the sensitivities of the assays, the nature of the kinds of assays that are being performed make any reasonable, meaningful comparison of differences difficult if sometimes not impossible. This is relevant to the extent that it provides meaningful clinical information to doctors and to patients but also that sponsors quite often use the immunogenicity data to promote their particular product. So, one of the questions to the committee is what is appropriate in this regard with regard to the label.

So, with that, I'll go back to the first slide that I put forward and simply say that we very much look forward to the input from the committee on these issues, particularly on the ones that we've outlined but I've certainly enjoyed the discussion and look forward to more input. Thank you.

DR. SALOMON: Great. Thank you, Bill.

That's actually a great introduction to the discussions now that we hope to flow from this. I think from the comments that we've already had -- I'm sorry.

DR. SAUSVILLE: I had a question for Dr. Schwieterman. In terms of the clinical issues, if you look over the large number of products that Dr. Rosenberg presented for which there is some information about immunogenicity, would the nature and type of the clinical phenomena associated with these be considered serious,

life-threatening? In other words, at what level do we consider -- when we say clinical issues, there's obviously different levels of gravity that one could conceive of. If you could comment on that, that might be helpful.

DR. SCHWIETERMAN: That's an excellent question. I think the easy answer is that the range of adverse effects that you see from immunogenicity range from the inconsequential to the perhaps -- I do not want to be too alarmist, but I could conceive of life-threatening adverse events from anaphylactoid and other types of hypersensitivity responses and so forth. I think that in fact therein lies some of the dilemma about how to pursue some of these concerns given that we have experience both with products that are immunogenic yet seem to continue to "work" in the clinic for long periods of time that don't pose these problems. Yet, there are other kinds of data that come forward that compromise the safety and efficacy long term or pose risks to the patient's long term, for example, with the chronic therapies whether they were to go off that therapy and be retreated and so forth.

I think that's why we're here today, frankly, is to get a handle on what the experts here around the table believe about these risks and how the agency ought to reasonably pursue recommendations to the committees with regard to that. But I guess the literal answer to your

question is it spans the gamut from nothing to really quite serious events.

DR. SIEGEL: Let me attempt to do what is undoubtedly not impossible to do well, but to kind of give an overview I think of what we've seen as a whole over the last 15 or 20 years.

I think it would be correct to say that the issue of loss of efficacy is an issue that arises frequently. Dr. Zoon pointed out that it has been observed in some settings with the interferons. Interestingly, she didn't point out when you lose efficacy, at least you also lose the adverse reaction profile and that's one of the --

DR. SAUSVILLE: A surrogate marker.

DR. SIEGEL: There you go.

(Laughter.)

DR. SIEGEL: Well, it is. It can often be one of the first signs of an antibody response, is a loss of the flu-like reaction.

I think that there are a number of products where there are suggestions of that, a number of settings we've talked about where it's hard to tell, but enough settings where the half-life of the product changes radically enough -- its clearance increases radically enough -- that that has to be a concern.

Now, when you get into the safety concerns, of

course, many or most of these products have been developed in the setting of serious diseases and radical concomitant therapies. It's not always clear to make attributions, but it's probably been limited. The issues of immune complex disease, I think it would be fair to say, generally don't arise outside the setting of monoclonal antibodies because the actual volume of material given is usually pretty small if you're talking about an enzyme or a cytokine. Streptokinase may be an exception to that rule. And even amongst monoclonal antibodies, there haven't been that many examples of what are clearly -- we've heard about the issues with Remicade and streptokinase, but beyond that not many examples.

Then the other major safety concern is the impact of neutralization not on efficacy but the safety implications vis-a-vis neutralization of the endogenous analogue. That has been in our minds for the last -- I've been at the agency for 17 or 18 years. We've always talked about that and not seen clear evidence of it. Frankly, I'm not sure that we would know it if we were seeing some modest amount of neutralization of endogenous interleukin-2, interleukin-11, interferon, because of all of these issues we've talked about of multiple redundant pathways for many activities. I think that the observations with TPO and some related molecules, though, have brought to the

forefront and in part led or one of the impetuses that led to calling this meeting, the realization that we are looking at the potential -- and it's no longer just theoretical -- for some significant adverse reactions in that regard.

DR. BROUDY: Just to answer very specifically, the neutralizing antibodies against MGDF dropped the endogenous platelet count to 10 percent of the normal levels, and that's the same level that you get to in a TPO or an MPL knock-out mouse, so completely neutralized endogenous TPO levels, and had a very significant impact on the platelet count.

DR. CHAMPLIN: In that regard, very few molecules are in fact so important, and the lives of many post-docs have come to naught because the knock-out model of whatever gene they're studying has no phenotypic difference. With only rare inclusions can you identify really critical molecules for certain functions. So, G-CSF and TPO and EPO are critical, but GM-CSF, the knock-out mouse has got very few manifestations, alveolar proteinosis, and the blood looks pretty good.

