have a slightly different view than the general comments that we're making today, and they have been asked to step up to the microphone and point out where differences may exist to the general comments that we're making this morning.

MR. CARVLIN: Mark Carvlin, Medical Imaging Contrast Agent Association. Good morning, and let me add my thanks and acknowledgment to FDA for what we've enjoyed up to this point, which is productive and cooperative interaction. And what I'd like to do is take just a few minutes to introduce the Medical Imaging Contrast Agent Association and touch upon briefly what we think are the major points which differentiate diagnostic pharmaceuticals from their therapeutic counterparts. So I'm going to approach the slide projector. One moment, please.

DR. LOVE: There is a portable microphone on the podium there.

MR. CARVLIN: Are you picking this up all right? Great.

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Thank you.

Once more, I am Mark Carvlin, representing the Medical Imaging Contrast Agent Association group. We are a recently formed coalition which represents about 90-plus percent of the companies involved with the research, discover, development, manufacturing, distribution, sales, and marketing of in vivo diagnostic pharmaceuticals here in the United States. This group was formed, first came together as a concept in December of 1998, and we've recently been incorporated, so we are a true legal entity and we have bylaws and elected officers. And I'm appearing here today as the Secretary-Treasurer for the Medical Imaging Contrast Agent Association, which I'll just refer to by its acronym MICAA in the future.

Our number one objective, our mandate as a group, is education, and it is our mission to make clear the properties and the unique clinical usefulness of in vivo diagnostic pharmaceuticals.

What are these products? These contrast drug products and radiopharmaceuticals are drugs that are used for diagnosis and monitoring in vivo, as emphasized in the guidance document. And, typically, these relate to specific medical imaging modalities such as X-ray in the case of iodinated

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compounds, nuclear medicine that has radionuclides with ligands and carriers, from magnetic resonance imaging, paramagnetic metal ions in a number of different forms, and finally in ultrasound we have a growing number of micro bubbles, micro aerosomes, and related particles that are used for altering the in vivo appearance of an ultrasound image.

FDA has worked very diligently to provide, in draft, guidance for industry with developing medical imaging drug products and biologics. And specific points raised in the guidance are that medical imaging drugs are generally governed by the same regulations as are other drugs and biologic products. However, as described in the guidance, many medical imagine drugs have special characteristics and help guide developmental efforts. The guidance document discusses some of these special characteristics and how drug development for medical imaging drugs can be tailored to reflect those characteristics. We'll spend the balance of today talking about those special characteristics and how that can guide developmental efforts.

What are those special characteristics? In short, I think it's important for us to emphasize that for diagnostic pharmaceuticals, physics and physical chemistry are almost

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as important as biology and biochemistry, which is distinctly different from therapeutic pharmaceuticals.

We have small mass doses. Typically, the diagnostic pharmaceuticals are administered one time or perhaps a limited number of times. It's unlikely that you would have a contrasting magnetic resonance image examination every day for the balance of your life, or a CT or an ultrasound.

And, also, these products are rapidly eliminated, most of them without metabolism, and there is near complete elimination within 24 hours.

Also, the clinical usefulness of in vivo diagnostic pharmaceuticals is not necessarily directly related to the drug's effects in vivo, and that's because they do have an effect on a medical image.

So how do these special characteristics impact on our development efforts? Well, first of all, medical imaging drugs do not have clinical utility in vacuole, as I said. Their utility is related to the medical imaging modality. And truly one of the successes in medicine in the 20th century--and we look forward to that in the 21st century--is medical imaging, as gauged here by the number of Nobel Prize laureates who earned their accolades in conjunction with their discoveries in medical imaging. So our diagnostic

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pharmaceuticals, medical imaging drug products and biologics, are directly related to these scientific efforts. How else are we different in medical imaging drugs and biologics? Well, I think that we can certainly lay claim to the greatest amount of chemical diversity among any pharmaceutical category. And you can see here with our periodic chart colored differently depending on whether these elements were used for X-ray, for magnetic resonance imaging, for nuclear medicine, or ultrasound, or in some instances for multiple modalities, that we have thoroughly mined the available materials as we look to bring in new products. So we're chemically diverse and our development is related to a physical modality.

What is the consequence for us as a regulated industry? The consequence I think is best shown here, and that is, the speed of discovery is remarkably brisk. And the way that I have captured this here is to compare how long a time period elapsed between the time that a seminal insight was gained in a medical discipline and the time when it was reduced to practice as a pharmaceutical.

If we take a look at antibiotics, it took nearly 260 years from the time that Anton van Leeuwenhoek looked in his microscope and identified bacteria to the time where we

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first had a pharmaceutical.

Antineoplastics, a little bit faster, 170 years, roughly, from Percival Potts and his observing of chimney sweeps and testicular cancer, to the introduction of nitrogen mustard; whereas, for in vivo diagnostic pharmaceuticals, it was a brisk six weeks. And here we see that we have chemical diversity and modality converging to make a very, very rapid cycle of innovation. And this poses special challenges to the regulated industry, to those who promulgate regulations, and to those of us who are bound by those regulations.

Other special characteristics with medical imaging drugs. As we said earlier, the mass dose ranges for medical imaging drugs are dramatically different from what you see for many therapeutic pharmaceuticals, and what I've done here is to highlight in yellow the active substance for representative medical imaging drug products on a modality basis. Nuclear, the technetium 99 complex is present in nanogram amounts. Also, in a typical formulation, you would have ligand or carrier in the range of 0.01 to 10 milligrams. Ultrasound, the active component is a gas, depending on dose and product that can range anywhere between 0.2 and 2 milligrams. For magnetic resonance, we raise up to 2 to 12 grams, and X-ray with iodinated moieties up to 150 grams of the active is

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administered.

Again, for each one of these modalities, we have different developmental challenges, and we'll be stressing that in our discussions with you through the balance of the day where we see dramatic differences and similarities amongst the diagnostic pharmaceuticals in cells, and to anticipate some of the later comments, just emphasize that the amount of the active component provided for nuclear medicine, ultrasound, is several orders of magnitude, almost six orders--three to six orders of magnitude less than what we see in MRI and X-ray.

Similarly, the elimination characteristics are dramatically different for the in vivo diagnostic pharmaceuticals. For the nuclear medicine products, 100 percent elimination, but here we have special properties at work in that we both have a physical as well as a biological half-life. Ultrasound, the elimination, nearly 100 percent, very challenging to document because of the minute quantities that are administered and the T-1 half-year is on the order of minutes. For magnetic resonance and for X-ray, similarly, within 24 hours we get almost 100 percent quantitative elimination of the drug substance and the drug product.

So how can we work together and what is our objective as an

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industry group? Well, I think it's captured here well in a paraphrasing of a notice that recently appeared in the Federal Register. It was in relation to a discussion about stakeholders. It is crucial that FDA, in collaboration with product sponsors, develop a shared understanding of new science and technologies and their effect throughout a product's life span. And we are asked several questions, questions that we need to answer in cooperation with FDA. What actions do you propose the agency take to expand FDA's capability to incorporate state-of-the-art science into its risk-based decisionmaking? Also, what actions do you propose to facilitate the exchange and integration of scientific information to better enable FDA to meet its public health responsibilities through a product's life? Well, several thoughts I would like to offer as MICAA to address these questions are the following: That is, we wish to emphasize that many of the properties--the physical, the chemical, the biological, and the pharmacologic properties of medical imaging drug products--are distinctly different from the therapeutic pharmaceuticals. Also, the manner in which medical imaging drug products are used by physicians and the benefits to patients are distinctly different from those therapeutic pharmaceuticals.

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MICAA believes that these differences are so significant that it is not always correct to apply to medical imaging drug products the same or similar measures of safety and efficacy as are typically used for therapeutic pharmaceuticals. And we are interested in working with FDA to define what measures of safety and efficacy are most appropriately applied to medical imaging drug products. One of the greatest challenges that we face in developing medical imaging drugs is our ability to accurately measure the potential benefits of the use of the products, and in part, this difficulty is due to the fact that the clinical usefulness of medical imaging drug products is primarily based upon qualitative rather than quantitative effects. And certain critical features in the medical image or medical imaging examination appear differently as a consequence of the drug's use. The clinical usefulness of the medical imaging drug is represented by the information its use provides is dependent upon the medical imaging equipment and the methods, the data acquisition, and it's critically dependent upon the medical imaging specialist who performs the examination and, finally, upon the medical imaging specialist who interprets the results of the examination.

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This means that even though the potential benefits of use of a medical imaging drug can be quite high, the actual benefits derived are dependent on the least clinically useful element in the medical imaging interpretation chain. Similarly, the potential risks are both objective--that is, related to administration of the drug--and subjective in nature--the risk of incorrect diagnosis.

So, in summary, MICAA asserts that all approved medical imaging drugs provide additional diagnostic information. The quality and the quantity of this information depends on the properties of the agents as well as the physiology and pathophysiology of the tissues being imaged.

However, the impact that this information has upon appropriateness of patient management, beneficial clinical outcome, and the provision of accurate prognostic information is largely independent of these intrinsic factors. The impact of additional diagnostic information can vary from negligible to profound, depending on the role of medical imaging in patient management and the options that are available.

Applying criteria that have been first elaborated for therapeutic pharmaceuticals to assess the clinical usefulness of a medical imaging drug places an extra burden

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on the entire class of these products.

Thank you very much.

DR. LOVE: Thank you.

MR. WHITE: I just want to make it known that we'll provide all of our slides and handouts tomorrow to the FDA.

DR. LOVE: Thank you very much.

Are there any questions or comments for Dr. Carvlin before we get started?

[No response.]

DR. LOVE: Thank you.

Good morning. Thank you. I enjoyed your comments, Dr. Carvlin, and look forward to a number of discussion points. You made a few things that I was about to say a little bit easier, so I am going to modify a little bit as I go along here.

We certainly agree with you that diagnostic products have a number of issues in their development that are unique in respect to therapeutic products, and we are hoping that we're all moving towards finding how to describe those things in guidance and to address them.

Since there are a number of people here today that were not at the first meeting, I thought I would just take a few moments to go back over very, very briefly some of the

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history that got us to where we are today. As you know, there was a lot of informal dialogue several years ago. There were meetings with the Medical Imaging Drug Advisory Committee. There are issues that affect the guidance that are derived from Section 122, particularly in FDAMA, that has to do with radiopharmaceuticals and developing approaches for them. There are also some issues in PET that we're thinking about, but we have not determined yet exactly how the guidance is going to affect the PET product, and that will be addressed in the approaches that are being developed for PET radiopharmaceuticals themselves. That's from Section 121 of FDAMA.

The guidance itself, as you know, was issued in October of 1998, and the comment period has been extended twice, but we think that this is very important to do so because of the type of dialogue that we're going to have today and the other comments that are coming in. And as you know, at the moment the period closes on April 14th, and these, of course, are just the lists of the two meetings, the one in January and today.

I wanted to just briefly mention a couple of key points that came out from the last meeting that are going to be certainly reheard as we go along today. One is, of course,

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the issue of the Group 1 radiopharmaceuticals and the points that you raised in your comment about both radiopharmaceuticals and possibly ultrasound products and how they might be considered in that, but also we'd like to hear about the other products as well. There may be other safety issues unrelated to mass, unrelated to half-life that would be relevant to determining whether or not a product is appropriate for consideration into Group 1, and we want to talk about that today; and, also, of course, blinded read. We'll come more to that in a moment.

Also, in preparation for today's meeting, the agency has received written comments and questions from both CORAR and MICAA, and we will try to address those as we go along. So that leads me then to a couple of format issues for the meeting today.

There are several topics listed on your agenda, and each of them begins with an update from FDA. What we're going to try to do in each section as we go along is to have an update section which goes over the questions, the written questions that have been presented. But the things that you presented as proposals we will not comment on those directly until we hear from you and hear the proposal, and then we'll respond and dialogue, because there's more information that

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we would like to hear as we go along with that.

Also, at the end of each one of the topics after our dialogue, then we will stop and open the floor to more spontaneous comments from those in the audience.

Okay. So then let's go on with the agenda unless there are any other questions or comments in relationship to the format.

Okay. Group 1, there will be this update, then some comments from CORAR, followed by comments from MICAA.

One of the concerns to us as we listened to the last meeting was that we're coming at this from different approaches, perhaps. We're all agreeing that there's a Group 1 and that there's a consequence to Group 1, and that is that the level of testing and clinical trials will be decreased, but how we're getting there may be a little bit different. So I wanted to spend just a moment on some of our thinking at the time we were developing the approach to Group 1. And we heard from you last time. I think we just need to talk a little bit more about it. This will help us in our deliberations as we move towards actually finalizing the guidance.

We were looking at Group 1 as a set of products where the safety profile that you've suggested was defined and

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justified by the data that's coming in, and the drug is justified and documented with some data to show that it has a low-risk profile and that it, as I said, would lead to this minimized safety testing in Phase 2 and 3.

We felt that that would be derived from a collective data set that was based on the animal data confirmed in Phase 1 with human PK and safety data, and that the Group 1 would be designated at the end of Phase 1.

Based on a lot of the discussions at the last meeting and other comments that we've received subsequent, there has been a request for us to clarify some type of designation process, what would you need to go through in order to get into Group 1.

We're still thinking about this, but it seems that some approach which would involve a summarization of the type of data that you have as you normally would before you go into Phase 1 and start the first studies in humans, along with an assessment at the end of Phase 1. So there may be a preliminary designation of a Group 1 product at the time the studies are beginning, just before the first dose is introduced into humans, and then confirmation of that, and some type of written request from the sponsors as well as a written response from us as far as Group 1. This is still

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under development, and we haven't really thought about it. I would point out that a number of the comments that I'm making, wherein because of good guidance practices, we are--and because we are still in a deliberation process and we're actually still in an open comment phase, we can't say for sure exactly what our final conclusions are going to be, but I'm trying to share our thinking.

As I mentioned, approaches may have been a little bit different, but also during the dialogue last time it was clear that there are some inconsistencies or perhaps some areas in the guidance that will need some clarification, and that has to do with the sections that not only describe Group 1 and Group 2 but also the ones that--there was another section that talked about the timing of certain pharmacologic studies in relation to Phase 1, 2, and 3, and we will seek to clarify that.

This next slide has perhaps the heart of a number of the discussions that took place last time. There were several key areas in developing the entry criteria for Group 1 that were under discussion. That was the dose multiple, whether or not there should be some focus on the length of time it takes for a product to be excreted, and the comments that were just made about the use frequency and then what types

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of studies should be done in animal models, one or two species, and then in the human Phase 1 study whether for radiopharmaceuticals there should be just follow-up of the radioactivity. And, of course, there was a difference in this dose multiple.

We've done a lot of thinking about this, and we're still in a thinking process, but wanted to share at least where we feel we are at this point in time. Number one, we do agree that some decrease in the dose multiple could be justified. Exactly whether it's going to be down to 1 to 125 or not at this point is not clear, but we feel that and intend to decrease the dose multiple.

As we go along today, we'd like to hear a little bit more discussion on the NOUEL, the no observed unexpected effects level. It seems that it possibly would have a consequence on that final phase of what's the clinical testing that would be done or not done. So we need a little bit more dialogue about that.

As far as the half-life, again, if we focus on radiopharmaceuticals, we think we understand some of the concerns or goals that you had in moving towards a less than 24-hour elimination half-life. But on the other hand, it seems that it might just be a little restrictive. There may

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very well be products that have a longer elimination half-life that are equally as safe. So we'd like to talk about that a bit, and understand whether that 24 hours is perhaps relating to your other recommendations on the clinical testing for clinical monitoring within a 24-hour period or is there some other thinking that's going on there, driving that particular recommendation. So we'd like a little discussion about that.

As far as the frequency of use, yes, it makes good sense that the actual intended use of the product, particularly if you're giving more than one dose for the purpose of the diagnostic study, then that's important and that would be considered in this process.

These two issues about whether or not the repeat dose is given within 10 times the mass half-life or within--or if the dose repeat--total mass is less than 2 percent of the therapeutic compound, we looked at those more as discussion points, things to think about or examples. But when you start to get very specific about it and start to do the dose multiples and the half-life and do calculations, then some of these can come right up to basic repeat dose, standard repeat dose kinds of criteria that have been discussed in ICH. So I'm not sure and I'd like to ask whether or not you

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were really intending this to be one of the Group 1 entry criteria or is this just an example that was being given. As far as expanded acute and repeat dose studies and the rest of these, these are things that we probably could address in waivers and describe certain conditions in which sometimes one study might be appropriate, sometimes two might be needed. A lot of that is going to depend upon the drug, its mechanism of action, the potency of the product, and a number of other related issues, because low mass may suggest safety, but also if it's a very potent product, then the low mass issue begins to go away or justification begins to go away. So there certainly may be situations where one study could be justified. Also this repeat dose study from our perspective provides more information than just issues about accumulation f dose.

The single dose expanded acute study tells you whether or not you will have an insult to a target organ on the basis of one large dose of drug. And it's also useful in determining what the starting dose would be. The repeat dose study provides information on the targeted organ sensitivity, gives us some suggestion about perhaps a certain subpopulation maybe more at risk and that might not be detected or suggested by an expanded acute study. So in

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single dose studies--or single dose drugs, this repeat dose study gives us other information to identify target organs that would be following during the initial safety studies in humans.

But on the other hand, there may be some information that you might have in certain situations that comes from other sources, other use of the drug, other information that you might have from in vitro testing, other information that you would have from just the basic selection of this drug, its physics, its chemistry, biology, or pharmacology, that could come into play here and help us in making some of these assessments on an individual drug basis. So waivers might be appropriate.

The same is true for species. There are certain species differences, so if you select one species, our question to you would be what information would you be providing that would suggest that that species is the most appropriate species to predict the outcome in humans. And, again, that would come from other preclinical work that you would be doing in the drug development process. So those are things that might be able to assist us in this area.

As far as radioactivity only, again, there may be some situations where this could be justified on the basis of

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other existing data, as I was just talking about, in vitro studies. You're suggesting that many products are not metabolized, so what data are available just to show that the product is not metabolized? Those would be the kinds of things that would be submitted to justify your Group 1 and the fact that you would only need radioactivity follow-up only.

On the other hand, I think you asked us a question about assay limits of detection, and you suggested or asked specifically whether 1 to 100th or one-tenth of the administered dose would be a reasonable justification for not pursuing a metabolic speciation of a product. That might be, but I think you'd really need to talk--go further into issues about what's the total limit of detection of the assay that you're using, not just looking at one-tenth or one-hundredth of an administered dose. The issue is much more complex. I think your question to us we take as what would be an appropriate approach to justify a limit of detection that prevents you from being able to do speciation. I think that would be an approach we would favor more, so just some data, specific data that you have from your assay model, what have you done to test and put controls in there to show what your actual limit of

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detection might be, thinking about other things in terms of total volume of dilution of the drug when administered to the body or whether you're testing it in urine, what would the dilution be, and then giving us more details to justify what you might do there.

Moving on, the other question, of course, then, is: What does this all mean when you get to the clinical Phase 2 and 3 studies? To some extent, it's a little hard for us to say that because we're still in an ongoing dialogue about what are the different pieces that will come from this particular puzzle and how are they going to relate. And I think part of what we have to do is sort out exactly what this means. Are we going to a very specific category, you're either in or out on the basis of a very precise set of data? Or is there going to be some flexibility from this data set that allows us to make some of these other assessments? How would we consider alternative information if it's not from one of those studies?

A lot of that is what we're thinking about in terms of what's the final definition and what's it going to mean. Our assumption from our dialogue from last time is that you would like to have a very clear set of information, clear set of criteria. This is what gets Group 1. If you meet

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those criteria, this is what the consequence is. If you do not meet the criteria, then it's Group 2.

Having said that, we would be moving towards finalizing that definition and coming up with the clinical monitoring. To some extent, it's not clearly exactly what it's going to be. We need to talk about whether it's really a 24-hour monitoring on the basis of a half-life. If the half-life is going to be one of the criteria as talked about here, then that might be reasonable. If it's not, then we would have to think about some type of multiple of the half-life and use that as a target perhaps for the length of monitoring.

Also, to some extent, depending upon what comes out of the safety pharmacology studies or not, there may need to be some monitoring just specifically targeted to the mechanism of action of the drug. So let's say that the drug affected calcium channels, then we would certainly want comprehensive monitoring of the EKG, but perhaps not other things so comprehensively. So that's along the lines of our thoughts at this moment in time, and we'll be listening to you as the day goes on.

I also just wanted to summarize the questions that I was mentioning as we went through this. We're interested in some more comment on the rationale and intent, how you plan

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to use the NOUEL, and some clarity on the half-life issues, both in relationship to the entry criteria and whether the half-life for the 24-hour monitoring, is this half-life of the radioactivity only, is this half-life of the biologic effect, how are you considering both of those.

That concludes my comments now for this, and if you have some questions, I'll take them. Otherwise, we can go into your presentations.

MR. KIRSCHENBAUM: Are your slides available?

DR. LOVE: Yes.

MR. NUNN: Okay. I promise not to be as wordy or as long-winded as last time.

How do you use our proposed NOUEL criteria? The guidance document proposes that the nonclinical dose from which the margin of safety for the clinical dose should be calculated should be with the no observable effect level. This implies, to us at least, that any observed effect is a safety issue. We believe that this is not so and anticipate that there may be a variety of effects in different classes that may be observed but which would not be relevant from the safety point of view, i.e., they would represent a low risk and should not be used to calculate the clinical dose for Group 1 membership purposes.

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For instance, transient taste perversions is a not uncommon effect after administration of a metal-binding compound, yet it hasn't been classified as a safety issue when it comes to high risk. Transient changes in the production of body fluids, such as saliva or tears, might also be such an event. Drowsiness is a common feature of decongestant but is not a safety issue per se, a life-threatening or serious one. Or pain at the injection site from--you know, you pick up a blunt needle or something, I mean, does that really--do you really consider that that is something that should exclude a compound from being Group 1?

So, in general, there may be pharmacological effects resulting from the administration of radiolabeled pharmacophore that are present at low dose but for which the dose response profile is shallow and well defined, and thus, they do not represent a safety issue.

Now, to accommodate the possible occurrence of effects that are not relevant safety issues, the last time we suggested the use of the NOUEL, or no observable unexpected effects level. So this is designed to encompass all those biological effects that may be produced by the drug but for which there are no safety consequences. And when I say safety consequences, I'm talking about high risk.

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However, it might be better to use an acronym that is already in use in the therapeutic field, which is the no observed adverse effect level, the NOAEL. No matter what the acronym is, CORAR feels that it's reasonable to accept that there are some expected observable effects that do not represent a high or unknown risk and which should not be used to set the clinical dose to minimal toxic dose threshold and, therefore, Group 1 membership.

Turning to what the threshold should be, there is already in the literature an accepted norm for the relationship between the NOAEL and the upper band for initial clinical dose for a Phase 1 clinical trial for a therapeutic drug. And this has an impeccable source. Consideration for toxicology in studies of spr-(?) drug product by, it looks like, half of the FDA--but, anyway, this article states that the upper bound for the initial dose for a Phase 1 clinical trial in generally a fraction of the NOAEL in animals.

Traditionally, this fraction has been calculated to be less than one-tenth the NOAEL in rats or one-sixty the NOAEL in dogs. Generally, a smaller safety factor is appropriate for comparisons based upon body surface area, and that's what we normally do, and with fi-(?) that means you divide by seven for rats. And when animal toxicity is reversible and

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readily monitored in humans, escalation to doses above the animal NOAEL may be acceptable. These are direct quotes from the paper.

Now, our past experience with radiopharmaceuticals has been that little or no biological response in animals is detected at doses up to about 50 to 100 times the human dose. Based upon this evidence, CORAR believes that to be included in Group 1, the NOAEL--not the NOUEL--as appropriately adjusted in suitable animal species should or could be about five times the maximum dose and doses to be used in the initial human studies. So for going into Phase 1, it would appear, based upon therapeutic norms which are already out there, that we could go down to about one-fifth of the NOAEL.

For continuation in Group 1, there should be no significant adverse events in the clinical trials, of course, and there should be a demonstration in animals that the human dose--you know, perhaps we shouldn't go as low as one-fifth, but, you know, 25 times less or something like that.

Now, I can see the vultures already gathering--

[Laughter.]

MR. NUNN: So let me just finish this last one. So assuming the acceptance of the idea that there are some expected observable effects that do not represent a high or unknown

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risk and which should not be used to set the clinical dose to a minimal toxic dose threshold, we need to define what the characteristics of those effects might be. And this can be done either by exclusion--it's not something that is a clinically adverse or serious adverse event from the MedORA terminology, or by inclusion, events such as taste perversion, transient dryness, dry mouth, et cetera. So what we're saying is every event you get--and we know we have to record lots of events--is not a high-risk event, and we need to define somehow, either by inclusion or exclusion, what those events are.

DR. LOVE: Just before we go to the specific questions, could you put back the first slide just to make sure we understand your proposal? The preceding one.

MR. NUNN: This one here?

DR. LOVE: Yes.

MR. NUNN: Just the bottom?

DR. LOVE: Right, just the bottom.

So you're saying Group 1 entry then is based upon one-fifth of the maximal human dose, the NOAEL is one-fifth of the maximal human dose to start, and then to continue--

MR. NUNN: You'd obviously have to have no significant adverse events.

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DR. LOVE: Right, but the second--the end of that sentence says there's a demonstration--so you're doing two things? You're looking at a one-fifth and a one-twenty-fifth?

MR. NUNN: Well, based upon the literature data, it seems that the therapeutic people allow in some instances to go into Phase 1 with an even smaller multiple than we were considering.

DR. LOVE: I understand, but before I go to that, I just want to make sure I understand this. So to start in Group 1, it's a one-fifth multiple, and to continue in Group 1, meaning by the time you get into Phase 2 and 3 you would also have to have a one-twenty-fifth multiple, is that what these two sentences are saying?

MR. NUNN: What I'm thinking of is the diagnostic index. Commercially, I would obviously be uncomfortable myself if I had a very small diagnostic index and wanted to go all the way through with, you know, next to no testing, obviously. And so I think this is an acknowledgment, but I think that if you want to continue with reduced studies, then you might need a higher one. But to get in--and if you then have no human adverse events at all, then it seems that you should be able to continue.

DR. LOVE: So Group 1 to start is one to one-fifth. To

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continue, it's a combination of absence of adverse events in Phase 1 and a one-twenty-fifth multiple--

MR. NUNN: Or something like that, yes.

DR. DeGEORGE: I think, since my name featured prominently on the list up there, I need to make some comments about this.

DR. LOVE: Can you introduce yourself?

DR. DeGEORGE: Joseph DeGeorge, Associate Director for Pharmacology, Toxicology, Office of Review Management. Before I actually address that, I want to point out one thing. I think if we're talking about blunt needle trauma, presumably that isn't occurring. Hopefully you're using nice needles for animal welfare purposes, and, in fact, one would expect if it did occur, it would occur randomly and would not be associated with the chemical. So that clearly is not a confounding factor for a no adverse effect level or a no effect level, for that matter.

The issue of the adverse effect level versus the no effect level, clearly there are some expectations of pharmacologic activity for some pharmaceuticals, but even those can be considered adverse effects if such that one might believe they would proceed to be an adverse event in human if occurring at a greater level. For example, hypotension, a

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slight lowering of blood pressure, may not be a problem, but if you cause severe hypotension, that can, in fact, be an adverse effect. So, clearly, even in that range where we would accept some change and call it a no adverse effect level, there's a qualitative assessment of that as well.

In terms of the numbers you put up here for starting doses and uses of NOAEL, this is actually designed for therapeutics where, in fact, the dose selection is based on repeat dose testing in the animal models, not based on a single acute dose study. And so there clearly would be very different margins being discussed if one were talking about single dose, which I think also was originally talking about acute dose levels and the factor, not repeated dose two weeks, four-week studies, and selecting an initial dose in humans. Clearly, these numbers would be decreased by significant factors as a result of that repeated dosing if the product had effect.