I think my own sort of major reflections on the conversation so far is that for the most part these immune reactions don't have monumental consequences. It's the rare patient where the normal homologue is going to be

affected in a way that is meaningful, but clearly there are symptomatic adverse events, or if the long-term efficacy of a product is affected, that is honestly a major concern. The rather relatively innocuous antibodies don't seem -- nonbinding or other binding, but non-neutralizing antibodies often don't inhibit activity much.

So, I think one needs to look at this much as you look at any toxicity. Is it a grade 0 or grade 1, just sort of a minimal problem, or is it a major problem that needs to be considered in the grand balance of the efficacy versus adverse effects of the given product.

DR. SALOMON: The follow-up on that is I would just for intellectual discussion take the position that I don't agree with what you said at all. This is an intellectual point. I think you've made a lot of good points.

But here you're saying that, well, we've got to see this really dramatic thing where you basically knock-out TPO, and that's what we have to worry about.

I'm looking at a future where biologics will be employed repeatedly and many different kinds of biologics in patients. And then these patients -- some of them might be children -- would have 20, 40, 50, 60 years left. If you find out that knocking out IL-2 may not make the patient fall down and turn purple and that's not dramatic

enough for us, but what if they have a 10 times increased incidence of breast cancer 10 years later? In other words, we should be very careful that we don't arrogantly interfere with these complex biological processes and then reassure ourselves that we haven't seen an effect acutely.

DR. CHAMPLIN: My point was that if IL-2 has a dramatic clinical benefit in renal cell cancer or whatever, that we shouldn't say that the theoretical concern should prevent it from going forward. So, you should consider it in the context of all of the attributes and negatives related to a given product, but not overreact to an asymptomatic presence of antibodies.

DR. SIEGEL: I think we'd all agree on that. But there are a lot of issues on a day-to-day basis that we face in the development of these products that we're seeking guidance, and they're outlined in these questions. When is the concern high enough that we should ask for a primate study --

DR. SALOMON: I thought as soon as this sort of died down, I would get us focused on the exact questions, though. It seemed like people had some concerns they wanted to start off with of more general content, so I didn't want to stop yet.

DR. SAUSVILLE: So, with those two polar, shall we say, points of view --

DR. SALOMON: It was done intentionally. I hope --

DR. SAUSVILLE: I would ask representatives of the agency then what seems to be emerging is a sense that this area, because of the longevity of immune responses, the capacity for recall, all these things, in a sense you may be in the position of developing a relationship with a marketing entity that may need to exist over several years. Do you have the authority? Or is it possible for you to say we've got to measure whatever for the next 10 or 15 or X number of years?

DR. SCHWIETERMAN: Well, we certainly have authority to monitor the safety and efficacy of the product. If we think the concerns are such that they'll significantly affect those two parameters, then they need to be asked. I guess it sort of begs the question, though, and it comes back to this committee, what should we be asking these sponsors to do in this regard for the reasons that you pointed out, that the chronic therapies are here now, that we're starting to get a lot more biologics in phase III, and that there are real concerns about adequately characterizing these aspects before they're put out to a broad population.

DR. SAUSVILLE: The key issue is the "before" because I don't see the relatively limited testing that you

do with any entity, drug or biologic, that before is going to be realistic in terms of the total universe that these products eventually run into.

DR. SCHWIETERMAN: Well, many of them, you're right, will not be realistic beforehand. I think, though, that before you would simply say that most of them come afterwards, you would simply want to know the likelihood of the thing you're worried about and the effect that thing has on the overall safety and efficacy. For example, if you had a highly immunogenic protein in phase I that potentially caused anaphylactoid reactions and so forth, you might want to very carefully analyze in phase III many of the -- I mean, we do this for most of our products anyway, but I'm just giving you an obvious example where you might want to really know all about the safety and efficacy of that profile over the long term before putting it on the market.

But you're absolutely right. If there are less real concerns and there's no real reason to be concerned about an overall risk/benefit, then you could reserve those questions for phase IV, which we often do.

DR. SALOMON: I think just another thing that's coming out here is we need to talk about things in several different time frames, and as we go further along, we're basically expanding the time frame. Right? I think what

Dr. Sausville is saying, very properly, is there's a series of things that you are going to request sponsors to do before you license the drug. Then there's going to be this phase IV which is going to enrich our understanding of the drug, but shouldn't hold up its use. And then there's going to be an argument whether or not a year -- and looking at sort of follow-up versus perhaps what I'm suggesting that some of these effects may be 10 years later. And I know at this point the sponsors and the FDA are both very unhappy with me, so I'll just sort of leave it at that.

DR. SIEGEL: The simple mechanistic answer to your question, though, as I think came through, is that we do have the mechanisms, most commonly at time of approval, to request and receive commitments for long-term studies as are appropriate or even after approval. To parallel what Dr. Zoon said about once you're on an advisory committee, we've got our hooks into you for life, once you get a drug approved, you're pretty much dealing with the FDA for a long time.

(Laughter.)

DR. SALOMON: Dr. Miller?

DR. MILLER: Well, I want to comment not just on the safety but the efficacy endpoint. These drugs are, in fact, often very, very expensive. So, I think it's very

important that you make sure that you're giving a protein that is still active because the diseases many times that we are treating with these biologics are the more chronic diseases, and I think you're subjecting your patients to a long-term, number one, expense unless you make them say, what happens when you give it six months down the road. Is there biologic activity still left? I think that's a major question that we don't know about some drugs that are out there that are very expensive. So, I think that's important as well as safety.

DR. SALOMON: Abbey?

MS. MEYERS: In terms of the long-term monitoring, maybe you ought to think about utilizing something like the Clozaril registry which has turned out to be so valuable. The patients are registered and you just keep track of where they are. I was reading the other day that there's some concern that maybe Clozaril is connected with the onset of diabetes. No problem. They know where every patient is and they can just follow up with thousands of patients. So, you might think in those terms.

But the other thing, which is a naive scientific question is, is there a way to develop appropriate tests so that physicians can test people before they put them on it or maybe even before a rechallenge with

the drug to find out whether they have these neutralizing antibodies?

DR. SCHWIETERMAN: Yes. It actually is one of our questions here about assays --

DR. SALOMON: We'll get to that.

DR. SCHWIETERMAN: -- so I think we'll get to that.

DR. SALOMON: Dr. Vose?

DR. VOSE: I just want to make a small comment. I think that it is very important for us to put any of this in the context of the patient population we're treating because what's appropriate for a very end-stage CTCL patient, for example, with DAB IL -- you know -- DAB may not be appropriate in another clinical situation where the patient is going to live 60 years. So, unfortunately, you're going to have to be very specific in each situation about that sort of thing.

DR. SALOMON: Dr. Champlin.

DR. CHAMPLIN: I just wanted to return. On one of your slides, you indicated that you shouldn't be studying these drugs with premedication, and I think you listed Benadryl. For many of the antibodies, particularly that target either tumors or T-cells, it's a biologic effect of the antibody to produce fever, and Pertexamab, for example, in the first dose produces lots of symptomatic

effects that tend not to occur as frequently or as severely thereafter. So, I think once one has defined that that phenomenon occurs, then it's the standard care for many drugs we use to give premedication, and it shouldn't be something that should be --

DR. SCHWIETERMAN: The question is one of definition, though. Many sponsors want to, at the very first time of introduction of the product into humans, use a cocktail of immunosuppressive regimens to suppress whatever effect they're anticipating. If it's a dangerous enough one and they're in an indication, then that's appropriate. But I was just pointing out that very often we have very little data with which to expect those things to actually occur and would rather have some data about that. Of course, it is a fine line. The minute you have a clue that something is actually causing adverse effects and you have a reason to understand it, then it's entirely appropriate to begin suppressing those AEs.

DR. SALOMON: What I'd like to do now is turn to the three or four specific questions that the FDA would like us to address. I think we've set a good context for that.

I just wanted to add there's a brief statement regarding CBER's intent on the committee discussion, and I just wanted to read that quickly, if nothing else, just to

focus us a little bit further.

So, the sentence is: "In particular, the committee will be asked to discuss the amount and type of data that sponsors should collect during the product development, what information should be included in the package insert, and what phase IV studies might be appropriate for sponsors to conduct." So, I guess in a way it's a reminder to us that we may be very interested in some of these broad-ranging scientific issues, and I think that's what we're supposed to be interested in.

There are also some practical matters here of great importance and that is just what should a sponsor be responsible for. And we have to think again, I think as Dr. Vose reminded us, of the patients that are going to be getting this and try and give some guidelines that are practical as well.

So, the first issue that we should discuss is what has been entitled preclinical issues. Let me read this, kind of paraphrasing it. Species differences limit the value of assessment of immunogenicity in animal models. While the potential importance of these species differences must always be considered, studies of relatively well conserved molecules in non-human primate species and studies of analogues of human molecules in the homologous species can still yield important information. So, here's

the typical problem. How far can we go with animal models in terms of establishing things in the run-up toward a phase I/phase II clinical trial?

So, the question is: Please discuss the role of animal studies in the development of protein therapeutics.

Dr. Champlin.

DR. CHAMPLIN: The rare examples that we talked about of the critical protein being neutralized actually was seen with both TPO and G-CSF in animals. So, for these type of single gene critically important pathways, those can be defined sometimes in animal models, whereas clearly the general concern that the proteins are different, the immune responses are different certainly comes into play. So, certainly not seeing something in an animal doesn't mean it won't happen in man, but you can identify pathways perhaps as opposed to specific immune toxicities.

DR. AUCHINCLOSS: Good work. You answered my question, which was, is there any example in which a mouse model would actually give you enough information that you'd learn something, or an animal model in general would give you information that would be useful? In general, I would think these events were so species-specific that you'd have to be looking in your human population.