So those numbers that you've extrapolated, even for single dose therapeutic administration, would be much, much lower if based on acute dose selection, and, in fact, the FDA does allow acute single doses in humans based on acute dose data, but we do not use the numbers as described up there. We use a much more conservative approach along the lines of 50,

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100, in that order of magnitude.

DR. LOVE: I think another issue that is of concern to us when we look at a multiple like this is that the multiples also assume a very comprehensive clinical test monitoring program so that, yes, you have a low-dose multiple but you also have a very comprehensive clinical monitoring. And that's part of what I was talking about. We have a balance issue here. If you decrease animal toxicity, safety tremendously and then you also decrease clinical testing, then either you won't find anything because you're not looking for it, or you'll only find things like severe anaphylaxis, shock, things that rise above a certain level of observation.

Obviously, we don't want to be on either end of those spectrums. We're trying to find a balance in between that considers what's the appropriate starting dose, what's the dose multiple, and then what do you need to monitor. So that's the other aspect.

Some of the other points you were making in the beginning, I think we would tend to--we certainly understand the issue about taste and tearing and other things of that sort. But those are things we wouldn't necessarily see in animal testing, anyway, because animals wouldn't tell us about

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taste perversion.

MR. CARVLIN: Not by single dose.

DR. LOVE: No. So, at any rate, those are probably not the kind of events we're talking about, anyway, in terms of making these assessments, in terms of what's the starting dose multiple and the like.

Joe, could you talk a little bit more about the single dose approach in single dose therapeutics where it's still one dose? Obviously, the mass, and there's a certain expected difference in terms of the effect of the drug, but could you talk a little bit about the starting dose?

DR. DeGEORGE: Well, I can talk a little bit about it. I mean, it's not a clearly defined absolute FDA policy, so I have to talk about it in generalities. And Jane is looking at me very concernedly here.

Basically, we expect that when we do do acute dose studies in animals to support acute dose studies in humans, we have an otherwise large database that includes both rodent and non-rodent testing in all cases. It includes large safety pharmacology studies, whole batteries of those as appropriate. Generally speaking, we have good estimation of kinetics so we know something about are there differences across species that we may have to worry about. There tends

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to be a significant pharmacology battery so you know what kinds of effects one might expect based on the pharmacological properties, binding, et cetera, across the species. So brought to the table with that is a significant database.

The way it is most often used where that database does not exist is in oncology where we're treating people who are in their initial studies who have short life expectancies and have an anticipated need for having some therapeutic effect. In that setting, we do not use these very--what one might call very conservative, or at least appropriately conservative for normal volunteers. And we use much higher dose levels, and we bring less data to the table. But there we think there's a risk/benefit that has to be weighed and judged.

For standard studies, we don't generally get that information. So we get a much broader data set in addition to acute tox testing, and it is usually, in fact, a setting where there are multiple very similar chemicals which have all been put through this same data set where a company would want to decide which product to bring forward into longer development after getting some initial human data.

MR. NUNN: We have had discussions about this in the past

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that in the future in nuclear medicine we anticipate and it is being shown right now that many of the radiopharmaceuticals will have the same pharmacophore as existing therapeutic drugs. And I think we've agreed that we can use the dose response tox/path profile of those other existing drugs, of which there's a large body of animal and human data, and say we would expect based upon that profile that this radiopharmaceutical would have a certain effect.

DR. RACZKOWSKI: Yes, I--

DR. LOVE: Go ahead.

DR. RACZKOWSKI: I'd like to shift gears a bit to be sure that I understand certain aspects of your proposal in terms of--from the clinical side, in terms of the safety monitoring. You used an example in Phase 1 studies of types of adverse events such as taste perversion, transient drowsiness from a decongestant, or pain at a site of injection, that won't be considered major safety issues. And I think there are two aspects of that proposal that I'd like to get clarification on.

On one level, you seem to be implying that certain adverse events can be classified as low risk versus high risk, perhaps based on the seriousness of the adverse event or its severity. Am I correct in understanding that?

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MR. NUNN: Yes. What I'm saying is that nowhere in the existing guidance does it exclude some low-risk events from being relevant to a safety profile, and we'd like to have that in to say that there are some expected events based upon known pharmacology that you might see which are not life-threatening and which you know dose response curves based upon therapeutic drugs which you will see, perhaps, which should not be factored into the risk equation, if you like, or when they're factored in, their prominence is small.

DR. RACZKOWSKI: Well, the other comment I wanted to make was that the example of pain, for example, is sometimes viewed as being a tolerability issue as to whether a patient tolerates a drug, although in the broader sense, when it's captured in clinical trials, it's included typically as an adverse event or a safety issue. But sometimes we've seen that broken out as to whether the patient tolerates the drug administration or not.

The other question that I have has to do with the adverse events that are captured during Phase 1. You said that they could be consistent, for example, with the MedORA terminology. Now, the MedORA terminology not only includes adverse events that might be reported by a patient, for

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example, if a patient feels irregular heartbeats, palpitations, they might report it as such, but it might also--but MedORA terminology also includes the specific results of laboratory testing, for example, the results of an EKG, certain types of arrhythmia, whether or not they're experienced by the patient. Another example might be elevated liver enzymes for a drug that affects the--potentially injures the liver even though the patient may or may not be aware of that. And in your proposal, were you primarily referring to events that would be reported by patients, or were you implying that there might be some sort of broader, more extensive monitoring, including clinical and laboratory testing care?

MR. NUNN: Yes, in Phase 1, we have never proposed that there should be no testing of--no lab testing, clinical testing of the patient. Our suggestions were that the length of time we have to test is excessive, but the testing would still be done until there's a return to pre-base--you know, baseline or pre-injection levels. So, no, we're not just relying on whether the patient tells us that something has changed or not. We're looking at the labs as well. But I would reiterate that as the guidance is written right now, in my Machiavellian mode, there is nothing that says

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you will not say that we cannot get into Group 1 because there was pain at the injection site. And we feel a little vulnerable in that respect, that we would like it defined a little bit as to whether there is an unacceptable event or a response versus where there's a reasonable event.

DR. RACZKOWSKI: Well, I have an actual question regarding how that determination can be made. I'll use the example of dry mouth. For example, dry mouth may be due to anticholinergic effects of the drug, and if a drug has very significant anticholinergic effects, that could really be a safety problem. So to rely on the adverse event which is the end product of perhaps some underlying pharmacological effect may not get at the potential seriousness or implications that are underlying that adverse event.

MR. NUNN: I understand, but that is ignoring that if you have a drug which is a known pharmacophore, you've got a musculinic (?) receptor binder, you know that that will produce certain effects based upon the therapeutic profile that you've got in animals and in man. And we've discussed before that if you can show what the relationship is between your compound and the literature, then you can quite well demonstrate a dose response profile.

DR. RACZKOWSKI: Okay. If there--again, this is for

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clarification. If you have a drug with known, let's say, pharmacological effects, in the clinical safety monitoring program would CORAR or MICAA be receptive to the idea of doing some selective monitoring based on the known pharmacological effects of the drug, perhaps in Phase 2 and Phase 3, for example?

MR. NUNN: Well, you'd do it in Phase 1 as well.

DR. RACZKOWSKI: Right, sure.

MR. NUNN: Obviously, if you injected a musculinic binder and you got dry mouth, you wouldn't be surprised. If you injected a bone agent and got dry mouth, then that would really get your attention pretty quickly. And that's what we're trying to say, that there is a large body of pharmacologic information out there that we should be able to use to select what is an expected response and what is an unexpected response.

DR. RACZKOWSKI: Based on the underlying pharmacology of the drug?

MR. NUNN: Yes.

DR. RACZKOWSKI: Thank you.

DR. LOVE: What would you consider--how would you consider the severity of that expected event in the assessment? Is it just--in other words, if you had one--if this no

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unexpected approach, not so much the NOAEL, but the no unexpected approach, if you had an expected event but it was severe, how would you consider that in your assessment versus the same event but less severe?

MR. NUNN: By definition, a severe event is a severe event. If you have a transient 10 percent change in heart rate, let's say, that might be seen as being a low-risk event. If you had a 20 percent drop for two hours, then, you know, that I think would be much more classified as some prolonged pharmacologic effect.

DR. DeGEORGE: I just want to make a comment. I think it would be useful to move away from the NOUEL. I don't think anybody understands really what that is because it's expected, maybe, it's expected that this is a lethal compound, then that can basically be at some dose level, therefore, an expected event and, therefore, not unexpected. So I think that that's not appropriate terminology. The NOAEL is a clearly defined term in toxicology. It means anticipated events can be included as long as they're not severe or significant or likely to have an adverse effect. It also means unexpected events which occur at such low frequency or low severity or incidence that it's not considered a significant adverse event. And there's a lot

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of literature around that that can be relied on. I think there isn't for the other terminology.

The one point I did want to mention, you brought up the issue of the pharmacophore, and the pharmacophore clearly is an important consideration, but also so is the molecular structure, because we all know you can make relatively minor substitutions in the molecular structure and significantly change the pharmacology of the underlying pharmacophore. So one has to consider that in addition to how much reliance is given to the other data, depending on how much of a change has been made to the pharmacophore itself.

MR. NUNN: Yes.

DR. LOVE: We've talked about a number of different things here in relationship to this. I'd like to try to get a little sense of--number one, it seems that you're moving from the NOUEL now to this recommendation of using the NOAEL. Is that correct?

MR. NUNN: Yes, I think we'd all be more comfortable with using something which is actually in the literature.

DR. LOVE: Okay.

MR. NUNN: The only reservation I have is that we should be cautious about applying the existing NOAEL for therapeutic drugs directly to diagnostic drugs. We must make some

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adjustments because we're dealing with diagnostic not therapeutic drugs.

DR. LOVE: I think a number of the features of the products that were mentioned earlier are certainly things that we would have to think about. I think also we have to think about the fact that the dose multiples that at least were identified in the article are made on an assumption of certain clinical testing consequences that normally occur in those clinical trials. So as we make an adjustment here, looking at what's the difference in the clinical monitoring--because we're actually talking about something new now. We're changing the monitoring in Phase 2 and 3, and so, in a way, some of the existing multiples may not be directly relevant, and we'll have to sort through this to figure out what are the most reasonable dose multiples to get started in Group 1. You've actually just made another proposal also here, and that is that there are two different dose multiples. One is to start in Group 1, and one is to stay in Group 1.

MR. NUNN: Yes. I'm not suggesting--I'm putting this up for discussion.

DR. LOVE: And that's fine.

MR. NUNN: I'm not suggesting that 25 times is the correct

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one, in the same way that I'm not saying that if we can go with one to five diagnostic index all the way through.

DR. LOVE: I understand and I appreciate that. Thank you. There are other things sometimes that come into the dose multiples, and some of that might depend upon the drug that you're seeking. Let's say you have a receptor, and we talked about species issues and the fact that there may be some very different receptor binding or affinities with one species or another and in humans. When you get into something that becomes that--that adds another level of complexity to this, how might you propose that that's considered?

MR. NUNN: If we were to rely on the body of literature which is already in existence for therapeutic drugs, the pharmacophore, captopril, an ACE inhibitor, let's say, if we were to radiolabel that, then obviously one of the things that we would do before--when we selected the drug is we would compare things like the binding to a receptor or enzyme in animal cells or transvected cells or human cells, and to see what the relationship was. I mean, that is going to be one of the ways that we will test the efficacy of our compound. So I think we'll have that information already, some crossover.

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DR. LOVE: And you'd use some of that to determine which is the appropriate animal model and then look for your ratio, your dose multiple, and the appropriate model.

MR. NUNN: Yes, yes. I mean, for instance, if you had a receptor binder where the therapeutic drug--or the diagnostic drug had a much lower--or much higher efficacy, much higher binding constant, for instance, you know, that's obviously going to be...

DR. DeGEORGE: How would you see that being written into the guidance, actually, since that's really in the realm of pharmacology where at least the agency is not--under our regulation does not specifically require certain types of pharmacology studies? That's not part--we're supposed to look at the safety aspect. We're supposed to rely on the numbers that you sort of put up here. Clearly, we do rely on them when we get that information.

MR. NUNN: Yes.

DR. DeGEORGE: But that's sort of how you modify from an existing data set rather than actually underlying foundation of it is.

MR. NUNN: I don't think you're precluded from using pharmacologic data to support a safety issue.

DR. DeGEORGE: But in considering establishing some number

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that is a threshold where in the absence of this additional data that threshold may not be appropriate, how would you propose we include that in the guidance, that that information would be essential in establishing some lower number or something like that? Would that be an approach?

MR. NUNN: I think you would have to demonstrate--if you're going to use existing pharmacophore data, you have to establish a link between your compound and the body of data--the compounds which represent the body of data. So in my example, if you took an ACE inhibitor and pharmacophore and attached a technetium kelate to that, you would have to demonstrate that your technetium compound behaved like an ACE inhibitor in binding and things like that and what the strength was, what the relative efficacy was. I mean, that's something we would do anyway because if we were targeting that sort of drug, we'd want to know that information.

DR. DeGEORGE: But you may do that for human, but it wouldn't always be the case, and you'd go back and look at your animal models to make sure that the safety you're assessing in that is also showing the same change. I mean, maybe you would, but I don't know that we would be able to know that without the data.

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MR. NUNN: Yes. Five years ago, I think it was much simpler, but now that we can put transvect cells and things like that, it becomes much more complicated.

MR. CARPENTER: Alan Carpenter. One possible answer to your question may be--and this is just for discussion--may be that by exception, where there are recognized to be no appropriate animal models or where there is not a known analogy between a human receptor, for example, and an animal receptor, that there should be a basis on which to require an exception, some different kind of multiple. But where the receptor is well understood and the models are established and the validity of the receptor target in certain preclinical models is understood, certainly a fixed multiple would seem to be possible as a baseline.

DR. LOVE: One thing that we've been thinking about is: What is the approach that we would need to take to be able to define a category of products that would need the limited testing, where we wouldn't have to do a lot of the balancing, although exactly what you describe is what we end up doing most often when we're looking at studies, and part of that is the challenge of writing a guidance because we start thinking about all the different exceptions and alternatives and how to balance once thing to another. And

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the idea of writing in the exceptions and the way to balance it sort of appeals to us because that's what we do, but we're also trying to respond to the request to define this in a very clear way.

Let me just put one other thing on the table for the moment, and that is, in Group 2, our feeling is--it's not that it's--Group 2 doesn't mean that you absolutely have to do everything all the time. There still is a great deal of room to modify or target the evaluation in Group 2 on the basis of metabolism, what we know about the drug and such. It may mean that there are maybe more comprehensive safety monitoring perhaps because a dose multiple is not what we're talking about. But, still, the monitoring could be limited. It doesn't mean that it has to go on for several days. It's still whatever is appropriate for the drug.

So what you're talking about now, where maybe we don't know an answer to something in the situation that you're just describing, but you want to see that as something that is written as an exception for Group 1, or would you rather see that written as this is a Group 2 with modification? Because, you know, we're getting into a lot of--it brings us into a lot of "what if" types of scenarios. I'm just curious what your thoughts are.

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MR. CARPENTER: I think it clearly depends upon the body of literature and what is known about the particular targets that you're going after, and I think it would be appropriate where, if there's an established body of literature and understanding of validity of the preclinical models, to have a fixed multiple as sort of an entry criteria; but, by exception, where there isn't that type of established link between the preclinical model in humans, that it would be appropriate to have an exception for some limited additional testing or perhaps some requirement for a different multiple. But certainly there must be a baseline at which where the models are well established and the receptor or the target is well understood in preclinical models as being consistent with human pharmacology and expression of a receptor, and we ought to be able to make the determination that a fixed multiple is okay.

DR. DeGEORGE: Mark, I just want to clarify. My understanding is that you would basically be looking at the established literature, the relevance of the model in the animal setting as well as in the human--

MR. CARPENTER: Yes.

DR. DeGEORGE: --predicted human outcome, and actually doing studies with your modified molecule to actually make sure

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that the relationships were still intact between those two models. Because depending on how you chemically modify your ligand or your entity to make it so you can use it as an imaging agent as opposed to a pharmaceutical, there could be changes and substitution and linkages and all these other factors. Are you still then going to do some specific studies to make sure that the relationships still exist as they were for the well-defined pharmaceutical, for example?

MR. CARPENTER: As a threshold, obviously, you have to show that you're targeting what you think you're targeting and that the issues about modification shouldn't really have a bearing on that, as long as you understand what the target is and its relationships between humans and animals.

DR. DeGEORGE: Well, let me give an example that may make it clearer, and I'll pick a very simple one. What if you substituted a fluorine for a hydrogen for some imaging process and there now is a difference in that the standard product having a hydrogen had a relationship between the animal and the human receptor in terms of binding affinities that differed by a factor of 10, and now you put a fluorine on there and the affinities differed by a factor of 100, although it still bound to the same target? In that setting, would we--the relationship that was still

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activating a receptor in both cases, but the binding constants had significantly--were significantly different due to molecular structure of the receptor itself.

So under that setting, would you be saying that here's a case where we're going to have to do additional work now? Does that kick you out of this lower threshold, or do you stay in that lower threshold knowing that the animal model where you've done your toxicology study is really less sensitive per se than maybe the human model might be? Differentially less sensitive.

MR. NUNN: I think as you have--as you know what the relationship is, you can use that when you build your case for what dose you're giving to say whether there is a risk or not that you'll move into uncharted territory. Obviously, in this hypothetical case where there's a factor of 10 difference between animal and man, it's only really relevant if you're within a factor of 10 of an adverse reaction. If your dose is lower than that, and frequently it's much lower than that, then the relevancy is much less.

DR. DeGEORGE: I wouldn't necessarily say that you have to be within that factor before it becomes a concern. If you felt when you knew the model that you should apply a certain factor, now you knew that the model is not performing the

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same as it did with your previous chemical in relation to humans, I would say you really are uncertain, you have an additional uncertainty, not that you are--okay, we can still stay there because our dose multiple is 25, as you have proposed, and now it's really 2.5 for safety margin. I mean, there are other factors such as kinetics, compartment, accumulation, and all these other factors that would be eliminated from safety margin under that setting.

DR. LOVE: I think what we're talking about are a lot of the different pieces that go into making some of these assessments. And I'd also like to ask one other question. On one of my slides, I talked about the fact that doing the repeat dose study helps us in addressing some of these things. When you're looking at all of this on the basis of one expanded single-dose study, looking at the multiples, it's a bit more of a concern if everything is based on just that. But if you're looking at that, plus you have a repeat dose study, it gives us some other information about sensitivity of various organs, ability to address some of these other issues.

One of the things we were--at the last meeting, part of the proposal from CORAR, as we understood it, was to eliminate the repeat dose study. We've been thinking about perhaps

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not requiring it as a study that has to go be completed before entry into Group 1 and before starting the clinical studies, but that maybe the study would be done during Phase 1 before you get into large numbers of patients with Phase 2 or 3. And that also helps us in coming to grips with a number of the issues that have just been discussed this morning. What are you feelings about moving that study into another phase of development?

MR. NUNN: I think that it's not an unreasonable suggestion, but I think that we must be careful that we just don't put it in Phase 1--it must be done in Phase 1 and if you hold us to Phase 1 only normals, for instance, because we're using radioactivity, it might be that you don't get any efficacy data in Phase 1. And then, you know--

DR. LOVE: I think, you know--yes, flexibility there. I think the real issue is making sure it's done before large numbers of patients are done. I agree. Phase 1, Phase 2 become very blurred after a certain point. I agree with you. So we could certainly think of language that describes it more as related to numbers of patients.

And, yes, we very much agree with you that data in patients, dosimetry, other types of information, is often more relevant in that population, at least to help you make some

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of your final decisions, so yes.

MR. MORGAN: Just for a point of clarification, with all the discussion that we've had, I've kind of lost what I thought was an understanding at the beginning. Taking the simplest case where you would have a pharmacophore that has been used as a therapeutic and you've made a modification where you're linking an isotope so that you can use it as a diagnostic imaging agent, and you've demonstrated that the characteristics of behavior of that now modified product that you're using as a diagnostic is equivalent, similar to the therapeutic agent, then I thought I understood that FDA was open to reduced testing of that diagnostic under those circumstances, that you could rely on much of the information that was collected for the therapeutic. And I just want to make sure. Is that understanding still correct?

MS. AXELRAD: I thought I heard our side saying that it depended on the degree of similarity between the two. You used the words "if it's similar," and I think the question becomes how similar.

MR. MORGAN: That's where I started to get lost, but if you take it in the simplest form where they are equivalent, then a reduced test package preclinically for the diagnostic

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agent is not inappropriate based on the information that has already been collected for the therapeutic.

MS. AXELRAD: Yes, that--

DR. DeGEORGE: I think that was what I was getting at. How would you go about--that's what I was asking. How do you go about demonstrating the similarity or the change or the lack of change?

DR. LOVE: Yes. It's a yes, but it's the data that--what is it and how. But, yes, we agree with the approach that you're talking--

DR. DeGEORGE: And where--

DR. LOVE: --about, and I think Dr. DeGeorge's question perhaps is more where would you like to see and to what extent would we need to clarify this in the guidance. I think that's part of the other part of the discussion that's going on, just how much detail is going to be needed or would you want to see in guidance to try to address a number of the issues that Dr. DeGeorge is raising.

MR. NUNN: Well, we did discuss this a little last time, and we pointed out--or I think we found that there was a misunderstanding between what you wrote in the guidance and what we understood you wrote. And this was in the section which talks about using established literature or well-known

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safety profiles, and we thought that you were referring only to the SNDA type of situation when you said, no, you understood--what you wanted to put there was to use the pharmacophore of other drugs and the tox/path. That's in the last--

DR. LOVE: I didn't use the word "pharmacophore." I know I didn't use that one.

[Laughter.]

MR. NUNN: You did not use "pharmacophore," but you did say that data on existing drugs of the same class.

DR. LOVE: Data from other drugs, other sources, things that are relevant, certainly is something that we take into consideration. I think what Dr. DeGeorge is now talking about is how do you take that into consideration, what kind of data would be relevant to show just what was mentioned a moment ago, showing that the product now as modified is comparable to the other data so that we know we can rely on the other data. So something--a bridging study, something would need to be done to show us that this drug is relevant to the other if it's now changed. If it's the identical drug and it's just given at a lower dose, then it-

MR. NUNN: Then it's easier.

DR. LOVE: --doesn't take that much to think about.

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MR. SIEGLER: Bob Siegler. It strikes me that what we have is a decision process that's sort of a little vague, but that one of the things we would benefit from is somewhat of a flow diagram, if you will, through a process where some of the things we're enunciating--okay, I have a pharmacophore, it has activity, it's a known activity, and I want to put this forward, so what I need to do is certain types of confirmatory studies that say the binding--you know, there's certain decision processes maybe that you could walk down, and maybe the way to structure this is something similar to what has been done in the ICH guidance in many cases where that kind of process is just kind on a flow basis done. I think that might really give us a good basis to know what we're both trying to achieve here.

DR. LOVE: Okay. That's a good point.

DR. RACZKOWSKI: Yes, I'd like to return to Bob Morgan's example where the substitution leads to a compound with what we defined as equivalent pharmacological activity, and I would say that certainly that would be taken into account in terms of the subsequent evaluations, but the pharmacological activity may or may not predict the toxicity, potential toxicity. So the extent to--I think we're all in agreement that, yes, that would be taken into account. But the

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question is what amount of bridging or what amount of additional information might be needed to show that the substitution didn't lead to additional toxicity that may be removed from the pharmacological activity.

DR. LOVE: We're spending a lot of time on the pharm study because it's really now going to be the basis for justifying decreased ongoing clinical monitoring, and that's why we're talking about this a great deal. And why--because that last study--that first study in humans is the final bridge between the two, and we need to be sure that there's enough information to justify the lower monitoring.

Any other comments on this portion?

MR. MORGAN: Just an example occurred to me, that there's a compound that we've been working with for treatment of DVT in one case and diagnosis of DVT in another case. It's essentially the same compound with the addition of a radioactive isotope. Under those circumstances, there's a wealth of information available around the therapeutic product itself. You go through and show that the behavior of the diagnostic is equivalent to the therapeutic. Are we then--what we have done is a full preclinical package, and I guess the suggestion is that that may be overkill. Do you need to go through and do two species? Do you need to go

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through and do mutagenicity, carcinogenicity, those types of studies?

I think what we're suggesting is that under those circumstances where there is a significant amount of information about the compound, you don't link it together; we're not saying don't do any preclinical, but there should be a rationale for a measurable reduction of what you do preclinically for the now diagnostic.

DR. DeGEORGE: I want to make a comment. I don't think that in FDA's original proposal it talked about mutagenicity or carcinogenicity or any of those things, certainly not for Phase 1. It may have mentioned mutagenicity. I don't know about that. But it talked about waivers.

Clearly, if you've already identified something as a potential mutagen, you're on one setting, and if the factor, the ligand or the radionuclide you put on there is a potential mutagen, you've already also answered the question without doing the study. So it doesn't seem you would need it in either of those two settings. There may be other settings that you might, but I don't think that a carcinogenicity issue is something that was clearly not a Phase 1 issue and may not have been a marketing issue, I don't think, for the imaging.

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DR. LOVE: Right. I think that was one of the places where it was clear there was some confusion between what was in the section that listed all of the pharm tox studies without relationship to Group 1 or Group 2, and then there's Group 1 and Group 2, and is there anything left over from the other one that needs to still be done once you get into Group 1. Those things were not sorted out.

But in the list, it does say that for radiopharmaceuticals carcinogenicity is not one of the studies, and the genotox and reprotox are usually considered by waivers.

DR. DeGEORGE: Can I just make one comment? Because I don't want to be definitive in that. We have experience with one imaging agent in development that has a half-life that is along the order of several months. There a single therapy becomes a chronic treatment, so not all radiopharmaceuticals or not all imaging agents are treated identically.

DR. LOVE: Right. I think right now we're talking just about the radiopharmaceutical in this part of the conversation. Yes, there are other issues with some other contrast agents, yes.

Are there any other comments on this section from anyone? Yes?

MR. CARVLIN: Just a comment. Mark Carvlin from MICAA, to

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say that there are analogous concerns in the medical imaging contrast agent realm, and I could just give a couple of very brief examples. One might be where the pharmacophore is exactly the same, medical gases, for instance, xenon can be used in a number of different applications for imaging as well as for other things, or sulfur hexafluoride has a therapeutic or a number of different applications, diagnostic and otherwise. Also, certain pharmacophores, actually quite a broad variety, have optical activity; either they will absorb light or they'll be fluorescent themselves. And that's another way of probing the in vivo state, using exactly the same pharmacophore.

The last example would be where you have in vivo diagnostic agent well characterized perhaps already approved for one imaging modality that has efficacy for another imaging modality, the exact same pharmacophore. What kinds of concerns lie in those particular instances? And if I understand, I think there would be some reduced preclinical package that would be required.

DR. LOVE: Before I address that, let me just try to do a little bit on our agenda here for just a second, because that's sort of getting into the contrast questions, and those are appropriate questions. But are we finished with

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the radiopharmaceutical CORAR presentation on Group 1, or are there some other issues that you wanted to do? And I'm wondering whether this is an appropriate time to take a break or what. That's why I'm asking.

MR. NUNN: Do you want to do pharmacokinetics and pharmacodynamics?

DR. LOVE: Pardon me?

MR. NUNN: Do you want to get into pharmacokinetics and pharmacodynamics now, or--

DR. LOVE: That's what I'm trying to find out, plus I also want to get comment from the audience in terms of where we are. So I'm just trying to identify where we are at this moment in time before determining the next step.

MR. WHITE: This is Rick. Why don't we break to the audience? Because we've dealt with one topic, and then we'll go to the pharmacokinetics, pharmacodynamics.

DR. LOVE: Okay. We can take the audience comments, and then we can take a break.

Are there any comments from the audience, please?

MR. LaFRANCE: LaFrance, Princeton, here for Bracco, and this is as much a personal comment. Some very thoughtful comments from the agency in terms of how the agents may vary slightly depending on labeling and so forth, which is

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appropriate.

I might remind the agency--and they probably certainly have considered this--there's precedent in terms of the radiopharmaceutical evaluation after being labeled with known products with your RDRC approach that was particularly popular in the 1980s. I'm not sure how much you see it now in terms of institutions. It might be worth looking at the types of things that worked well and perhaps didn't work well in those situations in answering those questions.