DR. SIEGEL: Well, the specific question here

would be relevant to studying murine homologues in mice or non-human primates. Most of these molecules have a high degree of commonality with most primates, sometimes 100 percent for certain factors often in the high 90s.

DR. AUCHINCLOSS: I understand, but you wouldn't want to use any mouse data or even non-human primate data to predict whether or not you were going to lose --

DR. SIEGEL: No. The way we utilize animal data would generally not be -- this question, of course, is focused on immunogenicity, although the "please discuss" doesn't say that. But the way we'd use it for any animal toxicology would rarely be to say we shouldn't do the human study or draw a conclusion, but rather to focus the concern, in some cases, to cause a more deliberate approach in terms of dosing or regimen exploration or numbers of patients exposed. You might want to expose a small number of patients and get several months of data when, if you had a higher level of concern based on animal profiles and so forth. So, that's basically what we're talking about, not using it to answer the question, but to focus on how to -- whether they should be used to focus on how we address the question --

DR. AUCHINCLOSS: Let me back up. It seems to me that in the big picture the data that you presented us,

which I think is fantastic, gives you the sense that there's an extraordinary lack of toxicity from new treatment in antigenicity of these biological products. The one that jumped out was neutralization of the endogenous molecule, and you gave us the example that that could in fact have been predicted in an animal model. So, bingo. That's something you clearly wanted to look for.

But the other big generalization is that the critical feature is the efficacy, the bioavailability of your products when you retreat because of an antibody response that may or may not be clearing the product. And I don't see how you can ever address that anywhere except in human patients.

DR. SAUSVILLE: I had a question for Dr. Champlin in this regard. So, the animal model that picked up, for example, the occurrence of the single gene adverse effect, was that one animal model? Was it more than one? The question that comes up invariably is, do we do one or do we do two? Do we do some number?

Let me preface this by saying that I actually agree with the thought that in a sense minimizing the number of animal models one uses before collecting the essential information is obviously of great importance to both sponsors and also not making a bad decision in terms of not bringing forward something that should be. But I

would be curious as to what species that was and could we, for example, only get away with preclinical studies in a most relevant species, which with these products would likely be non-human primates.

DR. CHAMPLIN: Well, first of all, knowing what the knock-out mouse phenotype does can show you what is a critical factor. But for many growth factors, the knock-out mouse has no clear phenotype but a phenotypic difference. So, neutralizing the endogenous factor wouldn't be expected to do any harm. On the other hand, those where the knock-out mouse has a major clinical adverse phenotype would raise your concerns that that would be one that would need some special examination.

Now, in terms of the examples, the Amgen group had given human G-CSF to dogs and then seen neutropenia in the dogs. I believe TPO produced it in monkeys.

DR. SIEGEL: But again, that confirms the criticality, but in the case of G-CSF, we haven't seen that in humans and so it may be that the immunogenicity due to the species differences --

DR. BROUDY: That's the exact point I would make, is that the studies did show human G-CSF given to dogs made the dogs drop their endogenous neutrophil counts three weeks into treatment, but that hasn't occurred in humans. So, in a sense it proved that it was an important

single gene, but it did not predict any adverse effect. If you think of all the people who have been treated with G-CSF for stem cell mobilization, normal volunteers with no abnormal immune system, they haven't gotten any problems with loss of G-CSF function.

DR. SALOMON: I think I'd also like to voice a little bit of caution. I don't think Dr. Champlin was specifically meaning to say that you can take a knock-out mouse and if it doesn't have an obvious phenotype, then we don't really have to worry about that particular molecule. I'm sure you weren't trying to imply that, but I wouldn't want anyone to think that.

DR. CHAMPLIN: Yes. My implication was that if there is a phenotype, then you should be more concerned about it.

DR. SALOMON: Right. But, I mean, we have recombinase deficient animals that have no T-cells and they're perfectly fine in our animal colony. But I don't think any human being would do very well without any T-cells. We can all come up with multiple examples of clotting factor deficient animals and growth factor deficient animals that don't have such gross phenotypes, but it has to do with the reality these animals are living in.

DR. BROUDY: I think the other problem is if

you give a -- the glycosylation differences may be very, very important. So, depending on what cell line you produce your species in, then it may be immunogenic in one mammalian species and not immunogenic in another mammalian species. So, I really agree. If we see a big problem in the animal studies, that would lead to more caution in humans, but these studies I think do have to be done in humans and all the data collected. The animal studies are not perfectly predictive.

DR. SALOMON: You know what? I'm sitting here listening. A couple of weeks ago we were in the same room. I was sitting there. Dr. Auchincloss was chairing, and we were at each other's throats over the idea of how could we imagine experimenting on human patients with xenotransplantation because these complicated baboon and monkey transplants models weren't giving us one-year survival. And here, we're sitting in the same room, slightly different cast, and we're going, no, you can't use non-human primate models really. Do a couple, but don't take it too seriously. You got to get it into humans.

(Laughter.)

DR. SALOMON: Abbey, I believe you specifically accused me of experimenting on humans.

(Laughter.)