The issues around monitoring, as I followed the discussions, I believe that much of the monitoring decisions in Phase 1 will be helped with not only dialogue in the sponsors, but certainly the preclinical pharmacology and the preclinical tox to help determine what safety issues need more attention or less in Phase 1. Hopefully that information from Phase 1 will build on what information you need to follow in Phase 2 and 3.

My plea is that there's lots of considerations around what may be continuation of very robust monitoring in Phase 3 studies from broad ranges of patients who have established disease where this monitoring is an interference with their ongoing treatment when there's not a lot of information to defend that continued monitoring either for parameters that

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are monitored or length of time. And perhaps information around that that might be required either based on a preclinical pharmacology or tox information be required in Phase 1 or questions that might not be completed in Phase 1 be requested in more depth in Phase 2, so by the time you get to Phase 3 there's either comfort level or not based on that, and the decisions around, say, more robust monitoring aren't reflex but really based on data.

Thank you.

DR. LOVE: Anyone else?

[No response.]

DR. LOVE: Okay. Then let's take a 15-minute break.

[Recess.]

DR. LOVE: I just want to take a brief moment to summarize what I think I heard from the preceding morning's comments, since there was a lot of information put on the table.

It seems that we have a new proposal now to reconsider the dose multiples for getting started into Group 1 on the basis of using the NOAEL and using one dose multiple level to get into Group 1, get started, get the rest of the clinical data, and then reassess on the basis of the clinical data and the dose multiple or different dose multiple on whether or not you would continue into Phase 2 and 3 as a Group 1

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product. And also there seems to be some willingness to accept a moving--to adding a repeat dose study in parallel with Phase 1 somewhere before you get into large numbers of patients in Phase 2, and that would help to justify the lower dose multiples.

Also, we've heard a request from you that we lay out some different approaches that might be needed if it's a brand new product that hasn't been given to humans before and doesn't have any other similar product versus products that are similar to something else and products that are identical to another product, and talk about different approaches that might be reasonable as a decision tree type of an approach, and also talk about other information that could be used to balance the information.

Is that consistent with--

MR. NUNN: Yes. This is Adrian Nunn. There is some confusion right now in Phase 1, Phase 2 patients versus normal volunteers, especially in radiopharmaceuticals. And I think it would be useful to clarify that a little bit. If we do dosimetry studies in normal volunteers, that's Phase 1. But if the pathology does not exist in normals, then we get no efficacy data. So if we need to do patients in order to get proof of concept, is that Phase 1 A or B or

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is it Phase 2? And how many patients are you thinking of before it triggers a requirement to consider repeat dose studies?

DR. LOVE: Right. I understand. And I suppose we hadn't thought about it in terms of specific numbers at this moment in time, but generally, we would consider--we look at it more in terms of the type of study that you're doing, whether it's Phase 1 or 2 or the blurred line in between, and I think doing dosimetry in patients as part of your concept evaluation is reasonable as a Phase 1 type of a study.

MR. NUNN: Well, I'm not proposing to do dosimetry in patients, necessarily. One can imagine that you might want to do--you might have to do your proof of concept study in a patient who's unstable, let's say, or who is not conducive to all the operations that are required of a dosimetry study.

DR. LOVE: Right. That becomes more complicated, and a lot of that depends upon the drug. Some drugs it's very easy to do routine Phase 1 type clinical monitoring, and even get some basic imaging information or dosimetry.

Once you start getting into unstable patient populations, then that's a different issue. Let's say you're developing

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a drug whose only known benefit is going to be patients with Class 4 CHF or something. Then you'd probably do something more gradually to move towards that population. But that's really related to the drug and what it's doing, a balance of what's the risk. Are we really dealing with a Group 1, or are you dealing with a Group 2? There are a lot of other questions that I would think would be related to what you've just proposed, but--

MR. NUNN: But remember that a classic dosimetry study, the first hour you've got probably 15 people around that patient with the bed moving. You know, if you hit that camera face, everything stops.

DR. LOVE: That's why I say there are a lot of issues that are around that, and what we're probably trying to do is figure out something that can be cleanly described in terms of entry into Group 1. What you're now talking about is how do you conduct a clinical trial to get the information, and that would be perhaps a separate issue that's more directly related to the patient population and what you need to do to take care of that population of patients as opposed to what do you need to do to decide if this is a Group 1 drug. So I would see those as issues in the logistics and implementation of the study, but perhaps not related to

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whether or not it's a Group 1--if I'm understanding you correctly. Maybe I'm misunderstanding you.

MR. NUNN: Well, if it's a true Group 1 drug, then the risks are the same for the normal as well as for the patients.

DR. LOVE: Yes.

MR. NUNN: But the issue is it's very difficult to do true dosimetry studies in patients unless they're essentially normal in every respect because it's so involved, and so we need some mechanism of being able to look at efficacy when the pathology is not there in patients early on without invoking an excessive amount of other tests.

DR. LOVE: Okay. Could you hold--I was going to say, could we hold that until we get to the clinical monitoring part? That may be where it fits. But you have something you wanted to say?

DR. RACZKOWSKI: The comment that I have is that I think some of--what I hear you saying is that you'd like us to be clearer in terms of how we define perhaps Phase 1 or Phase 2? We may end up not using those terms because is Phase 1 a dosimetry study, is it in normals, is it in the healthy people, or is it in patients? What is the type of study that's a Phase 1 study?

I think what I heard you say is that you'd like us to try to

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label out specifically in the guidance which patients we're talking about when they're in Group 1 and where monitoring needs to be done. Is that a fair statement?

MR. NUNN: And also when other tox/path studies might be triggered. Are we talking about doing repeat dose in parallel, but when do they have to start?

DR. LOVE: Okay. Thank you. I guess I misunderstood you. Thank you.

Any other comment, then, on general approach?

MR. MORGAN: On general approach, I think CORAR will commit to provide you with what we think is an appropriate decision tree, just--

DR. LOVE: That would be very helpful.

MR. MORGAN: --to help the discussion. So during the comment period, we'll draft out what we think is an appropriate decision tree and submit that.

DR. LOVE: Good. Thank you. We would appreciate that. Any other comments on this part?

[No response.]

DR. LOVE: Okay. To some extent, some of our comments were overlapping with other items on the agenda--which I have now lost--but I think we're going into pharmacokinetics, metabolism. Any other issues there?

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MR. NUNN: If you look at classical pharmacokinetics, PK, it involves ADMU studies, essentially, speciation. And we have a problem because we're a little too loose in our use of terminology. And (?) biodistribution of radioactivity in animals or in man has commonly been called pharmacokinetics, especially when referring to the data set that's used to determine the radiation dosimetry.

The distribution of radioactivity through those tissues of the body over time post administration is performed by invasive means when we do it in animals, but non-invasive means when we do it in man. But it's analyzed using classical mathematical PK methods, so we get area under the curve and biological half-life and things like this.

Now, for dosimetry purposes, the chemical form of the radioactivity has little relevance to the safety assessment. Thus, with determination of the chemical form or speciation of the radioactivity is not performed in metabolism. It is ignored for those dosimetry studies.

In order to try to separate these data from the full PK data, we tried to use a term pharmacodynamics, which is, as you all know, the change of signal, if you like, with time or dose, and in this regard, the radioactive signal is quite analogous to a blood pressure or a heart rate signal.

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Nevertheless, the use of these terms is still loose and confusing, especially when classically trained pharmacokineticists enter the nuclear medicine field. And so it might be beneficial to define in the guidance document what we mean and to use the term biodistribution of radioactivity rather than PK or PD when talk about the need to determine the dosimetry. That's the first issue. We all talk about pharmacokinetics when we talk about dosimetry data, but we're not doing classical pharmacokinetics, so I think we need this defined very clearly. I mean, you might have to define PK and PD as well as biodistribution so we're all on the same page.

DR. RACZKOWSKI: I think that the biodistribution of radioactivity clearly is an important concern, and perhaps we can consider using the term biodistribution of radioactivity to define that particular--the pharmacokinetics and distribution of the radioactivity. The other component that we are concerned about which potentially has eligible effects are the non-radioactive component of the molecule, and so that's what incorporate--that would also need to be incorporated into the guidance document as well.

MR. NUNN: Yes, I agree, and I'll come to that now.

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So if you look at how PK data are used in the therapeutic field, and it is the same reference there, they're used to set the upper limit, the clinical dose escalation study, to set the amount of escalation between doses, to set the margin of safety for irreversible toxicities or toxicities that are difficult to monitor, and when making comparisons between preclinical and clinical exposures in relation to toxic endpoints.

Now, even in the therapeutic field, PK data may not be available, and here is one from an oncology source. Without PK information, it's generally preferable to use dose comparisons based on body surface area rather than body weight. Other published sources state while, not essential, information on PD and PK is extremely valuable; although not required, PD and PK studies provide substantial additional support for the safety profile.

Now, this is oncology, but the point I'm making is that there are special cases where you don't have to go the whole route, and we believe that in the diagnostic field that's just as much of a special case on the benign side, if you like, rather than the risk/benefit ratio that oncology has. But perhaps more important is that traditional dose escalation studies are not done for radiopharmaceuticals.

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The amount of radioactivity administered may be varied, but the max injection is usually limited to the total contents of the vial or less. And under these circumstances, there is essentially no biological response, as we all know, and indeed, we made considerable efforts to try and achieve that aim, that there is no or little biological response if the whole vial is injected. So it seems that one of the major reasons for doing PK studies is for dose escalation purposes, which we don't do.

Now, the important point is here. PK data are traditionally used to established a link between the distribution of active drug and metabolites in man. This link is used to assess the proximity of pharmacological events seen in animals to doses used in man without approaching the toxic level precipitously. One would like this to be linear. There are no species that exist. PK studies are of most use when their therapeutic index is expected to be small, the dose response curve is steep and/or large species differences are expected.

As one moves away from these scenarios, then the return on effort diminishes and we believe we must seriously question the ethics of subjecting humans to the procedures necessary to collect the data.

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As with therapeutic drugs, there are a range of scenarios that may occur, and the first one is where radiopharmaceuticals have been traditionally, and that is, there is no animal toxicity. As stated previously, the experience has been that there is little or not biological response in animals at doses up to 50 or 100 times the human dose. In this case, we have no ability to establish a link using PK because we have no toxicity in animals. It would thus appear that it's meaningless to perform PK studies in man or in animals because there is no toxicity. So the link is--there's nothing to compare it to.

DR. RACZKOWSKI: I'd just like to comment. I think the last time we met with CORAR, when we discussed the concept of a link, the link was through--not in terms of comparable toxicities, but to establish the different amount of exposure, whether it was a thousand-fold or 25-fold, in comparison between man and animals. And part of the purpose of getting the PK data was to show that there was comparable exposure. And so you can make the link between the preclinical studies and the clinical studies.

MR. NUNN: But before you go into man, of course, you don't have any data on the human exposure. So you have to go into man without that, and the PK studies are normally based upon

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the relationship of exposure in humans and toxicity in animals. And if there is no toxicity in animals, then you're forced to rely only on any toxicity or adverse event you might see in animals, and exposure is somewhat--

DR. RACZKOWSKI: But I think we're talking about two different things here. Toxicity studies may be used to determine a safe starting dose, let's say, for a therapeutic. But that's a different goal than trying to determine whether the product is going to be considered Group 1 for all time and, therefore, have decreased safety monitoring in Phase 2 and 3. I think that the goals are somewhat different there.

MR. NUNN: Well, let's go through a scenario. You do animal toxicity, and you get no events, no response, up to 50 or 100 times the anticipated human dose. And then you going into man, and you get no response or benign responses. Okay. What are you going to do with the PK data?

DR. DeGEORGE: Can I address that? First of all, we don't even have to look at man versus animals. You can look between the animals. For one thing, it's important to know, when you think you have that equivalent dose causing an equivalent either toxicity or, in fact, absence of toxicity, that the exposures that you're using are, in fact, similar

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so you can say I know this fairly confidently that the exposure achieved in the animal, the half-life, the clearance, is very similar between these species, and I can use that information with confidence, with some greater confidence that exposure difference will exist, hopefully, in humans, such that if AUC, Cmax's, et cetera, are all similar between rats and dogs, which is not always the case, that that will also hopefully extrapolate to some degree to human.

If, on the other hand, the clearances are totally different in those two species and the Cmax's are very different, then one has to make the assumption that perhaps there's going to be a difference that also exists with humans.

When you get the human data, you can then verify whether those assumptions are correct, which one of those models more appropriately models the exposure that was achieved, whether it was rat or dog, whether the toxicities observed are the same, whether the exposure actually achieved in humans is--do you really have that 50- or 100-fold, or are you at 5- or 10-fold now not knowing anything about what the toxicities that might occur in humans are within the population, differences within humans, because you have no information about animals above a certain dose because

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that's the most you could give and you couldn't elicit any toxicity.

And so one would arguably say in that case you might need to do very careful monitoring in your clinical studies because you don't know what to expect. You have no guidance from your animal data, and you are very close to that area where you don't know what the human outcome might be.

So those are all part--which were captured in bullet form, I think, to a lesser degree in that first section, and I think are relevant to both the animal data and the confirmation in humans.

MR. NUNN: But if you don't get--I mean, the bottom line is whether you get a profile in humans.

DR. RACZKOWSKI: I think there is some understanding of what you're saying, and perhaps we could reduce it to the very simplest case, where if you had a drug that was given intravenously that did not distribute to anywhere but the intravascular compartment, and you knew that in animals and in humans that it was not, then the issue of actually getting specific pharmacokinetic data for the purpose of exposure is somewhat less. But if drugs are given by other routes of administration per se, like if they tend to be given orally in man and then the toxicokinetics becomes

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relatively more important for getting the relative amount of toxicity ratios.

DR. DeGEORGE: But you do want to keep in mind that there may be differences in clearance, even if given in sort of the same compartment, that you have to be aware of when using those safety--those projected safety margins that you thought you had based on your doses administered to the animals.

DR. RACZKOWSKI: Or differences in metabolism, et cetera.

MR. NUNN: When it comes to radiopharmaceuticals, the only one that I can think of that's given orally is radioactive chicken livers, so toxicity of those--but let me go on because I think I've got some other points here.

So the expected biological--the second scenario is that you do get a biological response in animals, well-defined on those safety issues, getting back to our benign biological responses. So the risks here--and I think this is what you were talking about--are that the PK of the animal species are so different from man in a detrimental direction, because, of course, they could be in a beneficial direction, man clears much faster, whatever, that toxicity occurs. And this can result from different metabolism or different clearance.

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With therapeutic drugs, risks arise because the masses administered are relatively large, and they are administered more than once. So that there may be the potential for build-up of toxic levels at different rates in animals than in man. But we submit that it's quite different for radiopharmaceuticals where masses are lower and administrations are limited.

In addition, we anticipate that we will have animal toxicity data up to possibly 50 or 100 times the human dose. That happens to be the maximum we can go because we're volume limited right now. So that there will be a 50 or 100 times margin of safety that we can use, and the risks for toxicity then are still limited. In other words, the human PK has to be 50 times worse than the animal before we get into an area where we don't have information based upon the animal data.

DR. DeGEORGE: That makes an assumption that the binding affinities for the target site are identical, and there can be clearly differences in affinity of the receptor that have to be factored in with the differences in clearance, et cetera.

MR. NUNN: Yes, we agree. But we believe that we will have those sorts of data as part of establishing the link between our compounds and therapeutic drugs or classes of drugs

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which are already out there. So we would have that information, I think. We're not saying that we would go in with a totally unknown compound which has no clinical history whatsoever or tox/path history whatsoever and propose this. Those would more likely fall into the third category: biological responses in animals are significant, PK in animals needs to be done and some toxicity dose response data may be appropriate in man. But the full PK may still not be necessary.

And the bottom note is one of mine, that I can't think of any radiopharmaceutical so far approved that's ever had full human PK studies done on it.

DR. MILLS: Adrian?

MR. NUNN: Yes.

DR. MILLS: George Mills. A little bit, though, in taking to--I'm a little concerned that the emphasis here should also be brought back that while full PK studies certainly aren't necessarily part of the usual spectrum, that a lot of what you do in drug development for a diagnostic radiopharmaceutical is related to dynamic pharmacokinetics and imaging and time point evaluation. And you're going to generate a significant amount of that type of data in the drug development process. And that approach, in terms of

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that information, should be at least acknowledged in some element here for you in terms of that development, and what's the realistic portion of this that you're going to do in your development process. Much of that information is absolutely necessary in the appropriate use of these.

One of the other concerns, and just a comment to it, is that certainly there are novel approaches in terms of administration, but remember such things as I-123 is given orally. And some of the more significant adverse events that you can experience clinically are from I-123 in the carrier in about one in maybe three to four hundred patients with it. So not always to forget that there are other uses to it and that there is a significant amount of PK that's absolutely necessary in drug development.

DR. DeGEORGE: And even by IV administration, the volumes of distribution for the products, the distribution to various tissues clearly can differ, and those margins--that information is very helpful in trying to understand what the toxicity data or absence of toxicity detected in animals means in relation to the clinical information.

MR. NUNN: Yes, yes. It should not be forgotten that radiopharmaceutical studies are not performed in a PK vacuum, because we will always have very detailed data on

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the biodistribution of the radioactivity. And in one sense, these data are much more extensive than those collected for therapeutic drugs because the temporal resolution is much finer for radiopharmaceuticals, and we can collect data for very many tissues in the body.

We also have high sensitivity and we have quantitation without extraction, with all the vagaries that you get there. So we benefit from the non-invasive nature of nuclear imaging and/or radioactivity.

So the question is: As the radioactive drug contains the same pharmacophore as a non-radioactive component, differences in biodistribution of the radioactivity between animals and man should reflect differences in the distribution of the non-radioactive active component.

In other words, if you have a receptor binder where you know what the distribution of the radioactivity in man and animals is, can you then say that that is representative of the non-radioactive component?

So we believe that we are well placed to detect differences in biodistribution that might lead to differences in the safety profile.

DR. DeGEORGE: That is generally useful--generally true for things that are not metabolized. But when you actually have

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materials that actually undergo metabolism, clearly there are differences, again, between species. So understanding what is actually the circulating entity into what exposure it has across the various species, particularly if that might contribute to toxicity, is something that needs to be assessed. If you knew that the proportions of everything across all species were the same, then just following around the radioactivity would probably be useful and acceptable. But if you know that the metabolism might differ between species, then following around a metabolite in one case and the active compound in another case might lead you to very different conclusions about the safety of that material.

MR. NUNN: But we do also have the response, the clinical response and the animal responses. I mean, we're not doing this in a vacuum.

DR. DeGEORGE: But if they differ, if the responses actually in animals is not an overt response but is, in fact, the histopathologic change, you're not going to follow that around very clearly or very easily in humans unless you have the unfortunate circumstance of patient death or something.

DR. MILLS: Let me just emphasize, again, from the PK across into the clinical area of nuclear medicine, you're going to have to be able to acknowledge the concept of, say,

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de-halogenation with an iodine-labeled product, and that we know that the iodine is going in one direction and one clearance pattern while the metabolite is going in another clearance direction. So when looking at the modeling and the discussion of this, you have to be able to take into account such circumstances where these are metabolized and split cleanly apart and been well known for years, and if it was I-131, which we wouldn't expect in a diagnostic, it would have an adverse event profile related to the I-131 separate and away from the metabolite.

MR. NUNN: Yes, I mean, the problems of halogens are a little different, and iodine in particular. But we can detect whether--the indication of technetium, whether it's separated from the pharmacophore relatively easily, and that might be the way to go, that if we can show that it runs through, then we've done the PK in a way which is far more extensive than you can normally do it because you've got biodistribution.

DR. DeGEORGE: Adrian, just one follow-up comment, because that was one of my areas in terms of looking at it from the clinical standpoint; the breadth in terms of various types of radioactive tracer labeling might well help you in terms of being able to establish various areas in which you're

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going to approach. Technetium products may well be one class that you could approach much more easily, say, than an indium product where there's a linker involved versus an iodine I-123 diagnostic where you might have the halogenation appearing also. So it's another area in terms of--both in terms of your elements here for PK evaluation and the confidence that you can present both to the clinical nuclear medicine community as well as to the classic PK evaluations.

DR. LOVE: Okay. Basically what I've heard is you're essentially proposing that routine PK is not done for radiopharmaceuticals but just the biodistribution on the basis of radioactivity. Are you addressing this as an approach for all radiopharmaceuticals regardless of whether they're Group 1 or 2? Or is this in relationship to the entry criteria for Group 1? I think we've been responding to you from all perspectives, but I would like to know--

MR. NUNN: Well, for entry criteria, of course, you don't have humans, anyway, if you enter before Phase 1.

DR. LOVE: But it's confirmed at--the final designation we were talking about would be confirmed at the end of Phase 1 with the human data as well. So is this the proposal that you're making for how one would approach Group 1, or is this

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the proposal for any radiopharmaceutical?

MR. NUNN: I think certainly for up to the end of Phase 1 where I would define Phase 1 as some proof of concept in patients, including proof of concept in patients.

DR. LOVE: Okay. I did have one other comment on the preceding slide. You were saying that--the wording on your slide said that the FDA had not asked for this information from any approved product. We've asked for a variety of different types of information to try to address this. Often products have been approved perhaps without this because we had other alternative information that allowed us to go ahead and be able to approve or to label the product as not having that information, but still feeling that we had enough information to describe the safety of the product. So we've asked for a variety of different types of information and have used other information to balance it. Part of the reason for the guidance in this area was to try to describe the types of data which, when they are available, assist in the development process. I think it was mentioned at the end from the open comments that a lot of the data builds upon another piece of data information, and often we find ourselves in Phase 3 in drug development not necessarily having all of the information together to be

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able to write a complete package insert or to make full assessments. So sometimes things are done at the end. What we're trying to talk about now is prospective development, thinking about what approaches would be useful if you're Group 1, what approach is useful if you are a Group 2. And we do look at the pharmacokinetics, both in the general and the specific terms, as you've been talking about. At the beginning, you talked about dose ranging, and I think there are probably two different things that have been discussed historically, not so much expanded in the guidance at this moment. One was whether there would be dose ranging to find the radioactivity dose. The other is the ligand. And I think we've moved away from wanting to see dose ranging for radioactivity. Certainly when you're using a lot of the compounds that are commonly used, then there are not questions about that.

When we talked about dose finding for the ligand, the question there had to do with the potency of the ligand itself and what's the best amount of the ligand that's needed to get optimal imaging and to try to get a balance between the safety factor that may be brought from both the radioactivity as well as the ligand and the combined product in terms of its toxicity or lack thereof. So we have talked

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about doing dose finding from that perspective, and that's more what was in our thinking in the guidance when we talked about dose finding. It's really looking at the ligand and what's the amount that you need there.

Certainly there are other chemistry questions in the vial and how much do you have.

MR. NUNN: That's the important point.

DR. LOVE: Right. Now, so we've certainly--that's more of what was in our mind in talking about dose finding, so before we get back to the metabolism issue, is that what you were also talking about when you're saying no dose finding? Or are you assuming that you would have done the work that you needed to do beforehand so that you've selected the appropriate amount for binding of the ligand?

MR. NUNN: I think we would have pretty well selected it beforehand, because remember that we're doing chemistry in the vial again, and that frequently the chemistry that we are required to do in the vial determines the amount of non-radioactive components that are in there. So we don't have any room to move, and obviously it's in our own interests to lower the amount of ligand as much as possible.

DR. LOVE: Some of that information is the type of information were talking about that we'd like to see, is the

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data that you've used to select the dose. And it's probably more relevant in a situation where there is demonstrated toxicity of a product, perhaps, than if you're going to be in maybe a Group 1 setting in terms of whether we would want to see a formal dose ranging study. But that's sort of the general--dose ranging was the general piece, not so much for--it was not identified specifically as a requirement for Group 1. So I think we can look at different alternatives to try to give us some information about whether or not the optimal combination has been developed. There are other ways to try to do it. I think the idea there is to provide information that gives us enough reason to agree with you that these are the appropriate dose and you have the appropriate risk/benefit profile to get started.

MR. NUNN: Well, we already provided you with information which tells you how we've determined the limits for all ingredients in the kit. That's normally determined by chemistry, not by safety.

DR. LOVE: And see, that's the issue. There are different questions going on at the same time. One is the chemistry information that comes in, and then there's another piece of information that has to do with the optimal combination of a product that's going into animals and the receptor affinity

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or participation in a metabolic process or something that's more non-specific. Whatever it might be, what approaches have been taken to identify and support the selection of the dose are the types of information that we would need. Sometimes that come in a formal dose finding study. Sometimes there may be other approaches that can be useful.

MR. CARPENTER: I was going to add by design the radiopharmaceuticals are prepared with the minimum quantity of ligand possible that provides good radiochemical purity and minimizes the potential for competitive binding to the target in vivo. So I just don't want--I want to make sure I'm not confused, but I don't think we're thinking about dose ranging from the classical study in humans for efficacy, because, in fact, the efficacy is established based on the imaging parameters, and those are optimized by having the minimum quantity of ligand present. But the safety considerations, of course, from what we've been discussing earlier are still important.

DR. MILLS: Right. George Mills. One of the points, though, is that many times I've seen products that have a change in the amount and quantity of the ligand as well as the amount of activity that's been put on in terms of determining that we have a specific imaging interval which

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is different than what was originally started with in a Phase 1 study to begin with that you might find that you want to, instead of imaging optimally at two to four hours, be wanting to image at 18 to 24 hours. Suddenly you want to double the dose of radioactivity. You want to add additional ligand. So as a result, yes, there are safety issues in terms of the formulation that are advanced forward, but number two is if there's an extensive amount of PK, quote-unquote, that's done clinically to determine what's the optimum use of this product in various target patient groups, which may change the amount of activity that you're going to administer to a various patient, depending both on the radioactivity and the amount of ligand. And that's been a common occurrence, especially as we go between Phase 1 to Phase 3 in the development of a drug product.

MR. NUNN: I'd like to go back to something you said, Dr. Love. You said that contrary to my statement, you'd never--you had asked for PK studies to be done on radiopharmaceuticals, but that you had been persuaded to accept other data.

I don't see in the guidance right now what that other data was that you used in lieu of PK studies, and I would like to know what sort of--

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DR. LOVE: Right. It is not in the guidance now because that was more retrospective. It's basically looking at a drug development program near the end of the process, recognizing that all the data may not be there, and then looking at what else is there and determining whether or not there is sufficient information to balance the absence of that data.

The guidance is not written from that perspective. That's why it isn't in there, because the guidance is written from a prospective drug development point of view. What we were asked by industry was to provide information and guidance that would help to eliminate problems down the line, so that's why those kinds of things are not in there, and we would hope we wouldn't have to deal with that once the guidance is out there.

David?

DR. LEE: David Lee, from Click Pharmacology Biopharmaceutics. I just want to piggyback on what Dr. Love said. There are many things that we--if we want to talk about fundamental and classical pharmacokinetics, sure, ADME studies are--you know, it covers pretty much everything. But as far as a distribution is concerned, I think it's my own thought that distribution is based on metabolism as well

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as distribution, the elimination, I guess, characteristics of whatever that drug is that you're looking at.

So if you want to just look at the distribution of radioactivity, I think I understand your logic. But I also would like to caution you that it's just not the radioactivity that is just a function of the route of administration but also, again, the metabolism, metabolite, or what have you.

As far as the sensitivity of the methods, I am not an expert on that, but I think I do know enough to comment that as far as the amount of radioactivity is concerned, Dr. Love said from a dose ranging study it's the ligand portion that we do ask for dose ranging, what have you. My comment goes in a similar way to Dr. Mills' comment that, you know, sometimes you do have to look at radioactivity doses, different doses. And I do see data submitted from the sponsors on the radioactivity dose ranging as well as the ligand, the total mass amount. So there are data there. It's just that we do not specifically ask for that.

The guidance, just like what Dr. Love said, I mean, we could be as specific as much as possible, but I don't think that's the purpose of that. I just wanted to comment on that.

DR. LOVE: Well, what I'm hearing, though, one of the

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comments that George was making I'd like to ask about, and that was that there may be different approaches that would need to be taken whether we're dealing with a halogenated product, a technetium product, yttrium or something else, versus another type of product. So if we were to develop the guidance to at least sub-group it in certain ways to address some of the things that have been talked about thus far--I know we haven't finished all of the discussion--would that be something that would be reasonable from your perspective?

MR. NUNN: It might be, depending on what you--

DR. LOVE: Sure, I understand.

[Laughter.]

DR. LOVE: That was an unfairly broad question, yes. Okay. Let me table that question for a moment, and let's finish the rest of some of the discussion points that you raised.

MR. NUNN: The only other--I mean, we talked about the last paragraph. The penultimate paragraph here is something that comes back quite often, and that is that, in general, all radiopharmaceuticals that image tissues other than the blood must clear rapidly from the blood to achieve the desired high target-to-blood ratio. And we can see this in every patient we image, so by definition, this precludes such

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compounds from having significant protein binding, which also indicates questions asked in the therapeutic drug field concerning changes in protein binding which could lead to toxicity in the therapeutic side.

We have been asked in the past to measure the protein binding of the radioactive portion of the drug and to see what changes protein binding. But we can see that on every patient that we do, and that is a far more efficient and more direct way of doing it than measuring protein binding under all circumstances in vitro.

DR. LEE: David Lee. One of the main purposes of protein binding studies is to look at the volume and how it's going to be distributed. Just like you said, in order to target or image the target organ, you want the rapid clearance because otherwise you're not going to see anything and you want to image as quickly as possible on some of these short-lived physical half-life, you know, radiopharmaceuticals. But protein binding information gives me some sort of a data and some assurance that it is actually clearing from the body itself and how much it will be bound if it is. But it's not the radiopharmaceutical portion that binds, but it's the ligand portion. So that information could be critical.

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MR. NUNN: In the past, we've been asked the same question for the radioactive portion, and I would submit that looking at an image is a better way to go than looking at protein binding to see what the image might be.

DR. LEE: If that was the case, then perhaps that would--it's just a miscomnmunication from the agency point of view or myself.

DR. LOVE: Okay. There were several points in your slides. This is shifting more to the other part of the process, the metabolism and looking at pharmacodynamics or whatever other terms one might use for that, anything other than the radioactivity. And you had three hypotheses: one, that there isn't any animal toxicity; two, that you would have information up to 50- to 100-fold times the maximum human dose; and another one, where there were significant animal events. And you looked at those different scenarios and made a proposal that on the basis of those things that human other pharmacodynamic or metabolic information would not be needed.

I guess just a couple of concerns that are underlying the things that have been mentioned. One is we certainly have seen situations where either there was protein binding--maybe those products did not move through the

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process for whatever set of reasons, and maybe they're not approved, but certainly in an IND stage we see products that have protein binding. We see products sometimes that may not be eliminated through the kidney, as you've talked about. We see products where the linking is not sufficient, and so you follow the radioactivity and it goes out in the urine and the other part of the ligand is still in the body somewhere.

We have some products that may be irreversibly binding to receptors, so something must happen if the radiation leaves and the ligand is still there.

So there are a number of other scenarios which are apt to occur as drug development moves forward, plus as you begin to move into the next few years, there are going to be different products that are being developed in a wide variety of other indications. Not all of them may be intravenously injected products.

So we're trying to write the guidance from the perspective of the future, all the other things that might happen, and indicate the types of information that would be used to try to answer a lot of these questions. So in the case where metabolism does occur, it seems important to know that, to find out about it, find out what the consequences are. Do

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you produce a more active metabolite maybe that happens to dissociate from the radioactivity?

Whatever else is going on in the process seems relevant. If it's a very potent product, then the issues of activity and toxicity may be picked up perhaps in animal safety pharmacology or toxicology studies. They may or may not be. So there's a lot of pieces of information that do go into this assessment. So for us to simply say no, you would not have to look any further on the basis of some other assumptions on the types of products that might be approved at this point is a bit problematic for the future.

On the other hand, you might be able to provide data that suggests some of the things that you're talking about, that you don't have metabolism in animals, maybe you do some in vitro studies to look at whether or not you have metabolism in liver homogenates, intact human liver homogenates or something else. You might look at receptor binding and other information that could be used to justify either waiving pharmacokinetic--full metabolic process evaluation or speciation in humans. There may be other approaches to try to justify that, but to still leave enough room so that when it does occur, it would be able to be identified and we could move forward with getting those products fully

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characterized as appropriate for those drugs and minimizing the evaluation for those drugs where the things that you describe do not occur.

I think that's more in relationship to my other question. If we are able to develop some guidance that tries to clarify those different pathways and approaches, would that be more reasonable?

MR. NUNN: Yes, I think a decision tree--the decision tree idea that we've talked about at this meeting is a way to go in that direction, because there are many ways of getting to the same points, I think.

DR. LOVE: And I think we agree that if you don't need to do all the work, then we wouldn't want you to have to do all of that. Unfortunately, it's not an all or nothing situation. We've got to look at the total set of radiopharmaceuticals products, both now and coming down the road. So we're trying to find a way to address all of these.

MR. KIRSCHENBAUM: Could I ask for a clarification?

DR. LOVE: Okay. Yes?

MR. KIRSCHENBAUM: You spoke about a decision tree--

DR. LOVE: Microphone, please.

MR. KIRSCHENBAUM: This may be a clarification from both sides. Does the concept of a decision tree cut across Group

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1 and Group 2?

DR. LOVE: It could. I think the question that Victor was raising also here silently was whether or not presence or absence of metabolism should be part of the decision of whether you're Group 1 or Group 2. I'm not--I think you could be metabolized into a safe product, so I don't know that I would exclude--I don't think I would use the fact that metabolism occurs as a reason to exclude from Group 1. But perhaps what happens as the end result of the metabolism might be something that's considered. I think this is in a--we're in a thought process here on this one, and what you're saying is also helpful to us to think about it. But, yes, we probably could devise a system to look at both Group 1 and Group 2.

I think that goes to a comment that I made earlier on safety monitoring, and Group 2 doesn't mean it always has to be everything, and a lot of the principles that we're talking about would still be relevant in Group 2 on whether or not you would or would not need to do certain types of analyses, and we could think about that. It's probably more related to what the drug actually does.

DR. RACZKOWSKI: What I was trying to get at was how broadly or how narrowly the community would like Group 1 to be

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defined. For example, it could be fairly easy to define Group 1, but it would be fairly narrow if you were to say that you might only limit it to drugs that are non-metabolized, for example. But I don't know if that sort of idea would be appealing to the community or not.

MR. NUNN: You obviously should not use metabolism per se as exclusionary because it could be metabolized in a beneficial way.

DR. RACZKOWSKI: Sure, sure.

MR. NUNN: But I think the intent of the act was to try and acknowledge that radiopharmaceuticals are different to other therapeutic drugs and that we should try and accommodate them. And I don't think the intent of the act was to have a very narrow Group 1 in which only a very small percentage of radiopharmaceuticals belong. So I think there's an onus us to try and work out how to include a significant proportion of them.

DR. LOVE: And we would agree with that. We would like to see it as broad as is reasonably appropriate for the products, and that was one of the reasons for the 24-hour limitation for elimination that was in the original--that was presented by CORAR at the last meeting seemed a bit too narrow for the reasons you're just talking about. Half-life

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may not be related to safety. Metabolism per se may not be related to safety. So it would seem appropriate to allow for those other products to get into Group 1 if they can.

MR. NUNN: Yes. I would agree that if you get 80 percent of your mass excreted in animals within 24 hours, that is a very stringent requirement because once it's out of the body, there's no way it can get back in.

DR. LOVE: Right. But I guess I'm saying we were thinking that that's too stringent, and it's better to not put that type of a limitation on there. So I think what I'm--correct me or tell me, the answer to Victor's question then is no, you would not want it limited to non-metabolized products.

MR. NUNN: Right.

MR. KIRSCHENBAUM: I would not like to see the question of whether PK studies are required become the same as whether a product is Group 1, because there are other facets to Group 1 than whether PK studies are necessary.

DR. LOVE: Absolutely. And also I think there are other types of information that can help answer the question, whether it's Group 1 or Group 2, of whether or not you need to follow radioactivity or do you follow--and do a full speciation. I think that's really not based on a safety profile. It's based on other factors of the drug and what

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happens to it.

Peptides are going to be metabolized. They're just going to be metabolized.

MR. CARPENTER: Well, I think that's for the sponsor to demonstrate. I would suggest that one of the considerations around the requirement of PK should be a careful characterization of PK in animals, and, in fact, getting back to what we talked about before, there must be a set of circumstances where there should be a de facto exclusion from doing a PK study in humans where you can show a lack of metabolism, a very good safety margin, and, you know, good recovery in appropriate preclinical models as a baseline, and then, of course, we want to discuss other aspects of it, I think. And to Dr. Mills' point, obviously there are going to be exceptions where, in fact, the radiochemistry and the pharmacokinetics are in the same concentration regime. That's a different situation. I admit that.

DR. LEE: I'd just like to add a comment to the in vitro metabolism. In vitro metabolism may not show metabolism, but that doesn't mean that in vivo the metabolism, you know, is not going to occur. So there's that--we have that up to some certainty in in vitro data, but yet it's not going to be 100 percent predictive in what's going to happen in vivo.

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DR. LOVE: Okay. Any other comments?

[No response.]

DR. LOVE: Okay. It sounds like then that we will have to develop some approaches to try to clarify these different aspects and when radioactivity alone is a reasonable approach and when others would not, and also try to relate this to pathways that are both relevant to Group 1, Group 2, and when they're different--when they're the same, when they're different.

MR. MORGAN: It seems that as we go through a number of these topics, we're coming more or less to the same general conclusion, that a very blanket statement is inappropriate. And I think what we as sponsors really need from the agency is your thoughts around where certain decision points are, the kinds of information that you're looking to guide us we come forward with our program. And I think that's a very rational approach to be going towards a guidance document, that it's important for us to understand what you're looking for, and possibly the rationale for why you want that piece of information. We talked about the need for repeat dose studies, and I think it is now becoming clear that you don't want repeat dosing for looking at the build-up of metabolites, but looking for another piece of information.

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And I'm not really sure that that was clear from our earlier discussions.

So that type of information I think is critical to us in developing our programs.

DR. LOVE: Okay. Fine. Thank you.

I realize it's about 11:30-ish right now, and we still had a few points from MICAA on Group 1, Group 2 issues. Is there sufficient time between now and lunch to do that? Or we can do lunch at 12:30 if necessary, or 1:00 if need be.

xx MR. CARVLIN: Because there is so much similarity in the MICAA concerns and the CORAR concerns, I think we can spend maybe five or ten minutes pointing out the similarities and emphasizing where there are points that may not be exactly the same.

DR. LOVE: And if we need to break and come back to it after lunch, we will do so. Thank you. Go ahead.

MR. CARVLIN: All right. We began this morning by trying to touch upon the special characteristics that distinguish the medical imaging drug products from their therapeutic siblings, and we've had a fair amount of discussion talking about those characteristics, and now what I want to do is emphasize the different characteristics that are particular for radionuclides and radiopharmaceuticals and those for the

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medical imaging contrast agents, the better known contrast agents. And physics and physical chemistry are as important or even more important than biology and biochemistry, and that just means that these products are largely biologically inactive.

Now, that's starting to change, as Dr. Love had mentioned earlier, with the introduction of peptides and as we had spoken about in relation to pharmacophores, where there actually is biological activity. Granted, it might be at a very, very low level, but this signals the next step in the evolution of medical imaging drugs and biologics, and that is that we are evolving from a simple demonstration of structure and anatomy to function and physiology. And, clearly, radiopharmaceuticals and radionuclides are in the vanguard for any number of reasons. The science is very well evolved, chemistry, physics, biology, and pharmacology, so that the structure and functional demonstrations possible by radionuclides are more varied and more developed than what you have for medical imaging contrast agents.

However, there will come a time when medical imaging contrast agents are there as well, and that's something that we want to receive in the guidance, is latitude for the future, because we want to make sure that the guidance is

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not too firmly entrenched in our current understanding of medical imaging drug products, that is, intravenously administered iodinated products for X-ray or intravenously administered gadolinium kelates for magnetic resonance where the kinds of micro bubbles and micro aerosomes that we're currently developing for ultrasound or even the radionuclides and radiopharmaceuticals that we have for nuclear medicine.

Okay. Another point was raised about the small mass doses, single and limited use, rapid near-complete elimination. That also does apply for the medical imaging contrast agents, and quantitatively, what we're looking at is drug substance and drug product in this range. And in the afternoon or after lunch, we'll talk about the grade point that appears between the nuclear medicine and the ultrasound products that are currently in development versus the magnetic resonance contrast agents and the X-ray contrast agents. And this is really the basis of mass dose ranges both for the drug substance and for the drug product. Elimination is rapid and near-complete, and this gets to the question about how are these products metabolized. Certainly that varies on an agent-by-agent, case-by-case basis, but for most of the products that are currently in

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development and those that are approved, there is virtually no metabolism. So some of the comments that Adrian Nunn had made on behalf of CORAR are immediately the same for MICAA. We would ask for FDA to consider those circumstances as applying, where appropriate, for ultrasound, magnetic resonance, and X-ray.

A case in point would be for the ultrasound products we're using advantagefully small amounts of material, somewhere on the order for the active component maybe as little as 50 micrometers, and that this gas is chemically inert and it's biologically inert and it's quantitatively excreted unmetabolized. So there are the same kinds of concerns that apply to this category, the ultrasound category, and the active component there of gases, as for the radiopharmaceuticals and radionuclides.

Okay. So those are pretty much the comments I have to offer regarding the medical imaging contrast agent. There are some specific comments about inclusion in Group 1 versus Group 2. If you have early designation as being in Group 1, is that in perpetuity? I think we've come to appreciate that as our understanding of the product's performance and most particularly its safety profile grows, you may want to reconsider inclusion in Group 1. Similarly, if you're

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designated as a member in good standing of Group 2 and with broader experience in the development of the product you understand its safety performance to be exemplary, that may be sufficient to justify a reconsideration and perhaps inclusion in Group 1. So that is an open question of you're in Group 1, are you always in Group 1, if you're in Group 2, are you always in Group 2, and under what circumstances might there be a change.

Also, Dr. DeGeorge had raised a question earlier and there was a brief discussion before the break about pharmacophore. I just wanted to emphasize the concerns of the Medical Imaging Contrast Agent Association that we also have identical pharmacophores for different applications, products that may have been developed for a therapeutic indication now seeing application and extension for diagnostic, and, interestingly, vice versa as well, although we're not really here to speak on behalf of therapeutic pharmaceutical development today, and also that there is a potential for cross-modality development, an additional extension where you do have the same pharmacophore. What kind of safety concerns would apply in that instance?

Also, Dr. Nunn had made a comment regarding proof of concept studies and how a pre-development phase is now common for

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radiopharmaceuticals and radionuclides, where up until this point, you could demonstrate to a very high degree of likelihood that the pharmaceutical was going to be effective from the lab bench forward. A case in point would be what I cited this morning, the Delholme, Conrad, Rankin, and Teitman's (ph) mixture that was introduced within six weeks. Teitman's mixture is really a very nasty concoction of cinnabar lime and petroleum jelly, and it was infused in a cadaveric hand, but all of the science that needed to be understood was understood in those first six weeks. You needed something that could stop or scatter X-rays.

As we moved from structure and anatomy and physics into the world of physiology and function, we are going to have to have a more lengthy pre-development program. So the same kinds of studies that are currently being practiced for radionuclides and radiopharmaceuticals, these proof of concept studies, are likely to be seen for medical imaging contrast agents, and the same kinds of concerns would apply there as well.

Regarding pharmacokinetics and pharmacodynamics, we have a much different set of concerns there, and just two points to raise briefly at this point, and then we could perhaps revisit that a little bit later. That is, what is the

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appropriate pharmacokinetics for medical imaging contrast agent? Is it necessarily that all components must be fully characterized? Or is it sufficient that just the drug product could be characterized, drug substance could be characterized? There are a number of points in the guidance document where there seems to be a slight difference in interpretation, a slight difference in the recommendation or the expectation that's cultivated. So if we could get some clarification, perhaps additional discussion on that point, that would be helpful.

The last point to raise here had to do with a discussion about the routes of administration, and Dr. Raczkowski had alluded to that earlier about systemic exposure being different for different routes of administration. And there may be a very low systemic exposure going by an alternate route of administration. An example could have been for a product that has prior development and approval for the intravenous or intra-arterial route of administration and is now being developed for an alternate route such as oral, rectal, or intra-articular. What special concerns apply in that instance, and how might we be able to facilitate the development for these alternate routes of administration, provided that there is low systemic exposure and we

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otherwise understand the toxic risks and profile of that product.

The last concern--and really more looking to the future--is that medical imaging contrast agents and radionuclides are being developed for a much broader range of indications, and we're also looking at all different phases of matter in addition to routes of administration. And there will be different concerns regarding pharmacokinetics and the potential toxicity depending on the phase of matter. And this then brings us back full circle to discussion about gas and ultrasound and the drug substance here.

Those are all the comments that I have to offer from the Medical Imaging Contrast Agent Association.

DR. LOVE: Thank you very much.

Just a couple of questions. I'll try to just address a couple of points first, and then I did have a couple of questions for you.

We were thinking Group 1, the question of Group 1 to Group 2, our thoughts on that were that you would get into Group 1, as we've been talking about, completely into Group 1 by the end of Phase 1. But there has always been an assumption that if there was a catastrophe, if a patient died, something terrible happened, and, yes, we would have to

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reassess whether or not this is Group 1 or is that related to some explainable issue that happened to just be related to the patient's underlying disease. So it would be a balanced assessment of that. So there was a possibility of going from Group 1 to Group 2, depending upon clinical adverse events, monitoring and results, but we would do that realistically.

We hadn't talked about going from Group 2 to Group 1, so you raise an interesting question that I think we'll have to consider. But essentially what you're saying, I would assume, is if Phase 1, Phase 2 data showed that there weren't adverse events, you're asking if maybe could Phase 3 be reduced. Is that essentially what you're talking about?

MR. CARVLIN: Yes, and also anticipating for the medical imaging contrast agents the impact of pre-development and the importance that the proof of concept studies are likely to serve for us in the future.

DR. LOVE: Right. I certainly agree that we would look at whatever data you had that would be relevant, so that if you had proof of concept studies or other things, to help make those assessments, those would be important.

MR. NUNN: I think we have issued--or have discussed going from Group 2 to Group 1, but in indirect terms. And I can

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imagine that the animal tox profile and PK profile is much worse than humans, and so you're in Group 1 because of the animal data, and then when you get into the human data, you find that the animal data does not predict human, and it's actually much better.

DR. LOVE: Right. But I don't know that we in our own dialogue at the agency have directly talked about going from Group 2 to Group 1, but you raise a question and we'll certainly think about that. But we don't have an answer for that one right now because we haven't directly talked about it.

Your next to the last comment had to do with routes of administration. Certainly other information based on a route of administration would be considered, and the example that you gave is a good one. If you know what the systemic exposure is if it's given intravenously, and if now you don't have any systemic exposure, then that would--we at least wouldn't need to be concerned about the targeted toxicity, perhaps, let's say, in relationship to the GI tract if it's oral. Intra-articular raises some questions about absorption and other things, and we'd have to look at that. But that would be based on the data that you would submit, and certainly that's the kind of information that

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would be used to make an assessment.

I think one of your written questions wanted to know does that mean it's Group 1. A lot of it would depend upon what you think the toxicity is, I think, to the target organ, meaning the GI tract in that particular example.

DR. RACZKOWSKI: But I think we're open to considering those types of scenarios and perhaps modifying the guidance document to try to encompass some of those scenarios that you described when we have systemic exposure and now it's given by a particular route.

DR. LOVE: Right. I agree.

Could you address a little bit what you were talking--your comment at the end about different phases of matter.

MR. CARVLIN: Yes.

DR. LOVE: Could you expand on that a bit more, please?

MR. CARVLIN: Yes. Just that--and we don't think that our accustomed approach to development is necessarily going to be predictive of what we're going to do in the future. We're very expert at this point at developing iodinated contrast media for X-ray or contrast media for MRI, and we've got a large experience in ultrasound. But products in the future are going to be a lot more varied than what we have currently, and I think that a lot of the examples and a

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good deal of the thinking embodied in the guidance document was based on X-ray, magnetic resonance, radiopharmaceuticals, and ultrasound as they exist today. But if we're going to introduce, let's say, a hyper-polarized gas as a magnetic resonance contract agent for one imaging, what special considerations might that bring?

Similarly, if we're going to be introducing capsules for magnetic resonance imaging, where there would be a different route of administration and absorption, is that anticipated in the guidance document, and do we have the kind of flexibility that's required in order to fully take advantage of the properties of those kinds of products?

DR. LOVE: What would you like to see the guidance do or say in relationship to new modalities such as those you've mentioned?

MR. CARVLIN: Okay. One is, where possible, to allow flexibility, not so much so that it is completely nebulous and ill-defined, because we struggle with that in the same way that you struggle with that. We'd like clarity and direction. But just to understand that it is possible that you could have for different indications or different routes of administration a single product being both Group 1 and

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Group 2, surprisingly. This we talked about. So those kinds of concerns I think we need to have anticipated in the document.

DR. LOVE: Any other comments, questions?

[No response.]

DR. LOVE: Are there any comments from the audience, please, on anything that's gone forward this morning?

[No response.]

DR. LOVE: No? Okay. Then I think we'll take an hour break, and let me just ask one question. Do you feel that this closes the issues from MICAA for Group 1 or Group 2? Or is there anything else that you wanted to put on the table? If not, then we would go to blinded reading when we come back.

MR. CARVLIN: We feel as though all topics have been addressed.

DR. LOVE: Okay. Fine. Then blinded reading when we restart at 1 o'clock.

[Whereupon, at 11:56 a.m., a luncheon recess was taken to reconvene at 1:00 p.m., this same day.]

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AFTERNOON SESSION

[1:09 p.m.]

DR. LOVE: For this section, the FDA received six or so questions from MICAA and CORAR. They were somewhat similar. We actually received a set of questions from each group, and what I'm trying to do is just put the similarities together on this slide. They had to do with the primary endpoint and its relationship to efficacy, clinical efficacy or utility, and then the rest of them basically had to do with the value of the blinded read itself and the number of readers, sequential unblinding, and basically was ending with a major question about whether or not information from a fully informed blinded read or open on-site read could be used in the package insert, and how might we do that.

The first question, I guess I'd really like to ask for some clarity from MICAA on this one. It's Question 2. Why can't information on clinical efficacy and utility of the test agent also be used as a primary endpoint? I want to make sure I try to understand what that question was. It would seem to me that that question had to do with perhaps several sections in the guidance that talked about using blinded read and trying to provide the information that determines the endpoint.

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I didn't actually find the place in the guidance where we said that the blinded read endpoint alone was the primary endpoint, so I just wanted some clarity. It seemed to me that it's more a relationship of the full set of information and how it's used. Is that more the question?

MR. BAUM: No, the question--Len Baum. The question is really right now we are using something--one primary endpoint is the blinded read. The unblinded data or other data that's collected--and I'll get through some of it during our presentation--is not allowed as the primary endpoint. Those are considered secondary endpoints. In some cases, they're not even--some data that's collected on secondary endpoints do not find their way into the labeling, and that's why some of the discussion is--the information that's collected during the conduct of the trial can also--and why can't we have more than one primary endpoint? In other words, certain information collected that is based on the clinical practice and clinical use of the drug could also be considered primary endpoints for the use of the product for its intended use. So that's the concept behind that.

DR. LOVE: Okay. We'll probably talk a little bit more about the endpoints themselves when we get into the

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indication part, and that does seem to be slightly different from the rest of it, so you're actually relating that then to the points that are on the remainder of the slide and that has to do with the use of the blinded or unblinded data in any sequential unblinding. Okay.

George Mills just gave a talk about sequential unblinding at the DIA meeting, and half of the audience probably heard your talk. I'm going to turn this over to him.

DR. MILLS: What I'd like to do is to take you through a process of definitions, and part of the problem we had in the last meeting was describing and identifying various elements and statements and so on. I'm just going to take you through definitions, and we'll put back again that list of questions that you had and try to address issues as we go through. But I'll try to focus you on some of these elements right now.

First of all, when we're looking at the blinded off-site interpretation, this is our classic model. It represents the off-site independent imaging interpretation for efficacy performance. And just as a side comment, one of the issues that I point out for you is that there's not safety here. You cannot reproduce the safety findings. When you're looking at an interpretation in a clinical trial, there's an

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extensive amount of safety data which is acquired on-site. This, the off-site, is for the efficacy interpretation, and that's a significant point. There's a lot of information that's on-site that can never be reproduced. But in terms of efficacy evaluation, we're looking at that off-site interpretation in order to remove any potential bias that might be introduced from the on-site interpretations.

Now, let's take a look at what are the classic elements that we would see with that type of interpretation in the off-site interpretation. Thank you. How do I work it? There's a little button. All right.

When we're looking at this blinded efficacy interpretation, it's typically performed off-site, away from the sponsor and away from the clinical sites. One of the elements that was introduced in the last question was in terms of using clinical sites from various other--to cross over, if you will, and in looking at it, we have small studies, as we typically have in biologics. It's usually not a question because there are an ample number of sites which might be available to us.

Within CDER, trials which are somewhat larger than ours, typically this is not always--it's been an addressed issue also. We did find within the agency, though, that there is

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a very large trial going on with mammography where they are introducing such a model where they're crossing over. There in terms, it was justified prospectively in terms of the development of that model that they had exhausted all available sites in the United States because they were all participating. So from the standpoint here, I want to point out that this is a classic model, and that if you're looking at a unique design in terms of use of sites or crossover sites, the agency, I anticipate, would be more than willing to prospectively look at it. But from the standpoint of retrospectively and in a classic model, this is the definition we're typically working from.

Centralized site for this interpretation or limited sites, independent monitoring away from the clinical sites, away from the sponsor, independent physician interpreters with masked films removing all the patient identifiers. The classic type of model when we're looking in terms of the off-site independent interpretation.

Now, when we look at what would be classified as the classic, fully blinded interpretation or a pure--and this is what most people are looking at when we start to describe the fully blinded interpretation, images only, no clinical information provided, no technical or clinical information

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is provided, and this type of fully blinded interpretation is applicable when you have a very standardized imaging modality that you're using, such as in this case as the examples in chest X-ray. It's a well-defined set-up. All radiologists typically understand the X-ray. They understand the imaging parameters. They understand the constructs. So they need very little information in order to render a fully blinded interpretation. So this would be your pure model, and it would be applicable for that type of imaging modality.

The next fully blinded interpretation, though, is with images only as a modified, another step in terms of looking at this, and that is typically for a non-standardized imaging protocol. Now, when we're looking here, we still have it fully blinded, but you're dealing with a non-standardized protocol. It is not a standardized imaging protocol, so the radiologist, nuclear medicine physician may not understand or know how to interpret those images. No anatomical orientation or detail. Many of our imaging studies, especially with radiopharmaceuticals, have very limited anatomical detail that's provided.

So now we can look at a fully blinded interpretation, images only, as a modified for non-standardized procedures--a

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subset, if you will, or a different set of fully blinded interpretations. Here it provides basic, blinded interpreters, the basic imaging protocol and the anatomical orientation. This is going to reduce the potential for concern for bias of limited or under-interpretation. So when you're talking about a fully blinded, there are already two ends of the spectrum that always have to be acknowledged when looking at this, and this should be defined prospectively when you're looking at your Phase 1 and Phase 2 development protocols as to how best to approach this imaging modality.

Are we dealing with a standardized imaging such as a chest X-ray where we're going to work with some new contrast agent? Certainly we need very little, if any, information for the interpreter. But if you're working with a radiopharmaceutical that has a very new imaging modality and imaging protocol, you would still have a fully blinded, but you need to provide information. But it's inherent upon the agency as well as the sponsor to identify what are the limitations going into a prospectively defined fully blinded interpretation.