DR. BROUDY: I believe I still see the scars.

(Laughter.)

DR. MILLER: Well, putting in a new heart is a little bit different than giving a drug. I think there are gradations.

(Laughter.)

DR. SIEGEL: It's more cutting out the original heart that is the problem.

DR. SALOMON: Well, if you're dying of end-stage heart disease, you might not consider it all that different, but anyway.

DR. VOSE: It clearly depends if you're a surgeon or if you're an internist.

(Laughter.)

DR. MILLER: I was impressed with Dr. Rosenberg's review, the fact that the antibody in animals really was so non-specific except for the one case with TPO where it predicted but there was also -- in most other species, it predicted the knock-out effect or the one-gene effect. But the antibody studies, if you looked through the list, almost every animal species study was positive for antibodies. So, I'm just wondering how important those studies are, if they're not going to be specific, unless you ask are they going to give you neutralizing antibodies. And the answer appears to be yes in the animal, but it doesn't predict the human.

Now, the question you're asking is an important one, but that really wasn't the object I think of these studies that they did which was looking for neutralizing antibodies.

DR. CHAMPLIN: I think you need to see what clinical effects of the antibodies would be in humans. I agree entirely that just producing antibodies in animals doesn't provide much information at all.

MS. MEYERS: Does anything besides testing in humans provide the information? Is there any other way to get that information? So, you have to give it to a human to see.

DR. CHAMPLIN: Yes.

DR. VOSE: Unfortunately, I think that a lot of the information that's coming down to, both for efficacy and for a lot of the toxicity, that animal models are not very predictive both ways, either positive or negative, and I think that's the only way that we can do it is to actually get it into patients and test it.

DR. SALOMON: So, if I try and summarize what I've heard so far from the committee -- and I do this only to make sure that I have some sort of general consensus reached to communicate to the FDA -- what we're saying here is that probably sponsors shouldn't waste significant amounts of resources in preparing animal data on this topic

prior to coming to the FDA to talk about an IND for a phase I trial.

DR. CHAMPLIN: I think particularly if you're looking at human factors being given to a non-human species, there you expect to get some immune responses. So, that has very little informative value with the exception of animals, their neutrophils completely because of neutralization of a critical factor. But antibodies in that situation is expected and shouldn't be viewed as a negative feature.

DR. SCHWIETERMAN: Yes, thank you. That's helpful.

DR. SIEGEL: I don't want to read in things that are not there, but the converse at least to what you're saying, though, is that there might be limited circumstances where there's high degree of conservation and where there's suggestion that loss of endogenous function might be important where you would gain information as to at least what loss of endogenous function might potentially look like and relevant information regarding that concern. Maybe that's an over-read.

DR. SALOMON: Well, let's get at that. Dr. Sausville?

DR. SAUSVILLE: Yes. Well, to follow on on that point, one could imagine molecules or treatment

programs that by their nature might entail this sort of thing such as, for example, a molecule that, as one expression of its action might induce a continuing immune response, raising the specter that you would be able to actually induce an autoimmune disease of one sort or another. As examples -- and again, it might not be in this committee's purview, but certainly there are vaccination strategies that seek to combine antigens with co-stimulatory molecules. There I think there might be merit to actually try and more precisely define an animal model to mirror in some respect the long-term effects of continued stimulation. And maybe that's what you're trying to get at, that you'd have to look and conceivably define worst case scenarios, as it were, for each molecule.

The contrast for that, a growth factor or something directed against a tumor antigen that is expected to act in an antitumor sense, if we're talking about cancer, there that to me is less on table for that type of molecule. There I think very limited studies would be very appropriate.

DR. SALOMON: So, I guess what concerns me -- I'm willing to drift to go on to the next topic except for the nagging concern that if the message to the FDA is that we don't have to do a lot of these preclinical animal studies, and that then gets propagated to the sponsors, and

then they come back to an expert advisory committee, and all of a sudden the expert advisory committee goes, why didn't you do this in a non-human primate.

I mean, there's nothing hard for animal modelers if Dr. Champlin's point is well taken. Okay, fine. You make the primate equivalent of thrombopoietin or GM-CSF or any of these others. The genes are easy to clone. You can synthesize these things relatively straightforwardly. If we thought that that was an important transition before going into human studies -- okay. I just want to get this on the table because if someone comes back with a study and you guys then nail them for why didn't you do this, then we've not done our job.

DR. SAUSVILLE: Yes, but there are converse examples like the mouse TNF story where basically it's different biology than what we've seen in humans. So, I think to tie inexorably a human experience to what goes on in a species would also not be, I think, a right message to send.

DR. VOSE: Yes. It also doesn't take 50 monkeys to find this out.

DR. SAUSVILLE: That's right.

DR. VOSE: You can do it in three monkeys and find out the answer.