Next is a definition of a fully informed but blinded to truth interpretation. From that standpoint, there is a

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subgroup where all images are provided, all anatomical orientation is provided, the imaging protocol is provided, and all data prospectively designed in the clinical trial protocol--and prospectively defined because, again, if you begin to start doing this retrospectively, you break up a lot of this structure. You must prospectively define it. This is where going into the Phase 3 study based on the Phase 1 and 2 development this should be defined for a fully informed but blinded to truth interpretation.

Now, once you identify that you have two spectrums, one, the fully blinded interpretation, and, two, the fully informed interpretation but blinded to the truth, then you step into the sequential unblinding that we talked about at the last meeting. And what does that really mean? Sequential unblinding is a combination design for blinded off-site interpretations, fully blinded and fully informed but blinded to truth, the two groups we've just talked about.

From whence does it come? Classic medical imaging grand rounds, clinical interpretation model, it's been around for decades in terms of looking at images. Classic four-step approach for sequential unblinding.

The step one is fully blinded interpretation. The image set is presented. No clinical history, no supporting imaging.

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Now, again, remember I told you there are two different subsets, and I did not limit your imaging protocol necessarily here or that information for anatomical orientation. But I did limit you in terms of any clinical history and any prospectively defined information within the trial. The blinded interpretation is then recorded and locked. Now you have your first step.

Step number two is once we have locked that interpretation, the complete prospectively defined clinical information provided with all supporting imaging studies that are prospectively designed in the study. An example would be is that CT scanning must be accomplished and interpreted prior to the performance on the imaging study, and this imaging study's interpretation is absolutely designed to have to have that CT information. It's appropriate to now pass the CT information to the reviewer because now we're going to provide all the prospectively known information. But no outcome or truth knowledge is provided to our interpreter.

Step number three, the imaging set comes back again presented for clarification for now the fully informed but blinded to outcome truth interpretation. This is, again, recorded and locked. Now you have two sets of interpretations.

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Step four then identifies what is truth and truth resolution is performed comparing the imaging agent performance in the blinded interpretation to truth, and then the imaging performance in the fully informed but blinded to truth interpretation. So at the conclusion of this model, you would have two sets of interpretation, one fully blinded, and then one fully performed with all prospectively defined information, to demonstrate how this imaging agent will now perform.

So that concludes this set of comments in terms of definitions. So let's put back those questions and see if we can look at them.

In terms of looking at the questions, number one, the primary endpoint, I think we've talked about that that's going to be talked about a little bit later. But from the standpoint here, I think you can look at it in terms of this model, and as you prospectively define it, to be able to, one, look at an independent evaluation, fully blinded so there's no biases introduced, but at the same time then look at a fully informed interpretation to demonstrate how this agent will perform with all clinically and prospectively defined information.

Number two, the value of the blinded read is to reduce

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obviously the bias introduction, from the standpoint there is a vast amount of information which is produced in the clinical trial design that has to be performed on-site and cannot be reproduced off-site. But from the standpoint of introducing and looking at the efficacy performance, what you're trying to do is to remove all the potential outside information that was not prospectively defined as well as the possible introduction of truth, which, frankly speaking, is--remember, every investigator is taking care of the patient, so they're going to discover truth many times prior to finalizing the report. So we remove that potential also. The number of blinded readers. One of the elements that I would also point to you is you have to prospectively define this. First of all, it can't be one. You have to demonstrate that multiple reviewers can look at the information. The size of that was a question, and, again, those of us in biologics where we've got maybe 100 studies, two to three interpreters can do that in an afternoon. With a drug's evaluation where they might have 600 or 700 studies, you may have to look at crossing over various types of interpreters and looking at that, but that needs to be prospectively defined as to the size and extent of it. And from the standpoint of this, I appreciate in talking to the

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people over in Devices where they're doing thousands of studies, certainly no single investigator or multiple investigators can actually review all the films, too. We appreciate that in terms of that size, but it should be prospectively defined. You know how the size of your study is going to be performed going in.

Looking at the same site or other sites as I've described, there are novel ways to approach it. But, again, it really should be prospectively defined, and it really comes down to the individual trial that you're looking at. Again, if we're only dealing with ten sites in the United States in a typical biologic, we don't look at that as a concern. If you were looking at maybe 50 sites, you might be. But, again, it should be prospectively defined.

Sequential unblinding, I think I can give you a good example of what--the agency now feels comfortable with sequential unblinding as a concept, but we also appreciate we need to incorporate it in the guidance document to make sure that it's fully understood. And you can look at that in terms of the information. There may be a great case for completely blinded interpretations if that's your design. If you can I can do an imaging study, throw it up on an X-ray reading room and make them make the call without any information,

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the fully blinded interpretation is the absolute way to go. It's a great study. Frankly speaking, I don't know too many radiopharmaceuticals that can do that. But there might be one or two. But I think sequential unblinding will help the most for those.

Other options, we'll leave that one to open discussion. Informed and partial informed and the package insert, again, it depends on your trial. I would make the case for my biologics most of the time that sequential unblinding, where you show how it performed without any information, just show them the limitations of performing that study without getting adequate information. You don't know the following pieces and parts, and you may not have an appropriate interpretation. So that may be the greatest value. But the other one is make sure your package insert doesn't grow too large by trying to put too many different sets of interpretations into it, also.

That concludes my remarks. Comments? I see one from the audience. You're going to have to come to the microphone.

MR. EINSTEIN: Hi, George. A question--

DR. MILLS: Yes, identify yourself.

MR. EINSTEIN: Steve Einstein from Bioimaging, and I had a question about the agency's opinion on the number of readers

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used for blinded reads comparing Phase 2 versus Phase 3. In general, we tend to use less readers for a Phase 2 study than a Phase 3.

DR. MILLS: My comment would be, first off, it's--I'm not so concerned about Phase 2, how many, as Phase 3 because Phase 3 is licensure, unless you're planning to push it to licensure with an accelerated Phase 2 suddenly that you feel so good about. But the element here is that in the types of studies that I would tend to approach from the biologics, I would tend to look at a minimum of two interpreters per any size of study, but I would want to see typically three in there in terms of being able to do the review and making sure the crossover numbers ares.

But, again, if you've got 600, you may need many more reviewers. So you have to be careful in terms of couching it in the size of the study and the prospectively defined elements to how you're going to look at this.

I'm always cautioning, because one of the things in looking at this type of--this information, when we're looking at the contrast people and their types of studies, they're vastly different in terms of the size and number versus the radiopharmaceuticals that are in CDER versus the radiopharmaceuticals in Biologics. And so the sizing--when

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I start to make an offhand comment about, well, I like two to three, you know, but you've only got 100 patients in your study. And that doesn't work when you've got 5,000 patients. I fully am sensitive to that.

DR. RACZKOWSKI: Let me just comment on that as well. I think that one of the main values of the Phase 2 blinded read is to help serve as a pilot for determining how you need to size the Phase 3 study or studies, and so the number of blinded readers in the Phase 2 study, I agree with George, it's generally a less critical aspect of the development plan, but it can be extremely useful in determining how to plan your Phase 3 clinical trials.

DR. MILLS: Absolutely, and to emphasize that, most of our better Phase 3 studies when they come in in terms of design have had a blinded interpretation, and they know that the problems they're going to face in terms of prospectively designed. If they don't, typically we get into the OPS (?) retrospective re-evaluation of how we want to look at the blinded, and that's where we start to break down almost immediately.

MR. LaFRANCE: LaFrance, Bracco, Princeton. It's more a question than a comment on your last bullet. I know it's difficult without having specific data to speak to, but what

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types of opportunities might be available if we're talking about, say, several blind reads or sequential blind reads? Historically, the blinded--the most robust blind read is really all that shows up in the package insert, and particularly say around indications. What are your opinions or what issues, again, recognizing lack of particular data for a particular product, what opportunities are there to expand if there are sequential blind reads to put what type of information from, say, the ones closer to a practice of medicine read? And would it be just in, say, the clinical studies part of the package insert, or might it be in the indications part?

DR. MILLS: From the standpoint here, you have to be careful in terms of couching what I'm about to say. My impression is that sequential unblinding for the biologics that I deal with in the radiopharmaceuticals is probably what I consider to be clinically the best approach, and from that aspect is to be able to identify that prospectively. I then come back and say if you want to, you want to approach it prospectively, we would present to you the fully blinded interpretation. We would present to you the fully informed prospectively designed with the clinical trial. But I would want to have that.

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Once you start to break down and go retrospectively and try to readjust it, then things start to come apart. I couch that very carefully for you in terms of saying that's an element there that has to be defined. And looking towards CDER in terms of their development to it, again, it's the same type of negotiation in terms of the development as to how far or what extent.

I also don't want the package insert to look like an origami exercise, which is so big that you don't get that much information. There can be a lot of argument made that, hey, that fully blinded doesn't represent what's going to happen performance-wise, and it's academic; therefore, go with a prospectively designed, quote-unquote, informed interpretation but blinded to the truth. And that's where those elements need to be titrated back and forth.

DR. LOVE: Right. I think as George was saying, sequential unblinding has been used more in CBER than in CDER, but the guidance indicates that both of us are willing to accept sequential unblinding.

We've talked about this a lot, and some of these issues were also discussed at the DIA. And one of the points we made there was that there probably needs to be more evaluation of the sequential unblinding process in Phase 2 to help

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determine what information would or would not go into the package insert and to help determine the unblinding procedure that's going to be used in Phase 3 to validate a hypothesis that you establish in Phase 2. And so I think that those things will be important.

Also, the sequential unblinding may begin to have much, much more importance in relation to some of the different indications. You know, if you're really going for this question at the beginning, the clinical efficacy, utility, and you're trying to demonstrate its value, let's say, in a patient management or therapeutic or diagnostic management indication, then all the sequential pieces of information have a much, much greater impact on that final decision than it might be in the initial description where you're looking at a structural indication and you can clearly outline the drug, the organ, or the area of anatomy, and there aren't any other real questions to ask.

So this becomes important in different kinds of trials, different endpoints, and the like, and, again, the prospective discussion is important.

DR. MILLS: And one of the most interesting things, after I presented this at the DIA meeting a couple of weeks ago, the third speaker following me was coming from the contrast

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industry and was raving about the concept of a fully blinded interpretation with no information, which pointed out to me that the perspective is that this is not widely applicable to all of the various imaging modalities we're talking about today. They may feel that it's the most necessary is to be able to throw the image up and make a cold interpretation. If that is from that perspective, that should be negotiated prospectively.

Again, what's good for radiopharmaceuticals may not necessarily hold entirely for contrast agents.

DR. ROSENBERG: Marty Rosenberg from DuPont. If you perform--let's say you have two prospective blinded reads, one informed, one not, it would seem to me--and I'm just trying to interpret your comments, Dr. Love--that it's possible that depending on which efficacy endpoint you're trying to develop may very well not be a paired blind read where they both achieve the same efficacy endpoints, but you actually split out your efficacy endpoints, so that you would achieve one efficacy endpoints, let's say, with a totally unblinded, yet if you're looking at something like a disease management, patient management perspective, those interpretations cannot take place without the clinical--

DR. LOVE: The fully informed--

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DR. ROSENBERG: The disease state that is in question. So you would foresee that that would be the way that could prospectively be set up.

DR. MILLS: And you said the exact word, prospectively set up, because from that standpoint you should know that coming off of your Phase 2. You should be able to come in to either, you know, reviewer and be able to say that indeed here is what we are going to accomplish. And you may say I want to have a primary endpoint of a fully blind interpretation, number one, and I want to have a second primary endpoint, which says with all of this information I can manage this disease state in a very specific way also. But there are two different elements to it.

I think if you design that prospectively and come in with the data, especially having had a limited but unknown blinded interpretation to support that, I think it would be very valuable for both, you know, our review as well as for your agent.

MR. KIRSCHENBAUM: Dr. Mills, you've talked about two types of fully blinded interpretations. One is pure and the other is modified.

DR. MILLS: Right.

MR. KIRSCHENBAUM: Would both of those types of

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interpretations have a place at step one in your sequential unblinding?

DR. MILLS: It would beg almost the issue of what the agent is. In other words, I anticipate a fully blinded interpretation, and in my narrow scope, I'd say that's probably a contrast agent working with a very typical known piece of anatomy that's got a lot of structural anatomy around it for an image, say a CT of the abdomen with a contrast agent, where I would anticipate that the modified would typically be a nuclear medicine setting with a very high target to non-target ratio, which may just have a couple of hot spots sitting in a blank field and they need anatomy. And they're not going to be able to interpret that without that and the protocol. So it would beg the issue. Yes, you could do it, but I'd want you to prospectively define it, and I don't see the two typically being in that.

MR. KIRSCHENBAUM: But there are some agents that the regions would be provided with some information in step one.

DR. MILLS: Oh, absolutely, because if indeed it's a couple of hot spots sitting in a blank field, it's very difficult to understand how they can adequately--and what they'll do is under-interpret, and that's what--we want to remove that potential by saying prospectively, when you bring them in

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for your blind interpretation, hey, they can't interpret this type of film without some minimal pieces of anatomical detail, and they define that for us in the Phase 2 blinded, and we're going to bring that in and show that to you and put that as part of the prospectively defined Phase 3 study.

MR. PRESSLITZ: Joe Presslitz from Immunomedics. You said at the outset that the purpose of the blinded read, whether it was modified or whether it was informed blinded read, is to eliminate bias in the read. Given that, then why would you want to do--or why is it necessary to do a fully blinded read? If the informed blinded read also eliminates bias and that's what you're trying to evaluate, what was the bias in the on-site reader, then why do a fully blinded read at all?

DR. MILLS: Oh, you--from the standpoint here, that's prospectively defined. You may say that there is no value, as we were talking about earlier, in a fully blinded interpretation; therefore, that should be prospectively defined. You're going to need the following elements for our defined primary efficacy endpoint. And you may come down and say the value of that blind interpretation is so limited.

Now, what I would suggest to you is you might want to perform it. You're going to have the information. But the

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other one is I couldn't argue with you that you necessarily need to perform that, but the other one is you want to prospectively define it. You don't want to come in retrospectively and identify it.

MR. PRESSLITZ: So FDA would be willing to accept, in terms of doing some sort of blinded read to evaluate bias, a fully informed independent read.

DR. MILLS: Well, from the standpoint--

MR. PRESSLITZ: If it was prospectively defined.

DR. MILLS: From the standpoint here, I think we would be more than willing to work with it. I can't in terms of saying anything about fully accept in this type of meeting format. What I can tell you, though, is that from the standpoint here is that what I've just described to you would be if you prospectively define such, I think that we would be more than willing to understand and work through that concept. But whether or not I can say the word "accept" in this meeting, I can't.

MR. WHITE: Gordon White, independent consultant. In the guidance document, you make reference to two or three blinded readers and that results from each of those blinded readers would be available. And you further comment about the consensus read, that a consensus read would not be used

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as part of the primary efficacy endpoint.

How will each of those blinded readers' results then be incorporated into the package insert? And what's the agency's view on the consensus read, if one is performed? And--

DR. MILLS: Well--

MR. WHITE: One last--

DR. MILLS: I was going to say there are a lot of and's here. I'll try to remember all of them.

MR. WHITE: One last topic. What is the agency's view on performing rolling blinded reads where several hundreds of patients are being enrolled in studies where groups of patients are being enrolled and are then being evaluated over a period of time as opposed to the entire data set, you know, evaluated?

DR. MILLS: Okay. Let's go back--you're going to have to work with me, Gordon. Let's go back to the first question that you want to have answered, and that is, two out of three, and how would you incorporate or look at two different reviewers.

I would not anticipate that you would want to prospectively define that you would have a package insert that would identify Reader A versus Reader B. But I would anticipate

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that if you were going to look at fully blind--or any type of interpretation off-site, one of the concerns any time of these review of images is their consistency of review. Does A seem to match to B seem to match to C in a reasonable fashion? The ROC curves, if you will. And from that anticipation, that's where I would expect that.

Number two is each time you notice I said lock down those interpretations because one of the concerns always is that a consensus interpretation has a potential again to start introducing bias back and forth.

Now, all of that should be put together in terms of the end of Phase 2 blind interpretation. What's the appropriate way to interpret this set of images? And if indeed you came up and said, gee, I've got a study that I think always requires two radiologists to interpret, I wouldn't understand that very well, but maybe you have that. Okay? Then maybe there's a concept for consensus interpretation as part of the package insert. But, again, that would have to be prospectively defined.

Again, it's unusual, when you start to have to construct that type of concept as to why you would need a consensus for it. All of us who have done clinical imaging have all run down the hall to somebody else and said, What do you

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think? Okay? And we all sometimes have gone back and even changed a report. Okay? You got a consensus read.

But from the standpoint of interpretation and how you would design and look at a clinical trial for an imaging agent, you would not want to have that potential that would be unevaluable unless you had it prospectively defined and you could really reasonably say why would we be doing that and what percentage. Do they all require consensus? Only 20 percent? Why? Those would be the questions that would come in.

MR. WHITE: So each reader would be evaluated independently of each other--

DR. MILLS: I would think that you would always--

MR. WHITE: --ROC analysis done?

DR. MILLS: I think that's pretty classic in nuclear medicine and in radiology that ROC curves looking at various interpreters would want to be an approach to make sure and see that you have a reasonably compared group. You don't want to have--and talking now in terms of one of the larger trials where we had ten reviewers, I would not want to see that seven out of ten went this way and three out of ten went that way all the time. Something's wrong here. And I think almost any classic imaging study would want ROC

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evaluations, and that's why you see within the guidance document comments about looking at Comparator A and B and no consensus.

MR. WHITE: Okay. And the last question was the issue of rolling blinded reads.

DR. MILLS: Well, it depends on how big the study is. I mean, what's the rolling? Okay. If the guys over in CDRH are over there with a mammography study where they've got 100,000 images, they're going to roll that because no one is going to sit down in one afternoon. They're going to do it sequentially over time. And so, again, prospectively. You may come to me and say I want to do a rolling over three months with 100 images. No way. Okay?

You may come over to CDER and say you've got 6,000 images, and we'd like to, quote-unquote, roll that over the course of two weeks. That seems to be something that can be discussed, because it's the mechanics we're talking about there. It's not concept of theory. It's how do you actually perform that review.

MR. WHITE: So you'd like to see that prospectively defined.

DR. MILLS: Absolutely. One of the problems we always get into is that retrospective scope. It starts to distort everything.

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Other questions? I see another--

DR. LOVE: Hold on.

MR. WELCH: Mike Welch. I just want to make an additional comment on the concept of a rolling blinded read. I think it's very important when you lock in your image set and think about having it evaluated, you have to consider biases if the data set is not randomized to order a read. So if you're reading them according to convenience or according to the way the trial was designed, you may have some bias in the way they are read.

You may also compromise your ability to look at the images either in paired or unpaired fashion, which may be necessary.

DR. MILLS: We've got one more question, and then I'm hearing that I'm supposed to get off this podium because other people want to talk.

DR. LOVE: That's right.

MR. LaFRANCE: LaFrance, Bracco, Princeton. You've now presented an option prospectively agreed to on a variety of blind reads. Not to back you into a corner in terms of a value judgment, but would you envision the agency selecting that one type of blind read may be more desirable, therefore, getting more favorable language? If historically

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a blind read might be--a fully blinded read might be viewed as putting the product under review under its most unfavorable circumstances, would that be viewed as the greatest challenge and, therefore, with the greatest reward? Can you put in some perspective what the various blind reads might do with the result to imaging indications? And would the more fully informed reads result in qualification language around the package insert?

DR. MILLS: Well, almost immediately when you present all the clinical information, you're going to have to qualify it because you're going to have to tell them what they're supposed to interpret it with. The other element, though, is it depends on the agent. Again, I don't see that you would bias in terms of one interpretation or the other because if you're dealing with a contrast agent, that fully blinded interpretation may be the most appropriate for that agent and that aspect.

It may be that the fully informed is the most appropriate for a diagnostic radiopharmaceutical, so I think you really would want to break it down by agent and by the trial design to say what's the most appropriate perspective, and that's where you come off of that Phase 2 to be able to tell us, as the sponsor, this is what's the appropriate way to do it. I

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think if you define it prospectively, I don't think there will be any bias in terms of weakening or strengthening. It's what's the--

MR. LaFRANCE: Might it be appropriate, for example, I view the blinded read, the customer in that case might be MICAA, and the fully informed might be another important customer of the package insert, the clinician who is ultimately using the agent?

DR. MILLS: And from the standpoint, that's why I'd also make a case that you may want to look at information of fully blinded and fully informed in con--or side by side within a package insert. That might be an approach also in terms of being able to say be careful, if you're fully--if you just put these films up, radiologists, this is all the more information you may get out of it. But if you get all this other information to support it, you will get the following performance also.

So you have to be careful, and I think that's really the sponsors--how you're going to drive that package insert, how you're going to market this agent.

MR. LaFRANCE: And you would see these data as fair game for package insert inclusion?

DR. MILLS: Mm-hmm.

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MR. LaFRANCE: Both--

DR. MILLS: And I think that that's one of the keys that's prospectively defined. Again, you need to be able to bring that forward to them.

I'm going to get off this podium because we've got other people to talk.

MR. BAUM: Good afternoon. My name is Len Baum. I'm representing MICAA today. I do want to clarify something for the record, though. I'm listed down here as "Attendee, Len Baum, Advanced Magnetics Blinded Reads." I know I've been doing this for a lot of years, but, no, we have not changed the name of our company to "Blinded Reads."

[Laughter.]

MR. CARVLIN: Advanced Blinded Reads.

MR. BAUM: Blinded reads, that's the topic for today.

A couple of things. I'll start with maybe the ending of the story, if you will, and George hit a lot of good points and things I'm going to try and pick up on today. The first thing is I think it's easy to say you're going to do it this way, and as all of us in this audience appreciate the fact that this has been a long-term process--you know, we started this five, six years ago, even willingness to talk and get together, and started with some points to consider. And the

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whole goal is here to define prospectively is the key word. To define, there's a guidance document that we can work with and develop these contrast agents, radiopharm, and develop the differences between the different agents and have an ending that we can all live with and make the process a little easier for everyone working in it.

Some of the things we want to talk about, though, is the blinded read is defined today--and I'm going to call it a blinded image read. The blinded image read, the way it's being asked, does not really reflect the clinical setting. We've said that. And in many cases, by looking at it this way, we've actually created a negative bias. We're worried about reducing the bias in the trial, but aren't we creating a negative bias because the drugs are not used this way. So the other word I want to put on that's used very heavily, or the phrase in the guidance document is for the intended clinical use of the drug.

So if we do that, we want to define prospectively what it is and also we want to define the clinical use of the drug or intended use. And I'm saying if you take all that information and put it together, you could still reduce and control the bias and use what you now call the informed read, but still maintain what is the real experiment, the

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truth, what is the real answer to the test question.

We want to make the data more reflective of the clinical use of the drug, and, again, use it in the clinical setting for which the drug is intended to be used.

Along the same lines, we want to have fair balance--fair balance also in the labeling. We always talk about it in terms of labeling/advertising, but labeling is also the insert. So we want to have fair balance in the insert, and that means putting the information which we collected in the trial, all of is, both the good, the bad, and the ugly, into the insert, fully disclose about how we conducted the trial.

Now, why we want to do all this--and this is the bottom line, and we'll present some examples--is we need this information now, one, to get to the learned intermediary, to the doctor who's going to use this product; two, for us to use in the insert; three, to use in advertising; and something that we have not talked about too much and it really cuts across even, I'll say, the FDA's jurisdiction but which we must begin to acknowledge, is the utility or the usefulness of this product. The usefulness is being now evaluated for reimbursement in HCFA. So we have another set of regulations and a whole new--another alphabet of language that we have to work with, all from these trials that we're

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developing.

So I'm going to take a couple of minutes and go through some of the things as we've seen and talked about them, and I'm going to use some of the information from the guidance document. And, again, since it is in a form to show maybe some places in the guidance document where we may be inconsistent, and an example might be needed, since that's what we're talking about, and then to answer the questions posed back to us as what would an insert look like. So that's the ending of the story. I'll try and get through it as fast as I can.

I did not make a lot of overheads of all the information that's in here, so I'm going to refer to some of the sections in these documents just to make it easy. I counted on almost everyone having these with them today. But I'm also going to start with another document here that we don't always use too often, and I will say one thing: We have issued a lot of guidance documents in the past, and it continues to go into the PDUFA regs.

The document I'm holding right now is one dated May '98, and it's a general guidance to industry on providing clinical evidence of effectiveness. This is the general one that describes what we're supposed to be doing based on the act.

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And I'm not going to sit here and read the whole thing, but the basis concept of 505(d) of the act states that the drug will have--its effect purports or is represented to have under the conditions for use described, recommended, or suggested in the labeling. So that's the key, is everything starts and stops with the labeling. We do everything based on the labeling.

I even notice in this week's pink sheet there's a whole new push--and I saw Matt being quoted on--to prospectively design and define the endpoints you want, build them into Phase 3, and even write the labeling and discuss that with the agency so we all think we're going to get to that point.

So if I go through now the other part of the guidance document, the one we're talking about today, we have a whole section on page 8, read together, as they say, responsive reading, that's under the clinical usefulness section. And it describes the principal reason for performing an evaluation with a medical imaging drug. It's determined that the diagnostic results will be useful to the patient and the health care provider. We want to develop information that's useful.

We also talk about that it's clinical useful, provides information that contributes to the appropriateness of the

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diagnostic or therapeutic patient management, contributes to the benefit of clinical outcome, and provides accurate prognostic information.

This continues on and talks about the validity--I'm not going to read it all, but it's A, B, C that I'm referring to on the use of the product. And then we get into C, defined clinical setting. A defined clinical setting should reflect the circumstances and conditions under which the medical imaging drug is intended to be used. It delineates the patient population, relevant available medical and diagnostic data, and diagnostic questions that characterize the circumstances under which the medical drug is intended to be used. And I think that is the key phrase, and that's a lot of what you've talked about, the informed read.

The last thing I want, which is now the introduction, if you will, into the blinded read--because all this is the set-up for what we're really doing. The blind read, I think we've all acknowledged, is really the trial net. And it's prospectively designed, but the independent blind read may not be entirely representative of the conditions under which the test drug will ultimately be used clinically. That's almost in direct conflict with what we're supposed to be doing for the labeling.

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Let me continue in that section: under which the test drug will ultimately be used clinically but to compel the readers to rely on objective image features in their assessment of the effects of the drug. These independent blinded read evaluations--excuse me, blinded image evaluations are intended to limit possible bias that could be introduced into the image evaluation by a non-independent or unblinded read.

Now, that's a very good design, but in reality--this is where I'm coming from--it is creating the negative bias. That read or the image read, the blinded image read, in many cases is an artificial read. We've acknowledged that because, depending on the use of the drug, it is not the way the drug is going to be used.

So let me go now, with that very brief introduction on some of the guidances and the inconsistency, and switch to some of these. The role of each reader--the role of each reader has to be defined prospectively, both the blinded and the unblinded reader. We want to know what information can we give to the reader. We want to know the order of reading, pairing, unpaired, pre, post; the analysis of the information from the studies, how are we going to analyze this; and then the last piece is how is this all going to

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come together for the package insert and promotional material.

And, George, you said this a number of times, and it's my first question, too. What am I asking? What am I asking this drug to do? Because one size does not fit all. What is the indication and how will this drug be used in the clinical setting?

I just took a couple of the items out of the indications section just to see how it would link. This is not meant to be all-inclusive. Is it going to assist in the biopsy surgery? Is it going to replace a test? Is it going to add a new test? Excuse me. Is it going to visualize, just visualize the anatomy and organs? Is it going to assess normal physiology? Or is it going--to take the big one, is it going to detect disease? And the question you also have to ask, Is this going to be used independently or with another drug or another--or part of an overall clinical impression?

The way I want to get to that is through three sections: the image evaluation, exactly that first step. I put the image up, and you say, What do I see? No information. Do I see the drug even in some cases? Then the second thing is: What's my diagnosis or medical impression of that? The

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last piece is: How is this information going to be used in the patient management? And when I say diagnosis and medical impression now, it is no longer just the image but what information am I being used, and how is this helping a patient, as I always say, coming in the front door and then leaving the back door with either a diagnosis or some type of triage into the system for further testing?

And in most of the trials, we do define what we are doing, so for a second, I'd like to--this is a list we worked on yesterday. What information for consideration--this is just consideration, say, for a blinded read, what you're calling now the informed blinded read. What information could we give a reader, still maintain or reduce the bias, if you will, and get useful information?

The other piece I will put on the table now, since it's something you mentioned, too, is depending on the drug, they cannot sit down and do these in one afternoon. We're looking at now--and I don't want to get into this part of the discussion, but pre's, and per's and post's and nodes or images and lesions that are marked versus unmarked and truth for histology. That is creating multiple levels of reads spread out over weeks and weeks between multiple readers. So that's actually adding on, and now you have lots and lots

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of data, and now you begin to come back, what is the endpoint and how do you judge the use and effectiveness of the drug?

So the information we're suggesting is that we could use an informed read that's prospectively designed--I'm going to call it a clinical read now--holding truth, and the information that could be given, along with the image, is the demographic information, the age, the sex, some of the physical exam information of patients coming in, the test results or medical history--again, if the person is presenting up to a certain point before they're having this imaging test, they're not coming to the radiology suite first.

I think this is also in your guidance document, which is pre and post. Let's not kid ourselves. The radiologists for the most part, they know what they're looking at. So we might as well state what we're going to give clearly up front, and then even in the region of interest that they may be looking. And I think that's coming from ultrasound and the radiopharm. You need to know what anatomical area you're beginning to look at.

The things that are on the no-no list--you want to say, no, you don't want to give this is you're not going to give them

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the treatment or the dose or the next administration. If it's a comparative, you're not going to tell them which drug they're looking at. You're not going to give them the final diagnosis, the truth.

We're also saying you're not going to give them information that has been collected from a similar test. So if I'm doing an MRI and the patient had a CT to the same area, we're not going to give them the CT. We can understand that there may be some potential bias in that. So you hold the other similar medical imaging tests back. But if someone had an EKG and you're now looking at that, and I heard people say this in high country this year, they'll start with an abnormal EKG and now they're looking to see if it's heart disease. You may want to consider that. That's what given in a regular realm of an evaluation.

Information on the protocol, we put that in that side, too, and we can probably define what information you want to give them versus not give them in a protocol. This list actually came from your guidance document because there are certain cases where you have the word "no" but there's other cases saying, "It depends on the drug or the situation."

So what we're suggesting is you really need to make a clean break. I think if we begin to make one list and even list

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for certain classes of drugs, or, better yet, list for certain indications, as you just said, George, driving it by what question you're asking, you could begin to get a very clear list that covers a majority of indications and uses driven by the question I want asked and then the drug that's being used, because radiopharm does have different issues. When I come back to the list that I prepared now, under an image evaluation, you begin to develop the questions. Are the images technically adequate when we look at them? It's a traditional one. An endpoint we all use is: Does the post have more than the pre? In the medical imaging side, the drug as defined in here, we agree with that. The drug has to add value to the test. These devices, if you will, are already approved for certain uses. We're enhancing the use of an approved device. So I could even--I don't want to go down that road. I can call these device enhances. We've already acknowledged they're drugs, so I'm not going to go to that side. But these really were enhancing an approved use of a device.

What information do I see on the slide? Do I see more lesions, more vessels, more segments of the heart? Is it better opacified? Again, what questions am I asking? Enhancement pattern. This is something new we're being

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asked to look at. When the radiologist looks at this, what does it look like? Can you describe it in words? Is the rim of the lesion thick? Is it a tumor? Describe what the radiologist sees so that someone might know what the patterns are for your drugs' use.

In the quantitative information, we have ROI signal intensity. And at this point, I also want to mention that we do have hard points in these studies. There are some quantitative measures, and we can't forget that, too.

The next thing I want to know is what is the diagnosis setting going to look like. Is it normal or abnormal? Maybe yes, maybe no. We have a huge gray area in the middle that we all must face. When you say to the patient, if you're looking for a diagnosis, when you say the patient is, yes, under a blinded, it translate to the patient as this patient probably isn't going to continue with a diagnostic test. He'll make the decision. If the patients says maybe yes or maybe no, they're going to continue to be worked up in the system somehow. So that all translates to the patient management, which I'll show you in a moment.

You may calculate sensitivity, specificity, PPV, NPV, and something I have up here which we need to acknowledge is confidence in the diagnosis. This is something that we need

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to acknowledge is a radiological term. You can have equivalent sensitivity and specificity--and I heard this in the meeting yesterday--and equivalent sensitivity and specificity, pre to post, and if the confidence changes, they feel better about that. I continue to sit back. If we take a poll in this audience of the radiologists, there is a term that they use. It's something that we need to put in and acknowledge. If we want to leave it out, then let's state let's leave it out. But then we can all argue that point, that it is a point that needs to be put back in.

So I think what I'm getting to--and let me just put this last slide up, patient management. We are getting patient management. And I will say that in a blinded read, we really are acting on a patient. Whether the doctor acts on that--we have this old double-edged sword where we say: How do you know that this is what the doctor would have done with this information because you didn't act on it? Well, we can't act on these because these are investigational drugs. We do have people telling us, though, I have changed it, I don't care what you tell me, I saw all the lesions in that slide, I canceled surgery.

But in a blinded read, an informed blinded read or a clinical blinded read, you actually do have the same setting

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you have in the hospital. So you can get patient information out of that, too, from the blinded read, because they're acting on the information there. The only difference is they're acting on a paper. Did the post help you make the diagnosis? Did it change or assist in the patient evaluation and management? And then what's the next course of action or test?

So if I take all that information now and sum it all together into that one little piece of paper called the package insert, I know it's going to get long, but I think if you took a vote or took a survey or if we put that out for a question, I think we would rather see it in there, no matter how long the insert got, than not being able to put it in there. Prospectively designed endpoints, properly define how the information was collected, with all the caveats. Maybe this was totally blinded, this was unblinded, this had one eye closed, this one had both eyes closed.

I think we're at a point that we will acknowledge that. The inserts may get long, but I think our managements would rather afford the paper, because the one piece that's also happening is DDMAC (ph) is coming down very highly on what you can and cannot promote based on the insert. It will

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make all of our jobs easier if it's in the labeling.

Then the last piece which I bring back in is the reimbursement issue. If we can get some of this information in--and I think we have to acknowledge in some cases the blinded read does have lower numbers than the fully informed, or unblinded read, I should say, and if we can get clinical utility information out there, which is really heavily used in this guidance document, I think it will help us also in reimbursement. It's something that we do have to face and which also the public is asking us today.

So I go back to the three points I made: clinical evaluation, diagnosis, and patient management. I could see a package insert looking like that in the clinical trial section of an insert to answer the question that was raised before. How the trial was conducted, that's there now. How the blinding was done, how the unblinding was done, and how the different information looked from the typical studies that we traditionally see, adequate and well-controlled design, Study A, Study B, many inserts. We're becoming very creative. We've now boiled it down to Study A and Study B with an unblinded and blinded.

The piece we haven't talked about, and I'm going to put it on the table here, is the use of the unblinded reader, the

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investigator. We've talked about blinding. They also have value. We either have to reach a decision of the use of the data, or I think we should reach a decision that we're not going to do unblinded institutional reads. It takes a tremendous amount of time to conduct these trials, and we can design different case reports on the trials using the investigational site if we're not going to acknowledge the use of these data.

So, in summary, where I'm suggesting we go is not to do three in sequential unblinding, which is going to create even more data, but to use a combination maybe of both of those. That's a little departure from what we talked last night.

But to use a clinical informed read or a clinical image read, prospectively designed, holding the truth, and using that information, which could be designed differently based on the indication you are seeking--and I do acknowledge, in certain cases, a chest X-ray you may--can make that diagnosis. The majority of the drugs we are using, though, for the indications, if you look at them, are to assist in the diagnosis. They are not used in a vacuum. I think if we make them more fully reflective, excuse me, if we make the clinical trial design more fully reflective of the

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clinical use of the product, I think we will be good.

I also think, and I have to say it this way, though, but I think we have to be very careful of overusing the statistics to come up a with a negative biased study, and it's a very difficult thing, but to bring more of the clinical use data back into the statistical, prospectively designed trial.

So I am going to stop at this point. Bob has a couple of comments, also, from CORAR.

MR. MORGAN: Good afternoon. Again, I am Bob Morgan from DuPont. I am up here representing CORAR.

As last time, when I came up to talk about blind reads, much of what I had to say has already been said. So I think, in the interest of time, I am going to cut through or skip over a number of the slides that I had. I had planned on giving a brief update on what had occurred at the last meeting, just to bring everybody up-to-date, but I think we can preclude that simply in a single slide.

What CORAR talked about at the last meeting was that efficacy should be based on the contribution to patient's diagnosis, help in monitoring a patient or providing assistance or info in assisting in making treatment decisions and that the blinded read should not be required to demonstrate that the radiopharmaceutical alone makes

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diagnosis or effects changes in diagnosis or patient management decisions unless that's exactly the indication that you are going after.

So, again, as we are starting to hear, and I am very encouraged by the words that I am hearing, that there is an openness and looking at how blinded reads can be conducted and coming forward with possibilities that we have not been able to use in the past. Again, looking at CORAR's positioning from the last meeting is that we agree that agent blinding is appropriate. Again, if you are using a comparator, then you should be blinded to that comparison. We put forward the idea that clinical blinding should be modified to allow for inclusion of clinical information, and that led to our support of the concept of sequential unblinding; that we agree that the appropriate read should include clinical information.

We recognize that the fully blinded read provides some useful information, but should not be the sole basis of efficacy. And these are all of the comments that you've heard this afternoon. We're all moving towards the same thing. So, I guess, in essence what we are saying is that CORAR fully supports the types of discussions that are ongoing, and what we really need to do is get down into the

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weeds. And this is what we have to look to FDA to include into the guidance document.

And this just represents one possible scenario for a blinded read. There is a randomization reading of the image to the level the data can be randomized. And the way that that is worded is that there are instances where there are data sets where you have to look at images in sequence, so that it's appropriate to have that information up there in sequence. So that's why that has that little caveat; that you randomize to the point that it's appropriate.

Clinical information from the case report form could include, for example, past medical history, physical exam, baseline labs, history of the present illness. But you are excluding the standard of truth or the reference of truth--again, what Dr. Mills was describing as a fully informed blinded read.

We still believe that efficacy determination has to include the information with the clinical data in it; that that is really what the determination of efficacy is focused on. Again, unless the indication that you are going after, as Dr. Mills pointed out, is based on a true fully blinded traditional read.

The other point that I think is a little bit different than

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what we've heard is that we believe that the institutional, as well as the data, the blinded read, including the clinical data, should be included in the package insert because we believe that that represents the most clinically relevant information. Again, we acknowledge that there is some utility to the fully blinded read in determining or trying to minimize bias or control bias, but our goal should be to get as much information to the physician, to the clinician, from a setting on how these products are going to be used.

So, again, I am extremely encouraged by the language that we are hearing today and the willingness of FDA to start to have these types of discussions, and I think we're in agreement that there has to be a change in the way that we're looking at our data, and now we need to get down to the weeds and to define just how we're going to do that. And I think that's going to be a significant challenge. That's what I have.

DR. LOVE: Hopefully not a significant challenge.

[Laughter.]

DR. LOVE: Thank you both. Any other prepared comments?

[No response.]

DR. LOVE: I have heard a number of different things and a

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lot of material. So maybe we need to spend a few moments just trying to make sure we sort through the weeds, as you are talking about, and at least get to the points that we would need to address.

It seems that I am hearing all three persons, Agency and Industry representatives, saying that it's important to use some type of informed read, and there are different ways to provide that information, whether it's the fully informed unblinded, whether it's the sequential unblinding process that gets to that information or whether there is a set of information from Phase 2 that identifies what type of read should actually be conducted in Phase 3. So I hear three different approaches to that, basically. You are frowning, Len.

MR. BAUM: I guess a comment could be the comment from the floor before was I guess using Phase 2. I would say it's even beyond that, too. Saying, based on the indication, we may not even need the information from Phase 2 because we would have prospectively defined what we're looking for in an indication I will say even well before Phase 2. It gets refined as we go.

DR. LOVE: Well, historic information during the drug development would help.

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MR. BAUM: Yes, or at Phase 2. If we could even get that end point, that's what Phase 2 will more or less tell us.

DR. LOVE: Right. Phase 2, ideally, would be designed to establish the hypothesis that you are going to test. Now, whether it's all of Phase 1, 2, whatever, but whatever information is used to do that. So it seems that there are several different approaches.

A number of the points that you raise, Len, were also related to things that might be discussed a bit more in the indications and clarifications part. And I think we all agree that the utility of the product, its usefulness, its clinical benefit, whatever the term might be, is relevant in the long run, and that's the most important thing. And then all of the indications provide information. Some of them have more specific demonstration of that clinical benefit in the context of the clinical trial and some would not.

Some of what I am hearing may, as I said, we may need to talk about a bit more in the next topic area, but some of it sounded very much like the patient management kind of indication or perhaps the disease-specific types of issues that I was hearing through your conversation. And, again, some others may not be so relevant when we are dealing with structure.

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I guess the HCFA-related comment, we do have some slightly different definitions of efficacy, effectiveness and such from the third-party payers, and we do recognize that, and certainly we may need to sometimes think about how to design a trial to answer everybody's question at one time. Most often that's not the question that's posed to us, but certainly we can see that there may be room for doing that. I would like to perhaps ask a couple of questions. From your comments, Len, and what you heard George saying, how far apart do you feel you are?

MR. BAUM: Well, if I start with the--let me get his terminolo--that's the other thing, too. We have to come up with one set of terminology for the glossary of--

DR. LOVE: Yes, we don't have the same set of terms.

MR. BAUM: I will use yours, also, the fully informed or what I am beginning to call the clinical-blinded read, withholding the truth, the end points. In other words, the blinded read is a test, and the only reason we put the indications, there is no way that you can design a blinded read unless you know what the answers say to the test. You want to know what your end point is; in this case, 100-percent accuracy, maybe. That would be a nice test score.

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I think we are very close together if we begin to acknowledge and define those settings where we can begin using the fully informed blinded read. What I am trying to get away from, and I will just say it as plain as I can, I am trying to get away from the sequential unblinding or the appearance that we need--we slowly begin to piece in more and more information.

And what I am beginning to have a problem with along those lines is that we are now beginning to develop lots and lots of data with multiple end points, under multiple conditions--pre's, and pairs and posts--with no information, with some information, and then also another set from the investigational read. That I see as a lot of data.

And depending on the indication you are seeking, you may not need that first read. That's what I am saying, is you don't need that pure image read with no information, period. So, therefore, you could start, your jumping off point could be the first read is the clinically informed read that is prospectively designed that withholds total truth, including histology, biopsy, or another imaging test that's meant to get to the same answer; i.e., CT, looking for a lesion in the liver and an MR drug looking for lesions in the liver.

DR. MILLS: Len, just to respond to it, I think we're

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absolutely in agreement.

The key that I look at is your set of products are different than Bob's. And so my concern here is only inasmuch to say, for your set of products, you may be exactly in the correct model, and we turn around over to Bob and say, "He needs to have a fully blinded, plus he needs to have a fully informed," and there is no wrong answer here. I think we're looking at a spectrum, in terms of being able to deal with multiple different agents in terms of imaging.

And so, as a result, I look across this and say both answers are correct. It's just a necessary--is we've got to look at the various types of modalities we've got in this room today because, frankly speaking, they all don't match up. Ultrasound is not going to match up to contrast, and it's not going to match up to radiopharmaceuticals in one absolute envelope. But you need to have that spectrum.

And that's why, again, just as we were reflecting, that word "prospectively designed," to be able to say, "Hey, I've got a contrast agent today. I don't need anything but the fully informed interpretation because of what I've seen in Phase 2 development to this point." And then turn around the next day someone walks in, and "I've got a radiopharmaceutical. I need to see the fully informed, and

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I need to see the fully blinded in mine because of what I've seen also."

MR. BAUM: I agree with you, George.

And the other piece, even in the radiopharm area, it's like, when you get to do the test, what information do you traditionally have in the clinical setting. And maybe that's it. We've defined a scientifically sound study, and this is where the statistics--and I can't get into that. It's not my field of expertise--and I recognize the need and the importance of having the statistical significance and the statistical test built in.

But our products deal with warm and fuzzy end points. And, unfortunately, we have to face that there. They are qualitative assessments. And as you just said earlier, you could take an image and go down the hall and get another opinion on that same image. We do that all of the time. The medical system that we all live with has first and second opinions and third opinions, and you keep shopping until you get the opinion you like. Does that mean the image is wrong or the person interpreting it?

But what we're trying to do now is it's not just the image, it's based on a lot of other factors that come into that, too. So, again, I go back to what we, which is correctly

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stated and very nicely stated, we are looking at drugs and the clinical utility of these products and then design the trial to produce the information then that gets into the labeling.

And the only problem I have, and I think this is the only one--and it sounds like we're not even disagreeing on this point; we are actually agreeing--is the blinded image read, that very first read, is not appropriate for every product in every situation, and that's where I saw the guidance document heading. That is the first stop everywhere. You must do that one.

And then we were leaning into a sequential unblinding, as a second read, added to the third read, which is the investigator reading. That's where a lot of us, and we spent a bit of time under the MICAA umbrella for that reason. The way it was heading, it was heading into three distinct reads, with a pre-only, and a post-only and then a pair. I will even come back to it if we have time, why a post-only is not always appropriate, what we said a couple of years ago. But that's where we were heading. So if that's not where we are heading--

And, again, I think the comment was made earlier, once we see it in a guidance document better described maybe by

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modalities or, better yet, tied into the indication, and that's the one thing, also, we need to link section-to-section-to-section, it's a straight line down leading to the indication. It starts with the indication, the study design, then the data, and then the indication, again, that gets refined. It's no different than the way we approve and develop the drugs. Did we test the hypothesis and can we still get the same indication we proposed when we filed the IND?

And I think that's the only thing I would criticize; that we need to link to section-to-section-to-section and not jump from one drug to another for examples, but stay with one example through the guidance; like a radiopharm, then an ultrasound, then a CT, and then an MR, all based on, driven by what's the indication.

DR. MILLS: Right. And let me offer to you one of the things that I think would be of great help to the Agency right now is, hearing this discussion, because I agree, I think we're consistent, and right now what I would look across and say, by the 14th of April, what we need is some additional input. And we need to be able to say, in looking at the discussion we've gone through this afternoon, when we're looking at contrast agents, what does MICAA see in

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terms of what would be that linear skeletal outline which would not limit, but allow you to develop a number of different agents under it.

And I would also suggest the same way for CORAR, in looking at radiopharmaceuticals, and then when you start to break out those subgroups of ultrasound and what have you. Because from that standpoint, we can certainly look at it from here in terms of regulatory. But from your perspective now is to say, "I know what agents are in the pipeline. I know what development directions." Frankly, we're probably working with pretty basic materials today as compared to where we're going to be five years from now.

So you don't want to create an obsolete document knowingly. We probably will, but knowingly, without the perspective of your input, to be able to say, "Gee, you need to be able to design it in this way and look forward for us, in terms of these areas that are subgroups." So that helps us subdivide our information.

MR. BAUM: Can I ask a clarification? This is just administrative for a moment because you mentioned comments. Is the transcript--this meeting is submitted as part of the docket, so really everything, both parts, everyone sitting in this room is comments to the guidance document docket?

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DR. LOVE: Yes, that is correct?

MR. BAUM: Okay, I just wanted...

DR. LOVE: Yes, we--

MR. BAUM: My comments are already written down.

DR. LOVE: They're already written, yes.

MR. BAUM: I understand what you're saying, George.

DR. LOVE: Did you have a comment?

DR. RACZKOWSKI: I had a question for Len just for clarification. There was a lot of material that you presented, and I want to be clear on one of the last points you made.

You said that everything should be linked to the indication. Are you--could you explain again, perhaps, if you already did, because I don't think I completely understood what you meant. Are you saying that for different indications, for a structured delineation claim versus a physiological claim versus a diagnostic claim versus a patient management claim, you would do different types of blinded read?

MR. BAUM: Well, you're going to ask the questions differently, too. That's really the issue. You'll do a blinded read, but let's just say if I'm looking for--let me take a very simple one, the diagnosis. If I'm looking for an absolute diagnosis that this drug is going to diagnose

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liver tumors, I need to be very good at doing that. If I'm going to say this is part of an overall piece, that this is one piece of information that's going to be used in the diagnosis of patients, or I'm going to say I'm not going to replace biopsy or a positive test, it means you need to go on to the confirming.

You know, I can go on and on for examples like that. Your blinded read are the questions you ask within that, and the way you set your blinded read up will be very different. If I say I'm going to make this the ultimate test that they will act on and there's nothing else ever being done, and they're going to act with no information, then I can't obviously have other information involved. If I'm saying this is to assist--and the phrase we used--and I'm not saying you've got to use it, but with the overall clinical impression. This piece of information is part of the overall clinical impression of all information that both the referring physician, the specialist now, are going to all get back together and render an opinion on what the diagnosis is of the patient. So that would be a very--you know, one that's an easy one for me to define.

Number of segments, heart segments and now the difference in crossover between ultrasound perfusion, let's just say, and

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assess the MIBI(?)-type perfusion, those questions, again, are very different. We have now new drugs being developed for indications that are already out there. One's a perfusion marker, let's just say, but yet perfusion--and this was the discussion we had years and years ago--is an indication--is a perfusion market an indication? No, but a perfusion marker can say you have a perfusion defect, and these are known diseases that are perfusion deficit diseases.

So if I've been able to show that I can mark perfusion--now, the radiopharm may do it quantitatively; the ultrasound, we'll have to see which way it goes--but the endpoint is what's the disease I'm going to study because perfusion has already been validated as certain markers of disease. The same thing with cerebral perfusion. We had that discussion a number of years ago.

So that's what I'm saying, is there's thing out there that we know about and we don't have to just take that one image I get from the study and try to take it as a naked image up there. I need to begin to put it back into the clinical setting and life that we know already, and that's what I'm saying. It's driven by the indication and the use of the product.

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DR. LOVE: A couple of the points you're making and some of the examples that you showed are also very important, and it implies something else that we didn't spend a lot of time on in the guidance just based on space and other things, and that's the wording of the questions in the case of forms and how they get to some of these different issues. And what you were talking about is do you assist in a biopsy, is that the next step, and you'd want to make sure the information is worded in a way to get that.

You've talked about in your slide the information that's useful in patient management, or at least suggests patient management types of information and how one might sequentially get that information. And then there's also, of course, this indication suggested in the guidance, which is an actual patient management indication. And some of the thoughts we had there were that those types of specific patient management indications are studied, specifically identified, and clearly determined that, yes, you can take this piece of information and do what you're talking about. You can stop a workup. You can select a certain therapy or non-therapy, as it might be, based on that information. And that's particularly important when it's a new situation also, where those issues haven't been fleshed out before.

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And then there are others where it's more implied. If you think you're truly making a disease diagnosis and you know how to treat it, then you don't have to do the rest of it. So, again, even within a blinded or unblinded or sequentially unblinded read, how that information is actually captured on the case report form is important. I just wanted to mention that. We have to think about it in the whole process.

It sounds like we're agreeing on something. We can't use the word "agree." It sounds like we're understanding and--

MR. BAUM: We concur. We concur.

DR. LOVE: --clarified--came to the same clarification. Okay. Yes?

MR. CARVLIN: Yes, Mark Carvlin from MICAA. Just a point of clarification and a question, and that is, to understand what is the proper role of the on-site evaluations, Dr. Mills had commented in his presentation about their essential character as far as demonstrating safety or evaluating safety, but that also begs the question: Are they necessary, sufficient, necessary and sufficient for demonstration of efficacy? Much of our discussion has been focused on the blinded reads. I was just wondering what recordation or what clarification you might have to offer us

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regarding the on-site evaluations.

DR. LOVE: We're all looking at one another saying who wants to tackle this one first.

I think the on-site read is important. It does give us a sense of how the product may or may not be used in the real world without a lot of other input or specific training and such that goes into the blinded reads. It's useful information.

The way we use it now, pre--since this is still in draft--guidance, the way we tend to look at it now is to see what's the consistency between the blinded read or any other informed types of reads and the on-site. Sometimes we see them going in completely opposite directions, and even the on-site read sometimes is the one that's incorrect. So there are problems. Then sometimes it's the blinded read that's incorrect, and it's hard to sometimes know until you actually get into the analysis of the study and try to figure out what went wrong.

An issue that was raised at the statistics DIA meeting was what about an unusual modality that is new, is different, the interpretation of the images is slightly different from what someone might do on a regular basis. Do you really need more venues, end user, usage type studies to see what

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someone would do in reading this without any real information and training? And how relevant is the training session? And is that biasing the readers in some way just because they've been trained and someone else has not?

So there are some other pieces that go into this puzzle, and the on-site blinded read does help try to sort out some of that type of question. It also helps us decide whether or not a training program might need to be extremely comprehensive when the drug is launched versus very minimal.

MR. BAUM: That's not different than a lot of the therapeutics, especially on dosage and administration. When you have a new drug that comes out for a brand new administration, can the patient administer the drug themselves? So that part I can see.

DR. LOVE: Right.

MR. BAUM: The one comment I just wanted to make, and I was thinking about this as you were speaking about other drugs also, we--fortunately or unfortunately, if you will--we've acknowledged that we are different in therapeutics than we would as a drug, but yet the funny thing is in talking about endpoints a little bit, our endpoints are multiple endpoints that come together, the same way a diagnosis is made. And it's very unlike most of the therapeutics that reside within

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the center. You know, if you're reducing blood pressure, it's a very good endpoint. If you're anti-epileptic, you're going to stop the seizures. The endpoints are pretty apparent. New ones now in the cancer agents with surrogate endpoints coming in place now, reduction of tumor size is now a surrogate endpoint for use--to demonstrate efficacy of a cancer agent.

The funny thing is what they're using to us as that surrogate endpoint is our imaging agents. And yet that's one of the endpoints that we need to look at, too, because now you have our imaging drugs being used in other therapeutic agents as surrogate endpoints, and it's becoming a whole new field. As a matter of fact, that's the DIA session coming up, medical imaging drugs.

So, again, just to reiterate in a slightly different way, what we're doing in the endpoints we pick for the contrast media and the radiopharm products and how we use and disseminate that information is many pieces of information we collect, and it's now being used into management of therapeutics, and that's the patient management piece. So we do collect this information, and people are acting on it.

And, again, we've set up this blind situation. So I'm suggesting that that blind read really is like a grand round

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where you have people sitting in there looking at something with no knowledge of what's actually going to happen, but yet the action on that is an interesting case. And people may say, hey, you're right, the same way you may run down the hall and get the third opinion.

They have no knowledge of the patient. They're going to act based on the information you tell them, too. So I put that out to look at another perspective, another angle of this whole situation.

DR. LOVE: Right. Use in therapeutics is becoming an issue that we'll have to have another guidance on.

[Laughter.]

DR. LOVE: Are there any other questions or comments on this topic? Anyone from the floor, please?

MR. PRESSLITZ: Joe Presslitz, Immunomedics. I agree with my colleagues from CORAR about the utility of an informed blinded read to evaluate the bias that may occur on-site. However, I would contend that for many imaging products, maybe even particularly for nuclear medicine imaging products, that it's the on-site reads that should be the basis of an approval rather than an informed blinded read, and these are the data that should appear on the label. Very frequently for these kinds of products, it's dependent

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on the attending physician seeing positioning of the patient when he's reading the imaging or doing the imaging, so that when he reads it, he knows the portion of the anatomy and how it was positioned when he did the imaging. And if you do a blinded read, no matter how you inform the blinded reader, he doesn't have all this information in hand.

So I think to just out of hand say that the on-site reading should only be supportive is really an improper thing to do, and I think that you need to reconsider that if that's what's going to appear on the document.

Thank you.