DR. SALOMON: Well, I wasn't discussing the

number. I just want to focus us here. Are we talking about no studies in this area are necessary because you won't be able to interpret the data anyway? Because monkey studies, A, have ethical issues. I do monkey studies, and I don't want to do them if they don't have any bearing on the process that follows. Right? I mean, I do them because I think that they're contributing to safety in human patients when we move forward to a clinical trial, but if in this area our advice is it won't do it, then let's spare the monkeys. The monkeys have to be protected too.

DR. VOSE: I think actually that we should require a non-human primate model just for a small number because I think that if something is going to be predictive, that would be the model that would be predictive.

DR. BROUDY: But we're just talking about immunogenicity studies here, but they're still going to do tox studies in animals for sure.

DR. SALOMON: See what I'm listening to -- I think Dr. Champlin made a really critical point and Dr. Sausville picked up on it, and that is if you're trying to do a human study, so you're going to use human GM-CSF, and you give that to the monkeys, which is usually the way they do these tox studies, that's really not the model, is it?

The model is monkey GM-CSF made in the same yeast you're going to make the human GM-CSF. And that's an important message to the FDA and that's relevant to what the sponsors do, if that's the message the group wants to give.

DR. BROUDY: Well, I guess I'd just like to say that some hematopoietic growth factors are very highly conserved. For example, human erythropoietin works marvelously well in the mouse and the monkey and every species in between. So, you really wouldn't need to clone a monkey -- I'm sorry. A monkey EPO is what I'm talking about. You wouldn't have to clone a monkey erythropoietin to do these studies. So, it varies a lot from growth factor to growth factor.

DR. CHAMPLIN: Or you may get immune responses to the human EPO for the non-conserved amino acid sequences and that might be neutralizing, but be totally irrelevant to the human-human experience.

DR. SALOMON: And that's the funny thing here. Just specifically this immunogenicity issue, close may not be enough. You may have to have it exact.

DR. SAUSVILLE: But I do think implying that sponsors would have to clone the animal X equivalent of whatever X is and have a whole set of studies before even thinking about doing the clinical, that to me would be the wrong message. It's not supported by the available data.

Although one could conceive of various scenarios, such as the autoimmune thing that I went through, that might impel you in that direction, I think in the main that would be the wrong direction to go.

DR. SALOMON: So, let's just put a scenario out. First of all, we all recognize that each of these biologics is being targeted toward critical pathways. We're not screwing around here. Right? They are major things because if they weren't major things, they wouldn't be worth targeting. Right? I mean, you want to cure this or save that.

So, here we are going to do a study where there's not a lot of animal data here, no preclinical. We go right into a human study, and the first 10 patients all get cancer or they all die. They never get their platelet count back or whatever horrible thing I can imagine happens.

DR. SAUSVILLE: It would suggest we have a problem.

DR. SALOMON: And Abbey comes back to us and says, you guys didn't even do animal studies on this. You went right to patients.

DR. SAUSVILLE: No, no. What you'd say is we did the same animal studies that we've done for, you know, whatever dozen or other types of products, and in this

unfortunate circumstance, there was an adverse outcome. Adverse outcome doesn't mean bad decisions are made. Right? You try and avoid --

DR. CHAMPLIN: Virginia made the point that you're going to do tox studies, just sort of general tox studies in animals, and this is one of the toxicities you'd be screening for there.

I think vaccines are very different than what we're talking about here. With vaccines, the whole idea is to stimulate an immune response, and they need to be thought of separately.

But here you're talking about giving biologicals and now you have an unwanted and often unexpected immune response. So, I agree that I wouldn't force companies to do this in a monkey before doing it in humans. I know again, with the rare exceptions that we had talked about, that animal models are not predictive and the only thing that counts really is humans.

DR. MILLER: Not predictive of the immunogenicity. I think you have to be very clear that we're not saying don't do animal studies --

DR. SALOMON: No, no, no.

DR. MILLER: Okay.

DR. SALOMON: I hope I keep repeating the immunogenicity. That's what we're talking about.

DR. SIEGEL: Primate studies are frequently done as part of development and for a variety of toxicological reasons. When they're done, usually immunogenicity data is collected and looked at as appropriate. But this question really was focused on -- but they're not always done in biologics, in particular because of species barriers, but in any drug development program, because of the costs involved, the times, the other issues discussed.

So, really we are focused on to what extent should immunogenicity concerns lead to an additional push toward a requirement for primate studies, and I think we received a lot of useful feedback on that issue.

DR. SALOMON: Well, I hope everyone forgives me for being the devil's advocate on that one.

The next question is on assays. Here CBER proposes the following approach regarding immunogenicity assays.

Sponsors should test all patients in clinical studies with -- key word -- sensitive assays for total antibody and, where relevant, neutralizing antibody prior to applying for marketing authorization.

Two, immunogenicity assay data should be carefully examined for suggestion of correlation of the presence, type and amount of antibody.

When such studies suggest important effects or are inadequate to exclude important effects of concern, then additional studies should be required.

And if data indicate that antibody status of an individual patient may be clinically important regarding the use of the product, then the sponsor generally should ensure that an assay is available in the post-marketing period.