DR. LOVE: Two other comments.

MR. CARPENTER: Alan Carpenter, DuPont. I just want to ask the agency if they have thought through the settings in which the on-site reads could be used as a primary measure of efficacy in an active comparator role as opposed to the kinds of studies we've been talking about where I don't think we've been talking about active comparator.

DR. MILLS: I can address in terms of looking at on-site interpretations as compared to the blinded off-site interpretations. And, again, there's an extensive amount of information that's generated from the on-site evaluations, both on safety and efficacy, but the problems of being able

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to exclude the potential bias and insertion of clinical information, which has not been predefined in the trial, it almost excludes the potential that we can have great confidence in the on-site interpretation independent and away from such a separation interpretation.

From the standpoint there is I would make the case very strongly that it's apparent that you want to have that physician taking care of the patient at the same time that they're doing the clinical trial. You can't exclude that information. There's leakage, unfortunately, and fortunately, to manage the patient as well as possible. And as we've talked about, people do, unfortunately, or fortunately, use information inappropriately to manage patient care from time to time. But all of these, again, suddenly produce an incalculable amount of bias introduced in terms of the on-site interpretations.

The question I know that Len had broached is: Should we even do them at all? Or should we, you know, perform them or what should be the value? My impression is that you can't do a clinical trial and not end up with an on-site interpretation, because a physician's going to have the film in his hand and he's going to do it sooner or later.

Whether he does it in a patient report which has to be made,

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because you've touched the patient, or whether you're going to do it in the case report form, legitimately both pieces of information will be generated.

But from the standpoint here for the agency, to have a comfort level that those on-site interpretations have been completely evaluated in an independent fashion, without potential leakage of information across, frankly speaking is very unrealistic in terms of the clinical trial information we're going to have. That's why this type of interpretation is to try to bring a fully informed but blinded truth evaluation to as close as possible present all of that clinical information with a confidence limit for the agency, as long as the sponsor as well as the attending physician is going to read that insert, that this is information that is best that can be reproduced in the clinical setting, or an information set, is probably what I think all of us would, at the end of the day, feel the most comfort in terms of being able to say that's an appropriate information set.

On-site interpretations, there may be potential in terms of secondary efficacy endpoints that can be utilized, but, again, it's how well you can control it and how big your study is. The bigger the study, frankly, the less control you're going to have. And I think the other one is, for the

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industry is the ability to control all of those sites. I think it becomes a logistic nightmare in terms of being able to say that you can realistically bring that information together comfortably, where this type of informational review presents a legitimate way that they can approach it very well. And I think that's why I was hearing that comment, is should we even do them at all. Frankly, you're going to do them, but it's how much reliance you can put on them and we can put on them is limited.

MR. CARPENTER: So your concerns of bias in terms of the study design are no different whether you're doing an accurate comparator study or whether you're doing a comparison to the modality without the contrast agent, or--

DR. MILLS: Again, in looking at your design and your structure to it. But my comments were an overall concept of an independent on-site interpretation that's uncontrolled. My concerns are always that we're going to have some difficulty with that. I would present it back to you and say the secondary endpoint I think I could understand that.

MR. CARPENTER: Okay.

DR. MILLS: The primary efficacy endpoint, I'd feel very uncomfortable to turn within the agency and say that's an appropriate measure that we all have confidence in five

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years from now.

DR. LOVE: Just a caveat on that. If what you're asking is does the control agent have to be blindly read or does the standard of truth, if it happened to have been an imaging modality, have to be blindly read, is that what you're asking?

MR. CARPENTER: If you are comparing against an approved imaging agent and trying to get similar labeling for that approved imaging agent, does it change your thinking in terms of how you might accept on-site reads versus--that's what I was asking.

DR. MILLS: Remember, cross-contamination also occurs many times at the site. Having been in that circumstance many times, my investigational interpretation study suddenly seems to have gotten a little bit of bias introduced into the CT evaluation. It happens many times as you run down the hall with it to try to figure out what's going on. So you have to be careful when you're looking at comparators. There's leakage going both ways at the clinical sites.

DR. RUNGE: Val Runge. I'm a diagnostic radiologist with the University of Kentucky. This meeting and topic has reached the academic community, and that's the reason I'm here. And I want to re-emphasize a couple of points that

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people made during this session.

The first is, in terms of blinded reads, I have been heavily involved, not in the last few years but in the past ten years, in the approval process for the MR pharmaceuticals, and the blinded reads, at least from a diagnostic radiology point of view, the radiologist's point of view, had been uniformly not very helpful and not very representative of the data. And so I am very much a proponent of an informed blinded read.

I am also and I think the academic community is also very supportive of the importance of the read that occurs at the site, the investigator's read. Oftentimes, in past clinical trials that we've seen, the investigator's read is where the information is, and the blinded read, of course, not being an informed blinded read, is not very helpful.

Another point that was made that was very good is that as diagnostic radiologists, they say about us that we're only 80 percent correct, and that is that we only make the right diagnosis or see the information 80 percent of the time. But the truth about diagnostic radiology is it's a confidence in diagnosis, and that's something that I want to re-emphasize, that it is not a yes or no phenomenon, and that contrast media often don't give a yes or no answer. It

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is an improvement in confidence or an improvement in the diagnostic information. And so any sort of measurement that looks like that, that looks at that parameter, is very important.

Thank you.

DR. LOVE: I think Len was also talking about that. That is an area that we've had a lot of conversation on how do you capture the increase in confidence since it's a subjective approach. So I would say that for MICAA and CORAR, as you're thinking about it, if you have some suggestions on how to capture that information in an--capture subjective information in an objective manner, that's essentially what we're talking about.

DR. RACZKOWSKI: I'd like to comment on that last point that Dr. Love made as well. I think it's not simply a question of how do you capture in a case report form diagnostic confidence. It's actually how do you design the trial so that you know that there has been an increase in diagnostic confidence. And so the design of a clinical trial ends up being very important in terms of when you're dealing with subjective endpoints.

DR. RUNGE: Yes. Just again to add a point on that, I've seen something in clinical trial designs that is often sort

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of pooh-poohed but I think is important, and that is that there will be a confidence in diagnosis and there will be a numerical grade given to that, a 0, a 1, or a 2, some sort of very limited scale. And I think that is a very important part of the evaluation process because it's difficult to measure, your confidence in diagnosis and assigning this to a disease category or your confidence in diagnosis that this represents an active disease process.

DR. RACZKOWSKI: Right. No, I understand that there's different scales to capture diagnostic confidence. Let me use an example to perhaps make myself more clear.

If we're dealing with a contrast agent where we have a pre-image and we ask the--and the investigator is asked what their confidence is in that and they know it's a pre-image, they can rank it low. Then if the post-image is given to the investigator and they're asked to rank their confidence in it, it could be ranked high, regardless of what's on the actual image itself. So the trial has to actually be designed in some way so that that potential bias is controlled in some way.

There's nothing wrong with a subjective endpoint per se. When you have a subjective endpoint in a clinical trial, it just has to be controlled for in some way.

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DR. RUNGE: One of the problems is that we need to take this back to how the drug is used in a clinical setting, and that is, if we look at diagnostic interpretation of these images, these images are interpreted in the clinical setting with pre and post there, and so one of the mistakes that I've seen in the past or one of the difficulties in interpretation of the clinical trial data is if you analyze the post-image by itself, for a diagnostic radiologist that is almost an impossible situation, and oftentimes the diagnostic radiologist--there may or may not be clues on the film that even tell him that it's a post-image. And so he may make the wrong interpretation. So design is difficult.

DR. RACZKOWSKI: Well, no, I agree. I mean, my question was actually independent of whether it was what we've called in the past a paired read or whether it's an independent post-read. I think the issue--the same question I asked could still be asked if you just showed the pre-image alone, then you showed both the pre and post together. How do you--the trial has to in some way be designed so that that subjective endpoint of diagnostic confidence isn't arbitrarily assigned to the film.

DR. MILLS: Well, what I was going to also reflect here is that confidence in the image, one of the elements that we

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would really like to get information on is, indeed, I have looked at images before and felt, yes, I've increased my confidence. But when asked a very significant pointed question, In what element and in what diagnostic point? I think we need in clinical trial design to be able to say your confidence has been increased and in what element and in what way, and to have this prospectively designed. And this is where that Phase 2 study is very significant to you, is to be able to say there's a confidence element that we need that we know will be increased, and it is in the specific item, and how are we going to measure it prospectively. Because it's very difficult from a clinical trial design to translate that tilt, if you will, in terms of that image interpretation being improved, and we're looking for a way that we can objectively translate a subjective endpoint. And, again, maybe the academic community back through industry can help us get that focus on that element. Because it happens clinically, but I have yet to be able to get a handle as to how to put that in a clinical trial design.

MR. BAUM: The only thing I can answer to that, George, is we're asking the question without an ending to it. In other words, what is the confidence? But actually it's confidence

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in something.

DR. MILLS: Yes.

MR. BAUM: And is it the confidence goes back--and I keep saying this now because you can't uncouple them. You have to go back to what is the question I'm asking. Again, the information, is it the confidence in exclusion of a disease now? Is it confidence in increasing the opacification of something? Do I see something clearer now? And can I see the anatomy better? Can I see more of the bowel now? Can I see more of the lower bowel now? It's confidence that I see--I agree with you, it has to be tied to something. And I think you can measure it, again, prospectively designed. A lot of the questions say what is your confidence in excluding additional lesions. So if you've now--that's part of the example I gave before. You will not change the patient, potentially, outcome. The patient may still have the same sensitivity and specificity pre and post, but now you've seen maybe more lesions. So the overall disease has not changed in the patient. It just may be more extensive. Then I go into the patient management pieces. How would that information be used differently from what I collected? Now I'm no longer doing a liver resection because there's more disease.

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So that's a very extreme case, but that's an example of how a confidence piece of information could be built into a trial legitimately with a very hard endpoint.

DR. MILLS: And I may offer to you that a lot of what you've just described may be what the industry and the academic community needs to hear as much in terms of trial development when you bring them to the agency and say maybe our radiologists in the Phase 2 have to define that, yes, we can't see more liver lesions per se, but we define that the bowel loop is much better, we're able to see the renal shadows now, where we couldn't before. These are critical elements in terms of improved biodistribution imaging, which are increasing the confidence. That would translate as subjective eye interpretation that we just heard about to that objective information that we can measure at a clinical trial evaluation.

DR. LOVE: Some of that relates to these other things we've often talked about. They're the technical endpoints. They're the more objective pieces. What do you see? How do you see it? How well do you see it? Describe it. Moving down from the initial thing that you see on the image to the point where it starts to get transcribed into something else in your mind and try to identify all of that. And putting

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those kinds of--capturing that type of information on the case report form before you get to the question of what's your diagnosis, what's your confidence in the diagnosis, what is it of the above that increased or decreased your confidence, then that kind of step-wise approach might very well be helpful.

Yes?

MR. PATT: Rick Patt, Berlex. One of the things we as radiologists do and do in grand rounds, much as the model you've suggested, and do routinely is, after we've made our interpretation, with or without the clinical data, we make recommendations. And whether they're recommendations for management or for clinical management or recommendations for additional imaging tests, that might be one way certainly to capture a change in diagnostic confidence. How has that diagnostic confidence affected perhaps your final recommendation?

Getting back to the blinded read panels, and also looking at management questions answered by basically the people reading the films, I haven't heard a lot of discussion on that. I know that there are some that may have issue with recommendations made by selected panels towards management issues that may be outside of their areas of expertise, and

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perhaps we could discuss that a bit.

DR. LOVE: Right. That sometimes is an issue, and it would mean if the indication which talks about actually having identified patient management elements often would almost imply that you would have to have a read or some discussion between the imager and the treating physician, and there are some reads that are designed as--not so much in the sequential unblinding process, but after you've gone through the radiology read, then you have a read of the radiologist plus the treating physician, or a discussion between the two, depending upon what the issue might be.

MR. WELCH: Mike Welch, Biometrics. I just want to make a comment on the confidence in diagnosis issue. There are statistical methods that sort of will handle this if you're thinking of making a specific diagnosis on a continuum from absolutely no disease to some disease and you're somewhere on that continuum in terms of your confidence based on the image, and certainly ROC analysis or receiver operator characteristic approach will handle that for different readers and different types of controls. This is something, I think, that is certainly underused and could be a valuable tool in looking at this.

I have one comment for Len. I'm curious. He mentioned the

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idea of negative bias from using totally blinded readers, and I guess from a statistical perspective, I'm a little bothered when we start to introduce more information to the reader, either in a sequential method or all at once, and how this additional information--how we can be sure that the additional information is not confounded in the outcome when you're trying to estimate the treatment effect. And unless you control for that somewhat, for example, do a fully informed and a fully uninformed read, you know, you're not going to be able to get a good handle on that. So it sort of bothers me from that perspective.

Again, we're talking about clinical use, and I think one may argue that in the field, perhaps, the radiologist that will be using the particular contrast agent, for example, certainly will be of the caliber of those, perhaps, you know, in the study, in the blinded read, or in the on-site. So whether the information will be, you know, transferable or not is another question, whether it's based on fully informed or not.

MR. BAUM: Len Baum. The comment I can make is that I agree with you. If you were to design--and I fully appreciate the difficulty in this, because if we design the statistical trial, it would be a very easy thing to do, just take a

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piece of film and put it up. But now we're trying to design the statistical trial that has the clinical relevance piece to it. And the reason I'm saying a negative bias is in a way I look at this, have we overreacted? Have we moved the line too far over?

So what I'm saying is a study is still a valid study, it's still scientifically valid, because the test is really can I make the proper diagnosis based on the use of the product. So the real test is with that last piece of information, I know whether it's truth or not, even if it's comparing against another approved product. I still don't know what my endpoint is because I've withheld that one piece of information, the truth.

And all I'm suggesting is that we try to move that line that we're using for statistics now over a little bit more to call it clinically statistics a little bit more rather than pure statistics. And I recognize this is a very difficult thing to do and somewhat uncomfortable for you, also. And by making the statistical analysis marry together with more clinical information, it may make everyone a little more uncomfortable from a biometrics standpoint. It may make the clinical people more uncomfortable, and yet we produce information that's more clinically relevant.

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I know the comment was made today about going totally to unblinded reads and recognize that would be, you know, a quantum leap, if you will. But I do agree we should use that piece of information. It's a valuable piece of information collected. It's a very hard thing, I recognize, and it's going to come down to who makes the final decision in a guidance document. We recognize that.

I think I heard a lot of things today that were very, I'll say, pleasing, and, you know, George and I both said the same thing in a lot of different ways with different definitions. But the sequential--what started out being called sequential unblinding, and maybe you'll do it, maybe you won't, maybe we'll put the information in, maybe we won't--no matter what side we all come down on, I think I would like to say there is use for a clinically informed read, and the information is very valid and should be in the labeling. It ultimately is going to come down to a center decision, is can we in those cases clearly define, not due to the pure image read, and include and define what cases from a statistical standpoint and a clinical standpoint you may need then.

I can't disagree with you. I'm not a statistician, and I recognize the less information you give someone, the less

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bias potentially could be introduced to it.

MR. WELCH: And the less variability.

MR. BAUM: But then I come back to if you gave them some information from a clinical standpoint which more reflects the use of the drug--and we've done this. Iodine and gadolinium products, we gave a lot--you know, there were a lot of different trials designed. We're slowly raising the bar. As we finally look at these guidance documents, we are moving the bar up to a higher level because we're writing all the words into it. We're almost trying to anticipate everything. And I do recognize that difficulty.

MR. WHITE: This is Richard White from the Alpine Group. This is more of a housekeeping matter. We do have another topic, and we estimate it would be about an hour. There is one more comment, I think, on blinded reads, and if we could close after that and move on to the next topic, we do have people who are flying out, so--

DR. LOVE: Right. I did want to ask that same question. Thank you for raising it now because I also wanted--we could take maybe a ten-minute break or else we can move straight forward to the end. Some people have said they have to leave exactly at 4:30 to catch planes. So do you want after this last comment a ten-minute break, or do you want to keep

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moving? Five minutes, I'm told now.

MR. CARVLIN: A five-minute break.

MR. BAUM: We'll keep going. Those people who need to break go on your own. Sequential break.

[Laughter.]

DR. LOVE: Please go ahead with your comment.

MR. HAGGERTY: Bob Haggerty, Diatide. With the number of mentions of prospective approach on the study design, I'd like to ask the agency to consider possibly recommendations on gaining timely review for the clinical study design and protocol reviews, if you can.

DR. LOVE: Thank you.

I'm told to take five. Thank you.

[Recess.]

xx DR. LOVE: Okay. This should be just a very quick introduction. We are moving into indications and areas that might need some clarification. We received basically five or six comments from MICAA that fell into subtopic areas on the indications, the effectiveness clinical benefit comparators, standard of truth issues, what if a standard exists or doesn't exist, and how do you develop it.

Some of the comments from MICAA seem to be more proposals. Two of them seemed to be clear questions, so I will address

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the two that seem to be questions, and the remainder, then I would ask for your discussion.

Here, just a reminder of the four indication categories as identified in the document draft, and the first question was: Could we get some examples of drugs that have been approved using these indications?

Well, it's a draft document and is not yet for implementation, so no, but there are some similar ones that are out there. Recently, the Acutect product was developed as a receptor in a disease-specific indication. As you know through the public meetings that have been held with ICT, there is a lot of discussion about some of their products that have a combined type of an indication looking at metabolism, disease specificity, and possibly even patient management. So that's all on the record, and it's public information.

Then we talked at the DIA meeting about another example where you had--let's say you had a receptor-based product or metabolic product and thought about just ways that one might think in trying to develop the whole approach to that drug. And if the receptor-based product primarily had benefit in outlining a structure, then that might be the most appropriate indication. If that receptor-based product had

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a wide variety of uses that were clearly known or could be developed and identified during the drug development process, then you might think about developing that product for the physiologic structural type of indication.

Sometimes, though, within even that same context, the drug might have more use in a disease or pathology detection approach because, really, that receptor's primary value or use is limited to that particular disease or pathology. So that might be a more appropriate indication.

Certainly within that context, it's easy to think of a drug that's for a specific disease or pathology to also perhaps be useful for a patient management, either diagnostic or therapeutic management type of indication.

So there are a number of ways that we think that this could be used. A lot of it does depend upon the drug and what you're seeking, and a number of different issues can come into play. What we would see is it depends. You could have one indication or you could have several, and it really depends upon the sponsor's goal and intent and what you think the clinical settings might be.

The other specific question was how would you select a standard of truth and what kinds of things would we think about, and I think it varies here. If you already have a

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standard of truth and it's clear and it's an accepted standard of truth, then, of course, it's either the approved label and device. It might be a clinical standard of truth where you might decide a truth panel might be more relevant, where you have very specific prospectively identified criteria that take essentially the rest of the clinical information that's been discussed in the previous session that's relevant to determining the truth. That might be an approach.

If there really isn't a clear standard or if perhaps there's another modality that's out there but just has not yet been completely recognized by the agency as a standard of truth, then either literature or some other types of approaches might be useful to try to get that modality documented as a standard of truth

Sponsors have asked us how to do that, and at least at the moment, what we are suggesting is that that type of indication would need to come in in the NDA to try to document the standard of truth. Some sponsors are trying to do that prior to the NDA so that it's clear that that particular standard can be used in a Phase 3 study. It varies. I think there are probably a number of other options that could be considered in that realm.

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So those are the two specific question. Do you have a question for me? If not, then I'll turn it back over to MICAA.

xx MR. CARVLIN: Well, this paradigm for drug delivery is simple and straightforward. It's almost a tautology, and that is, it begins ultimately and ends ultimately with the patient, so that we'll be talking for the next several minutes about Section 4 and Section 5, about establishing claims for medical imaging agents.

The guidance document is very clear in the charge that it gives to sponsors, and that is, to establish a claim for medical imaging drug, a sponsor or applicant should characterize the drug's clinical usefulness and demonstrate that the information provided is, first, valid and, second, reliable.

Clinical studies should be performed in defined clinical settings. These overarching principles are discussed in the section, as are the methods of establishing effectiveness for specific claims.

However, as we embark on respecting those overarching principles and designing our clinical trials and implementing the clinical trials and gathering the data and supporting our claims of indications and ultimately

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advertising and promoting the products, we have some pragmatic concerns and hurdles and many challenges. And whereas in therapeutic pharmaceuticals the path is somewhat direct--that is, we can go directly from patient--excuse me, from patient to patient management with the intermediate step being the pharmaceutical--for a diagnostic pharmaceutical there are a number of stops along the way. We have to have an imaging examination, the byproduct of which is an image, and then we have highlighted here in yellow a potential point here to introduce bias due to medical interpretation. And if we go even further into patient management, there's another highlighted point here where bias, confounding bias, could be introduced as well. So there are additional challenges that we face in bringing out the medical imaging drug product.

Now, the therapeutic pharmaceutical is relatively straightforward, and there are some parallels, again, dissimilarities also, with medical imaging drugs. Therapeutic pharmaceuticals, as I said, we have the patient here who has either no drug or drug, and this results in some medical state, and we make some observations. In our clinical trials, in our protocol, we have hypotheses and endpoints, and in our case report form, we also have those

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endpoints when we gather these data to support our claims and to seek indications.

The usefulness here, the benefit to the patient and to health care, is a clinical one, and it's due directly to a pharmacologic effect. There are risks. There are risks first related to drug administration, and actually there are other risks related not to administering the drug. But basically we can come up with a benefit/risk balance here or an assessment. And there are endpoints here, and in the best of all possible worlds, those endpoints are quantitative, so much of an adjustment in cholesterol or lipid or blood pressures, and they're also objective. You can measure them directly, and there's very little here as far as bias is concerned.

Now, the direct parallel for us in diagnostic pharmaceuticals is a technical evaluation. We talked about this earlier today, and we'll talk about it a little bit more when we get to the specific categories of indications, the A, the B, the C, or the D. But here we have our patient with and without the diagnostic pharmaceutical, and the byproduct of this treatment, then, instead of a medical state one or medical state two, it's medical image one, medical image two.

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If we want, we can identify endpoints that a quantitative and objective. They just may not have direct clinical relevance. But as a byproduct of the medical image, we can measure things such as density or intensity or ecogenicity(?) for a number of counts, signal-to-noise ratio, the size of the image--excuse me, the lesion, the number of lesions, or anatomical feature or some important component of the image.

So the usefulness here is technical, and it's related and determined ultimately by the reliability and the validity of the modality, the acquisition technique, any reconstruction algorithms that you might have used post-processing, how the data is stored and displayed, and all of this is reflective in comments made in the guidance document. And the risks here relate really to drug administration.

But what we want to do is to bring out diagnostic pharmaceuticals that have clinical usefulness, and this is the charge in Section 4 of the guidance document. And here we have a slightly different, more complicated flow chart because we've introduced another point for potential bias here in this yellow box, our medical expert number one, who could be a radiologist in some instances, a cardiologist in others, and other medical imaging specialists.

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What's more, without and with, we have our medical state one, medical state two, our images that are interpreted by the medical expert, the byproduct of which is medical information.

Now we get to the foundation upon which we build our claims and ultimately indications, and we promote our products. Clinical usefulness, we need to define that. We need to know exactly the appropriate endpoints to support that usefulness. These endpoints have gone through this intermediate step, that is, the interpretation, so instead of being quantitative and objective, we now have qualitative and subjective, as Dr. Mills had said. And there may be some parallels in the development of other therapeutic pharmaceuticals that could apply, such as the development of an analgesic or a psychiatric medication where you go from something that is subjective, the way I feel or the way I see it, to some other objective, independent, quantitative endpoint. And we'll be looking at those parallels to see if they apply to answer the questions that were posed earlier today.

Then ultimately we do have risks. We have the risks related to administering the drug, but we also have another category of risk that is highlighted in the guidance document, and

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that's the risk posed by incorrect diagnostic information. So once more we've kind of changed the focus. Here we're focusing on the pharmaceutical, but now we have an element here of testing the quality of the medical imaging expert, and also trying to minimize bias wherever possible.

So if we take this to the ultimate indication, the D level indication, where we're trying to secure labeling that indicates that this pharmaceutical has a clinical utility that embraces diagnostic and therapeutic patient management, we have an additional medical expert introduced here and an additional potential source of bias as various treatments are recommended, ultimately dependent on the patient. So for the balance of the discussion, we'll be using these principles to ask for clarification from FDA and to make our specific proposals.

DR. LOVE: Is there another speaker?

MR. CARVLIN: No. What we probably would do, just to make it a little bit easier than have a stack of reference material here, is to step through the various points that MICAA has raised in the eight-page or so document that we faxed in. And I thought I would begin at Section 3, which is indications for medical imaging drugs, which is guidance pages 3 to 8.

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The first point I think you've already addressed, Dr. Love, in your discussion of FDA's most recent thinking, but we were questioning, given that multiple indications for a single medical imaging drug may be possible, MICAA was requesting more information on how a given trial could be designed to satisfy the requirements for the multiple indications, i.e., can one clinical trial lead--if it's properly designed and has the right quality and quantity in the data, embrace indications A, B, C, D, et cetera. Those would be the structure delineation, the functional physiologic or biochemical assessment, disease or pathology detection or assessment, and ultimately diagnostic or therapeutic patient management.

DR. LOVE: Right. Just before answering that, one other thing from our perspective is we were listing these different indications. Some of it depends upon the perspective from which you want to approach it. Are you looking at it before or after the fact? Which category does it happen to fit? And then what's the overall relevance of the product in terms of how you plan to actually use the drug and how is it going to be promoted, marketed, and the like?

So we'll ask questions from two perspectives. How do I get

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an indication for--and maybe this product hasn't even been developed yet in the laboratory, versus now you think you have some information from Phase 1, maybe even Phase 2, that looks like it's moving in a certain direction and what's the next step, what's the best approach to use to describing the product.

To some extent, a lot of those different types of drugs fall in these different four categories that have been identified, and in other situations, there really is an overlap. We're often asked the question also--or sometimes there seems to be a need for clarity between the issue of what's the mechanism of action of the drug and what's the indication. So a mechanism of action might be to look at a receptor, use a metabolic process to develop the image, but the actual use of that information is to make a disease or pathology detection assessment.

So, in that situation, even though the mechanism of action is receptor identity or metabolic process function, the actual use of the product is something different. So I would try to distinguish that from products that actually have an indication that's different, a little broader.

So let's say, again, as I was speaking earlier, if you had a receptor that's available on a number of different cells and

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a number of different types of disorders or pathologies, and they cross into different spectrums, or a metabolic process that's found in a number of different sites, then that product very well might be appropriate for development as a functional physiologic or biochemical marker for a wide variety of disorders. And you might want to study a representative sample. We're not requesting that every single disorder is studied.

On the other hand, there might be some very specific--there may be a very specific advantage of that information in one or more diseases or pathologies over and above what might be in the broad setting. So there you might want to actually seek two types of indications, one for the specific and one for the general.

So then going to your question, could you do all of this in one study, or do you need more than one, I think some of it depends upon the complexity of what you're trying to study.

It's certainly possible that one of the--the specific target disease might be part of your overall study approach to try to get the physiology-biochemical detection type of indication. But it really also depends upon just what are you seeking with the disease or pathology detection and what would you need to put in that trial to get a second

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indication for that. So some of it depends on what you're doing.

On the other hand, it might be very easy to go from a disease detection indication to a patient management indication in the same disease. So there it might be conceivable to design two trials that directly address that. Something else, somewhat related to that, is we often talk about two trials per indication, but these trials don't have to be identical, and you can look at different aspects of the disorder from different perspectives.

MR. CARVLIN: That certainly helps us because as we were reading through the guidance where the various indications and claims were laid out, there was language referring to the diagnostic or therapeutic patient management claim on page 7 that says the therapeutic patient management may be studied explicitly, and we weren't sure whether explicitly meant solely or exclusively or specifically.

DR. RACZKOWSKI: "Explicitly" in that sentences was not intended to mean solely, but it meant that it had to be essentially prospectively designed and a protocol defined as an endpoint, et cetera, et cetera. But that was not intended to exclude the possibility of perhaps evaluating other claims, either within that clinical trial or others.

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DR. BRANDT: Gordon Brandt from Sonus. So, Dr. Love, if I can just clarify, it sounds like it is possible, then, depending upon the design of the study, that multiple categories of indications might result from a given study. You mentioned it may depend on how the drug is used, and I think that the guidance is silent or at least somewhat quiet on this issue, and it might be helpful having some information included in the guidance. If there's a big distinction in the agency's decisionmaking process between whether a drug is an adjunct or a replacement or a new type of drug entirely, it might be helpful to include that information in the guidance so that we on the industry side can better understand the thought process.

DR. LOVE: Certainly. Go ahead.

DR. BRANDT: No, please.

DR. LOVE: I was going to say, one of the--that was an area where we were struggling in terms of making sure we can clarify all those points, and I appreciate that that needs some more clarity.

Some of the thoughts we had in this were along the lines of what was raised in the previous session. Adjunct, assist, sometimes are relatively non-specific terms, but if it's an adjunct to determine or localize a tumor, if it's assist in

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identifying a site for biopsy or something like that, those are certainly approaches, and the study would be designed to try to address that specific point. Also, the issues of the clinical setting, when we are talking about that, is to find the patients who have that question. So they've been worked up to a certain point. They're now at the point of making that decision. And that would be the setting that's studied, and that would get that type of very specific indication.

So are those the kinds of things you're saying you'd like to see amplified, whether it's an adjunct to, it's a replacement of, how might it be used in different settings? Is that the kind of information you're talking about?

DR. BRANDT: I think that would be helpful. It's come up several times today in our various discussions so far that there is often a different thought process, depending upon whether this is an addition or an instead of. That might be interesting data to help us understand more how that changes your thinking.

DR. LOVE: Okay. I thought I saw another hand. Yes?

MR. NUNN: Yes. This question of defined clinical setting, if you go through the guidance document, it first comes up on page 10 where you use as an example imaging for duodenal

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ulcers. And you state there that defined clinical settings--there could be here, for example, four different clinical settings.

Then on page 12, you talk about appropriate representation means that the studies should generally include subjects that adequately represent the spectra of normality and abnormality, e.g., including subjects with chronic bronchitis, pneumonia, asthma, and cystic fibrosis, and also subjects with localized and diffuse disease for a drug intended to assess bronchiectasis.

And then on page 13, you again talk about the full spectra of normality and abnormality, e.g., including patients with inflammatory neoplastic and infectious intracranial processes for a drug intended to assess regional cerebral blood flow.

And then, finally, on page 14, you say in most disease or pathology detection or assessment indications, pooling of efficacy data across defined clinical settings would likely be of limited value, and a medical imaging drug should be separately evaluated in sufficient numbers of patients in one or more sub-settings.

I wonder if you could clarify for us a little bit. It seems here that we start off with four clinical settings for

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duodenal ulcers, and then we have to include in that the full spectrum of disease, which seems reasonable, but to include a full spectrum on top of four different clinical settings is stretching the imagination a little bit. And then you ask us to include in the case of the brain all different diseases that you think might masquerade such that now the number of patients we have to do to get one indication could add up to an enormous number.

Is that what you're proposing? How do we get all of these different examples that you have in with our defined clinical settings?

DR. LOVE: I think that's a little over-read on what we're talking about. It may link to something that was also raised a moment ago for us to try to clarify taking one example and walking it all the way through the process. What we were trying to do is give different examples of different types of issues and how one might use them, but not necessarily intending that they would be linked together in a way that you have done. So I can see that this is a place we need to clarify.

On the other hand, what we are talking about is in this clinical setting, you would go through a process of looking at what are the types of patients that would be relevant at

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this point in time where a medical imaging process or study would be introduced in their clinical context, and thinking about what's the range that needs to be considered in that setting.

So if you're looking at a screening study, the kinds of patients and the types of issues and questions that would go into the consideration would be very different from if you're on the last end of the process where you're getting ready to decide what's the final diagnosis or what's the final definitive therapeutic intervention.

So there would be different issues that would be considered. It sounds like this is a place we'd need to clarify.

Victor?

DR. RACZKOWSKI: I agree with what Dr. Love said, and I hope that was clear, that these sections weren't intended to be linked perhaps in the way that you did. I think giving an example, perhaps, of what was intended may be helpful, and the example of duodenal ulcers where it says that duodenal ulcers may be used in patients with gastrointestinal bleeding or to confirm suspected duodenal ulcer in patients with equivocal findings on radiographic examination of the upper GI tract or to evaluate healing of duodenal ulcers in patients after initial treatment, those would be three

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distinct defined clinical settings, and potentially a sponsor could go for one or for all of those indications. Performance measures such as sensitivity or specificity of positive and negative predictive values may be very different in each of those clinical settings, and so this may have been referred to somewhere a bit later in the document with--where it doesn't necessarily--it may not make a lot of sense to combine sensitivity and specificity from, let's say, a low-risk population with an imaging drug with the sensitivity and specificity of the same drug in a high-risk population, because they're two very different clinical settings, and the average sensitivity and specificity or positive or negative predictive value may not have a whole lot of meaning. That's what was intended there.

I think the section on other sorts of--the performance of a drug in other lesions--and I'll use the example--let's say you're trying to develop a drug to evaluate brain tumors. What the guidance was intended to say was that it would be useful to have information about how that drug might perform when you have other potentially confounding circumstances like--or similar or related types of diseases. An example might be, you know, looking at how it performs in brain

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abscesses, let's say. It may not necessarily be in the same clinical trial, but that could potentially be useful information that would complement the main action of the drug and its ability to identify brain tumors, knowing how it also behaves in these other circumstances.

MR. NUNN: So you're suggesting that there should be two clinical trials in that case? You said you could get that from another trial.

DR. RACZKOWSKI: Potentially. Or potentially in the same trial. But sometimes it's difficult to get all the patients in one trial.

MR. NUNN: That's my point. The only way you can get it in a single trial is to enroll inflammatory as well as neoplastic as well as infectious intracranial patients. So the numbers then start climbing quite dramatically.

DR. RACZKOWSKI: Well, I think it would depend on what your goal is. I mean, if your intent is to just evaluate brain masses that perhaps are suspect, then you could get the whole spectrum. But, on the other hand, if you already know that you have some sort of mass space-occupying region in the brain from other source of information, there maybe just to--and you think it's a tumor, or you have--then you may want to--the trial may be designed just to look at a

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relatively narrow group of patients who are suspected of having tumors as opposed to other pathology.

DR. MILLS: Adrian, one of the things that is always a concern, whether we're looking at a biologic or we're looking at one of the drug indications that we've been talking about most of the time here, is the concern about how far and wide you open up your patient population. And I would express a concern each time that as you widen out that population that you want to draw in, we increasingly become concerned that the indication groups are going to include patients who have compromised organ system functions. And one of the areas that this was to address was that concern, is that suddenly as you broaden it out, maybe this agents works completely different in a renal transplant patient versus a patient who has an inflammatory bowel disease where we may be affecting various clearances.

So suddenly that section as you read through, what's happening is we're mentally starting to expand the patient group as we're talking about, and almost immediately you start to see additional groups being added in and additional sub-groups, and, frankly, as you say, the trial size becomes enormous as you try to actually develop a screening agent. That's why focused indications are much easier for us to

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deal with in terms of clinical trial design.

MR. CARVLIN: Just a few more questions, if we could, please. I was wondering whether there is a hierarchy amongst the indications, A, B, C, and D, because there was some language in the guidance that said if you were able to secure an indication for a structured delineation, you could make these claims, but you could go no further. And if you had functional physiologic or biochemical assessment, you could go this far but no farther.

So I was just wondering if there's any relationship amongst the different indications, particularly a hierarchical one. If you have provided information, data sufficient to secure disease or pathology detection or assessment indication, does that mean per force that you've done B and A before that?

DR. RACZKOWSKI: That's a good question and an interesting one. Let me try to answer that, and it relates to a question that I perhaps have for you as well.

I think there's an implicit hierarchy that the Category 4 patient and disease management, that particular--diagnostic or therapeutic patient management is clearly directly related to what you're going to do with the patient, and so in that sense, I think there is an implicit hierarchy that

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that indication is, by virtue of being more directly relevant to patient management, is demonstrated.

I think the language in the guidance document about what you can and cannot claim was simply intended to specify that the claim should be supported by the underlying data, and just because you have an underlying claim for structure delineation, it wouldn't necessarily--you may not have supporting data that directly shows that you can affect patient management, so those sorts of claims should not be made, unless they are supported by the underlying data.

The question I actually had for you was whether or not if--I'm sorry. Why don't you go ahead and ask your questions? I'll try to formulate mine better.

MR. CARVLIN: Yes, thank you.

Progressing to page 9 in the guidance, this is the second full paragraph which begins: In addition, for a contrast drug product to be considered clinically useful, the product used in combination with an imaging device should provide useful information beyond that obtained by the imaging device alone, and that's kind of a qualitative statement. But what follows is something--so that's very difficult for us to understand or we might actually object to that, but what comes next is something that I think gets closer to the

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heart of clinical usefulness for a medical imaging drug. Stated differently, imaging with the contrast drug product should add value when compared to imaging without the contrast drug product. And I think it's up to us collectively to come up with the right kinds of examples, for instance, what is of value.

We talked a little bit earlier about diagnostic confidence, and there were other endpoints and hypotheses that would be part of the clinical trial design. Are there any other specific examples of value that you would care to offer at this time?

DR. RACZKOWSKI: Well, I think in your position paper from the Alpine Group, you mentioned a case where an imaging agent may not provide--a contrast imaging agent may not provide more information per se, but it may, let's say, speed up the imaging or make it easier to do in some way, and that potentially could be a claim.

DR. BRANDT: But it's important to note that that would fail the test of going beyond what could be obtained with the device alone.

DR. LOVE: Right.

DR. RACZKOWSKI: Yes, that's right.

DR. LOVE: We looked at that question and actually think

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that this is a point that would need some clarification, because there are reasons for advance either on the basis of time convenience or any other--what we often call compliance-related, patient compliance, things analogous to that for imaging. So certainly that would be a type of indication.

I think this is talking about in comparison to the previous modality, but sometimes even staying in the device for a shorter period of time might be relevant. So that's fine.

You mentioned something, I think, also, in your paper about the other modality, and the relationship to another modality, if it's just alternative information, maybe there wasn't anything on the previous image, or there wasn't a previous image in the case of a radiopharmaceutical or maybe even some of the ultrasound products. So, yes, looking in comparison to a different device is certainly a relevant comparison. That's essentially the control. So this is an area that would need some clarity from our part.

You talked about other information on the image. One of your examples was that there was disease-specific information on the pre-image and also information on the post-image. As I would look at that--and perhaps you can clarify it for me, but it would seem to me that

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understanding the information that's on the pre, understanding the information that's on the post, and looking at them in comparison would be important to establishing the value of the drug, and a lot of that then goes back to the questions that we were talking about before, and also comparing the pre and the post, it would seem it would help determine labeling instructions for use of the product. Is this a stand-alone where you don't need to look at the pre at all? Do you really need to look at the pre and post together? Is there some sequence that's relevant? I think that was raised earlier also about res-dress (ph) and radiopharmaceuticals or ultrasound agents where you need to maintain the sequence or the relationship in a pre and post, then those kinds of things seem important in determining the overall value and the instructions for us.

MR. CARVLIN: Just a brief statement about the validity of information provided by a medical imaging drug, and that's on page 9 as well of the guidance. Sentence two here, demonstrating that the use of the product contributes to beneficial patient outcomes, and that's just to say that the understanding of outcomes is directly related to medical imaging or medical imaging drug product is very much in its

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infancy. And it's something that the field of medical imaging is struggling with at this point, is what are the appropriate indices and what are the proper ways of measuring outcomes as they directly relate--clinical outcomes can be indirectly related, as we said, through the medical management decision, turning back to the interpretation of medical information ultimately to the image itself.

DR. LOVE: Is there a question on that?

MR. CARVLIN: No, just a statement.

DR. LOVE: Okay.

DR. RACZKOWSKI: Well, perhaps that would be better worded that demonstrated that the use of the product contributes to the appropriateness of subsequent patient therapy or management. But I understood your point.

MR. CARVLIN: Yes.

DR. LOVE: Well, I guess one other question there is this relates to two things. Where it says that this could be done in at least two ways, meaning it doesn't have to be one--both of them, but there are options. But certainly outcome endpoints can be relatively simple, or they can be very complex, depending upon the trial and the indication. So that can be a challenging issue, depending upon the

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indication.

DR. BRANDT: On the issue of a truth standard, you mentioned before, Dr. Love, that analysis of the literature may in some cases be appropriate. I think it would be very helpful for the people in the industry if we could expand in the guidance on how one goes about demonstrating the validity of other truth standards, perhaps giving some examples. The issue of meta analysis has been raised, and perhaps Dr. Welch would like to mention if there are specific types of analyses or thoroughness of analyses, quality of data, something so that we have a better idea of what would be appropriate to justify an alternative gold standard.

DR. LOVE: Okay. That's a whole other discussion just about how to use a meta analysis. Okay. Did you want a more specific--or we--

DR. BRANDT: It would be helpful if there were more in the guidance. I'll leave it at that.

DR. LOVE: Okay. Victor, I think, wants to--

DR. RACZKOWSKI: Part of the reason for having those two statements, one is validity can be established by use of a gold standard, and the other one is by looking at clinical outcomes, also to highlight that doing an outcome study of some sort or a patient management study always remains a

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viable alternative. We've encountered a number of situations where there isn't either a well-defined or well-accepted gold standard for a particular disease process, and what you do in that situation. And one alternative that should always be considered is the possibility of doing some sort of management or clinical outcome study.

MR. WELCH: Let me just clarify something on the truth standards. Talking about demonstrating the validity of a truth standard, we were talking about coming to agreement that a particular modality will serve as a standard of comparison or gold standard in the course of the trial, and that the medical community, in fact, agrees that this is, in fact, an appropriate standard. Is that--that's sort of where it's coming from as opposed to looking the literature and making some sort of analysis.

Certainly in terms of evaluating a product versus a comparator or something, an active control, and wondering about the ability of that control to provide certain information, that can be based on historical information as well. But you're talking about a truth, truth or gold standard. Is that correct?

DR. BRANDT: I guess what I was specifically talking about

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is a new imaging modality that may have attained the role of truth standard in the medical community, and it's my understanding that the literature is that acceptance of the medical community went down--I mean, it's the best we can put our finger on.

Those standards change over time, and it may be helpful to industry to have a process in place where we can demonstrate or propose the validity of a new or different standard from what had been used in the past.

DR. LOVE: Right, and I think that that's often the major issue, certainly one that's currently being faced, is there are some new technologies out there that we have not been using as the truth standard for some of the clinical studies. So for that, yes, the literature is probably a useful approach.

There are concerns sometimes when another standard--when the truth standard also involves a drug. Let's say it's--if it's another device or if it's a device without a drug, that's easier to demonstrate and document than if it also involves a drug that's not yet approved for that indication.

So there are a number of issues that have to be considered, but, yes, we would try to address that and clarify what might be needed. Sometimes you might even need the

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cooperation of another sponsor, which can help answer some of those questions more clearly.

MR. CARVLIN: I guess this becomes less problematic for us in the face of rapid change, and as our standards are being rewritten with the introduction of new modalities or your diagnostic pharmaceuticals, what had been long understood to be the standard is no longer perpetuated as the standard of medical practice.

DR. LOVE: Right. We're concerned about that as well, and as I say, we realize, sort of separate and apart from the guidance document at this moment, there are issues and concerns about how to move the standards along to keep pace with current technologies.

Next?

DR. BRANDT: Along the same lines, I guess a question that I've heard brought up from the MICAA members is the issue of having both a comparator and a truth standard in a test. Where there is a drug under test and there is a comparator, each of them is independently compared to a truth standard in some study designs, and I read the guidance as advocating a design like that.

The difficulty that I've heard from other MICAA industry members is essentially it puts one in the position of

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reproving the efficacy of already approved drugs, so that rather than finding sensitivity and specificity of a new drug compared to a comparator, we're really getting differential sensitivity and specificity of each of those compared to a truth standard. And the question that I've been asked to put forth is: Is that strictly necessary?

DR. RACZKOWSKI: Well, there's--the way that the document is written, no, there is no expectation or requirement per se that if there is an approved drug already out that a comparison study be performed. The guidance takes the position that that's encouraged.

There is, however, a potential upside to doing that sort of evaluation, particularly if you're trying to show that your product is superior and you want to make some sort of superiority claim. If you have that sort of trial, your drug versus some already approved drug, compared to a gold standard, that opens up the possibility for that type of claim.

DR. LOVE: Right. Often we're asked or faced with an issue of can a product be promoted as comparable to, equivalent to, an alternative to, and to seek those kinds of claims in marketing, then we would look for data that tries to identify or document that.

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We are, of course, recommending a comparison to truth, whether it's an image or whatever, as we just talked about. So a truth standard certainly seems important in order to demonstrate what you're talking about. But the issue probably comes down to what happens when--is truth a comparator or is it a separate issue? I think that's the other part of this?

So truth is often considered to be an external--something separate and apart from the test modality that you're seeking. So let's say you have two gadolinium agents that are being compared. The second gadolinium probably would not be considered as the truth standard in that situation. That's an agreement study, and often agreement studies fail, unfortunately. Within the same patient, you'll get different answers, and that's why if you're doing a study against a control, then we're recommending that the truth is included in there to determine what the issues are. Sometimes--it's not so much a revalidation of the other agent, but just determining how your product performs and also being able to perhaps identify some situations in which one product might have an advantage over another or a certain subset of patients.

I think your other question was would we approve on the

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basis of truth alone without a comparator. Yes, we've done that.

MR. WELCH: I think from a design perspective, if, for example, you do have a diagnostic contrast agent, and you evaluate against the truth standard in a clinical trial, and maybe your outcome in sensitivity and specificity or some other measure of diagnostic performance, that's essentially your outcome. And without a comparator, you essentially don't have a control in that study. You have to sort of have recourse to some sort of information from outside the study such as performance of the comparator to show that that measure of diagnostic they're getting in the course of a trial is above some appropriate threshold, or better than some standard of care.

So with the comparator, you have your two outcome measures, sensitivity and specificity, for example, for each--for the comparator and for the new test drug, and you can show that they are an appropriate reason for accepting the results of the trial.

Another problem without the truth standard, if you just have a comparator, for example, in a new drug, and you really can only talk about agreement, you can't even talk about diagnostic accuracy per se, and the trouble with agreement

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is it's often driven by prevalence and not necessarily the performance of the test drug. In fact, you can often show that random selection of outcome drives a certain agreement rate based on prevalence, which really doesn't put it in a good light.

I suppose agreement could be useful, and I think you can come to terms of saying, well, agreement in a very high range, I think just hypothetically, 99 percent--if you can come to terms with that, if that's meaningful in a clinical sense, I think it could be useful.

DR. ROSENBERG: Well, sometimes I think that agreement--Marty Rosenberg, DuPont. Agreement is sometimes, I think, maybe a valid endpoint, especially in trials of medical imaging drugs where your prevalence of disease is so high, and your trial makes it difficult to use just changes in sensitivity and specificity, because if you have a high prevalence of disease in your trial, it's very hard to show a difference in sens and spec. But it could be more easily demonstrated in agreement, and I'm wondering whether that is reasonable or not.

MR. WELCH: Well, for example, say your prevalence is 80 percent, and if your agreement threshold is 80 percent, you can get that just by selecting all outcomes in one--you

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know, in a disease, for example, which would be totally unrelated to any drug effect. So I think you really have to think about what your prevalence is and what your agreement region should be.

DR. RACZKOWSKI: Part of the reason that the guidance document takes the position of encouraging comparisons with other approved agents, of course, with a gold standard in place, is ultimately that is the information that's probably most useful to clinical use of the product, whether Drug A versus Drug B or Modality A versus Modality B is appropriate in a given clinical situation. If you do a head-to-head comparison, then you directly ask the question, and you can directly answer it.

MR. CARVLIN: Just a couple of additional points in Section 8 which we've been talking about with truth standards and the controls having to do with image evaluations and how to choose the images and what potentially constitutes a set of images and what is an accurate representation of clinical practice.

For instance, I'm thinking about the clinical practice in contrast-enhanced ultrasound where if you are performing echocardiography, you're doing it real time. And there is a lot--there's an on-site evaluator, clinical investigator

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that you're seeing that might not otherwise make it into the set of images. So that's a concern, and also the methodology that's used in the imaging evaluations, we've evolved the way that we handle images, display images, communicate images over the last several years so that an imaging standard, the (?) standard has been elaborated. In the meantime, we find it has helped our productivity, at least our efficiency, to adopt these standards and encourage, wherever possible, that we have standard-reaching formats to better communicate between sponsors and FDA.

DR. LOVE: I'm trying to understand--yes--

MR. CARVLIN: Yes and yes.

DR. LOVE: We're familiar--the yes was yes, we're --imaging and tape-handling issues are important, but I'm not too sure that I understand the question that you're asking us at this point.

DR. MILLS: As you formulate the question, back again, you're aware that we're currently in the evolution of developing electronic submission standards at the present time. And you might want to look to that draft guidance which is being developed by CDER and CBER at the same time to take a look at some of the issues that you're raising there in terms of image submission, uniformity of the actual

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structural development of these images. I think it will be of great help. From the standpoint within Biologics, we've had a number of electronic submissions along the way in the past several years, and I know that a lot of those standards are being evolved in the industry. I see some of those people within the audience still at this moment.

So one of the things that I would look at for us is, yes, we're sensitive to a lot of these concerns, but there's parallel development of guidance at the present time, which isn't--and I've been asked this question: Why isn't it in the medical imaging guidance? Well, to be realistic about it, I know that there's another guidance being developed at the present time, and the last thing we want them to do is cross at this moment.

DR. LOVE: Right. And I think the other thing you were mentioning earlier about the echo tapes and when we talk about the information that's relevant to the conditions of use, then certainly it seems important that the whole tape that the on-site person would see is the image that we want to be used by the blinded or sequentially unblinded, or whatever other reader that's going to see it. So we do get concerned when the tapes are separated or the images are separated from the total body of information. So those are

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things that you'd want to think about in looking at that. If someone is intervening along the way and making some selections, then we certainly get concerned about what that might do to the read, and is it introducing some type of bias in that process? Or if images are submitted with circles on them that say this is the spot, then we begin to get concerned about that as well.

So those are some of the things that we were talking about in that guidance document that would be principles to consider when looking at this. But, yes, as George is saying, electronic submissions are incredibly valuable to us, and they speed the review and certainly help us in assessing what's happening, and it also helps us to see what the on-site readers and the blinded readers are actually seeing. So it makes it a lot easier to do the reviews. So we encourage that.

Okay. Yes, as Doris says, we were asked whether or not this could be part of the guidance, and we do think it's an important piece. But it would probably be a second guidance.

I see that a number of persons are leaving. Are there some other specific questions from MICAA at this point?

MR. CARVLIN: No. Actually, we've gotten through all of the

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specific questions.

DR. LOVE: Okay. Are there any questions from the audience before it dwindles drastically?

[No response.]

DR. LOVE: Okay. The last topic really was to be open discussion for anyone to raise any other issues that have not already been raised. So if there's anything else, please feel free.

xx FLOOR QUESTION: [unintelligible] for MICAA [for Mike?]. Is there any plan after this guidance becomes more official to be something similar on the statistical side?

MR. WELCH: That would be nice. I think we have an internal effort in the statistics group to look at some of the more statistically oriented problems in this area. So we have some working groups that are kind of working on some internal guidelines, and I think those could feasibly be developed further. But we're just getting started on it.

DR. LOVE: Right. There are some unique issues in imaging that are relevant to a lot of other diagnostic products, so it seems to be developing here.

Next?

MR. LaFRANCE: LaFrance, Bracco, Princeton. My comments are less new than perhaps some comments based on this

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afternoon's discussions and some from this morning, if that is acceptable.

The first is--and you mention this in the guidance document, and I don't pretend to try to present your opinion, but historically you've been very clear about saying a pathophysiologic process in terms of the study design is preferably attached to some disease process. As product development continues over the ensuing years, I think most companies recognize that the effort and new products will be increasingly towards targeted activities, and those typically will be pathophysiologic or physiologic processes. I would like to respectfully ask the agency in their review of the guidance documents to consider the fact that some clinical designs might be well served by a focus on the pathophysiologic or physiologic process that in the former case, certainly definitionally, requires a disease process, rather than they be dominated by one single disorder, perhaps. Certainly in the practice of medicine, even having information around a pathophysiologic or physiologic functional or metabolic process may be a legitimate and an important piece of information that will supplement the whole diagnostic or patient management process.

So I'd ask that that consideration--even though you've been

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clear about your position, that there might be room for considering just that endpoint as opposed to that endpoint attached to a disease. Victor's kind of giving...

DR. RACZKOWSKI: I'm not sure I'm completely understand.

MR. LaFRANCE: For example, in the past, if I came in and said, gee, I have an agent that shows ischemia, you would coach me to say, well, that's great, let's have--you know, let's have a study that shows ischemia in diagnosing CAD, as an example. All I'd ask is that the agency consider that the pathophysiologic process using that example may be sufficient for an endpoint in selected considerations, perhaps in a prospectively accepted and discussed manner. Many times that piece of information alone is important and sufficient in the clinician's management of the patient rather than going to diagnosis. For example, it might be someone with known disease. In a broad variety of disease entities, you're not after a diagnosis, for example, but you may be after what the status of that pathophysiologic process is--mild, moderate, severe. So my plea is just to consider that in terms of the document issues.

This morning we talked about, I guess, PK and those thresholds and some of the preclinical activities. I'd offer that there are some modalities where just the mass of

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impurities in a product may exceed the total administered amount in some other modalities, and some consideration around the--I'll call it discrepancy. Perhaps that's not the best word--the discrepancy and what's required for some modalities to document safety or evaluation of either excipient or impurities that may be many milligrams as opposed to micrograms for a nuclear medicine product as an example, and that kind of difference of expectations be considered by the agency in their review of the documents. Discussed this morning also--and I don't know if it was Victor or George mentioning around the risk/benefit, to use the oncology portfolio, and although it's very clear in therapeutic applications to severe disease situations such as in oncology, I believe the same type of combination should be at least considered and hopefully is considered in the guidance documents that in some disease entities the risk/benefit for diagnostic applications to those patients should have the same types of consideration of risk/benefit as the therapeutics enjoy.

Two other quick comments. The guidance document now seems to be evolving as an umbrella document, which seems to be, you know, a very rational way to approach things but I think makes your job very difficult to include all things. And

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considerations around, say, the timing, if it becomes an umbrella document with, say, appendices, for example, if there are parts of that that might be ready for publication or completion such as a document with a radiopharmaceutical section, since by CORAR that's been ongoing for a number of years as opposed to MICAA, which is much more recent, and probably much more challenging to be considered rather than holding up a guidance document that might cover everything to its full conclusion.

Then finally, I would like to compliment not only the agency for having today's meeting, but an upgrade on the Group 1 versus Group 2 designation, and I think there's a lot of suggestions by MICAA and CORAR that are excellent in terms of the criteria that might lend itself to the definition of a Group 1 or Group 2. I appreciate the agency's extending and upgrading that document--those criteria to those groups, but recognize that the benefit of those criteria may be applied to Group 2 agents, even though they may not fully qualify for Group 1. I'm not sure that was well presented by the industry panels, only because I think they appropriately focused on a Group 1 or Group 2. But I certainly at a personal level appreciate your upgrade, that it doesn't have to be all or nothing on that.

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Thank you.

DR. LOVE: Thank you.

Any other comments?

[No response.]

DR. LOVE: Any other comments from the panelists?

[No response.]

DR. LOVE: I think it looks as though we're ready to adjourn. I'd like to thank everyone for coming. We certainly appreciate all of the input and the hard work that has gone into this and appreciate it very much, and we'll look forward to the other comments that you will be sending in, and any other recommendations in response to some of the questions that were raised today.

Thank you very much.

[Whereupon, at 4:13 p.m., the meeting was adjourned.]