So, assay issues. It raises a lot of interesting points.

Dr. Auchincloss?

DR. AUCHINCLOSS: I thought it was a good outline of reasonable steps to take, but I thought it was overly focused on antibody responses. As I think you've demonstrated to us very nicely, there isn't a good correlation between antibody responses and either bioavailability or bioefficacy of many of these products, so that the antibody assays you would do, but they shouldn't become the absolute focus.

In particular, point 4 in your outline there, which is before you got out there, you need to have the antibody assays sort of in place and available to everybody, let me just use the example of OKT3 where we know an antibody response to the product very significantly affects the bioavailability, but clinically I use OKT3 all

the time without an antibody assay against OKT3, the assay to determine an antibody response to OKT3. I measure the effectiveness of T-cell clearing as my measure of whether I'm giving enough OKT3. So, I don't need an antibody assay. I need a way of determining bioavailability or bioefficacy.

DR. SALOMON: Yes, that's a good point.

Dr. Sausville.

DR. SAUSVILLE: I would say everybody would agree that where one has the relatively luxurious position of being able to just do a CD3 positive count, that's the ideal position to be in. Unfortunately, many of the agents that we develop don't have that type of thing.

Here I think it's unclear to me actually whether mere existence of antibodies will or will not correlate with clinical phenomena.

One thing that struck me from this morning's presentation is that many times the data is reported as titers, and I don't know what titers mean actually. I would strongly try and encourage sponsors to develop ultimately mass based assays so that you can calculate back to an actual antibody concentration that mediating something. Then I think there would be a firmer footing actually than to put with correlations in the clinical phenomenon. Because again as we discussed briefly, it

really does relate to the dose and how frequently you get above potentially a threshold of antibody that combined a certain amount of product. I don't think you have any way of telling that unless you really devise an assay that can go after those quantitative endpoints.

DR. SALOMON: Well, the problem with quantitative assays, of course, is that these are polyclonal immune responses, so quantifying the antibody in serum rather than titering it out is a big leap technically.

If we talk about assays for antibody, do we generally agree that it's not just antibody but it's actually neutralizing antibody that is important? Do we want to make a distinction about that, or if you're going to measure antibodies, measure both? Or does anybody care?

DR. MILLER: Don't you measure the binding as a screen? If the binding is negative, the neutralizing is never positive.

DR. SALOMON: Okay.

DR. MILLER: So, it's one step. I think it should be a gradation. We think these are potentially low risk. We screen a lot of patients' serum, and so you want to have the first test to be as sort of easy as possible and then focus, at least talk about number 2 here specifically. You have a screen and you see binding. 98

percent of the patients don't have any binding. So, you can just ignore the rest of those patients. But in the patients that have binding, then you have to look for patients that have neutralizing.

Then I think you should go then and repeat pharmacokinetics potentially because I think those are the patients that you really need to predict whether or not they are having the biologic effect, et cetera, et cetera. So, you have a three-step approach doing the studies and you're not doing excess tests on any one --

DR. CHAMPLIN: Although examples were pointed out where binding led to altered pharmacokinetics without neutralizing the biologic function. So, if you've got binding, then at least you need to be concerned about alterations of pharmacokinetics.

DR. SIEGEL: Yes. I think we'd agree in most cases, the ELISA or whatever total binding assay is more sensitive than neutralization assays. So, I think it's correct, we don't see neutralization where we don't see binding, and often if the company only tests for neutralization if binding is positive, that's generally considered an acceptable approach.

But I would also reconfirm that, that non-neutralizing antibodies can be clinically significant. Certainly they can give rise to immune complex disease, and

certainly they can alter pharmacokinetics and biodistribution of the product.

DR. SALOMON: I'm cognizant of the fact that Dr. Goldsby is also with us, again the miracle of the -- this gray thing is Dr. Goldsby here.

(Laughter.)

DR. SALOMON: It's actually quite attractive.

(Laughter.)

DR. SALOMON: A triangular, Star Trek looking thing.

Do you have any comments about this? I realize it must be difficult for you to contemplate jumping into this discussion.

DR. GOLDSBY: No, nothing specific. Just a general comment that this is not exactly a new area we're entering now. A great deal of experience has been built up over several years, and I think that probably ought to inform as well as temper our concerns in this area.

DR. SALOMON: Thank you.

DR. SIEGEL: Let me explain some of the phrasing of this question. I think it has become increasingly apparent to us in reviewing the database that there hasn't been consistency in the types of data that have been asked for or collected over the years, and I think the committee, in looking at this, would also know

that there are certain holes. There are certain important questions that haven't been answered.

So, this has given rise to a little bit of thought as to what is a rational process for collecting data and how much should be collected. Basically the process that's proposed here, which is what we do I think some of the time, maybe even most of the time, would be in the pre-marketing phase collect everybody's serum, test it for binding, and where appropriate for neutralization, and then use those data to look for correlations with whatever clinical data you have but not necessarily to do specific studies designed at exploring those correlations except where either there's a signal from -- you know, and to look at all of that and to be required to look at all of that -- I should go back a point -- at the time of marketing. And then where either there's a signal there that it looks like there may be something there, or there's a signal from some other reason of concerns that animal data, pharmacological data that raise a higher level of concern, only in those specific cases we might then think about ought there be additional studies, either pre- or post-marketing depending on how high the concern is, what disease is being treated and so forth. That's the general paradigm outlined here.

DR. SALOMON: Dr. Champlin?

DR. CHAMPLIN: Just reflecting that what often

happens in real life is it works the other way around where instead of prospectively looking for antibody responses, people recognize syndromes, loss of interferon effect, your blood counts aren't coming at them anymore, the T-cells aren't being suppressed. So, in looking at the clinical events with equal scrutiny from the outset may again tip off where you're losing biological efficacy for whatever reason, and so that in situations where that can be actually measured with each course of treatment, that would probably be the best screening test of all for antibody responses.

DR. SALOMON: Abbey?

MS. MEYERS: The binding test or whatever laboratory test. We're talking here about clinical trials and then the sponsor would do these tests. Let's say that throughout the test, he finds some patients have the antibodies and some don't or some have it worse than others. If the result of that is that everybody who is on the drug, who gets on the drug after it's approved, should be tested every time they're rechallenged anyway, are these the kinds of tests that can be done on Main Street General Hospital or they have to be sent away to special labs? What would the cost be to --

DR. SALOMON: Well, I think part of the answer is that any general lab can do a well-developed and

validated ELISA assay, but when you're doing a clinical trial, they're not going to have a well-developed, validated ELISA assay. So, I think you will end up with central laboratories where samples will have to be sent. You're not going to suddenly distribute hundreds of kits with recombinant antigen on them.

DR. SIEGEL: There are two or three paradigms that can be followed. This is sort of what we were addressing in the fourth bullet. I think Dr. Auchincloss pointed out some important cautions, but there have been cases where it is clinically important enough that we think a test needs to be available. Then we might ask or even require the sponsor to make that test available.

It can be done in a number of different ways. There are sometimes where you can make a commercial kit that measures, say, human anti-murine antibody. You could have it as a service offered by laboratories, or it could be a service offered by the manufacturer of the drug product themselves. So, there are different ways that can be achieved.

I can't speak to what the costs involved might be.

MS. MEYERS: Well, if this happens down the road -- and I'm sure maybe five years from now you might be retired. Somewhere there should be a registry that under

managed care you can send your blood off to the laboratory that you want to or your doctor wants. You have to send it to the one that contracts with your managed care company, and that could cause a problem. So, I ask you to remain sensitive to that so that if people need a repeated blood test, it does not run into the reimbursement problems that we're experiencing now.

DR. SALOMON: So, again trying to get the drift of where this is going, I think Dr. Miller put it well in that perhaps we're all sort of thinking it should be staged. You first screen for antibodies at all. If you can't find an antibody with a reasonably sensitive test, you're probably done right there. We made the point that antibodies isn't everything, but at least from the point of view of this assay aspect.

Then if the antibody is present, do we all agree that we should look for neutralizing antibodies? And then if the neutralizing antibodies are present or if antibodies are present, we ought to look at the pharmacokinetics of the molecule in question and compare that with some quantitative measure of the antibodies, whether it's titer or a molecular definition of it. So, in other words, asking questions that high titer patients or high responders might have a different pharmacokinetic than intermediate or negative responders.

DR. SAUSVILLE: But there are kinetics as well as dynamics because kinetics, in the absence of some dynamic quality, would be important.

DR. SALOMON: Right. So, I guess I was going to say that the fourth level would be to have some sort of biological parameter that would then, of course, be unique to the product and the patient population. So, that we can't really define. We'll do that I guess when someone puts something specific in front of us.

I think that gets to something. Dr. Auchincloss made the point. I share his experience using OKT3 and more recently the anti-IL-2 receptor antibodies in transplant patients. Again, we don't typically measure the antibodies. We look at bioassays.

DR. CHAMPLIN: One has to distinguish the clinical trial phase pre-approval and then long-term practice where in practice you're not going to do all these things. During the clinical trial phase, you need to define the biology and what's going on. Once those principles are established, then you can find some cost effective strategy to treating the patients and still gathering the same information.

DR. SALOMON: Dr. Stein.

DR. STEIN: I just wanted to comment that in many instances with monoclonals, because they are product-

specific assays, that even in instances where there has been relatively few immune responses, we've asked companies at post-marketing that they make that assay available if a physician feels a patient has a reaction that they would like to know might be associated with an antibody response, that they have a place where they can send the serum to be tested. This wouldn't be an assay for which they would charge necessarily. It would just be a service. This would be for products where it wasn't necessarily critical that this be measured in all patients, but just a service to be available if a physician would like to know whether an antibody response occurred.

DR. SALOMON: Dr. Vose.

DR. VOSE: Just a quick comment. I think it's important again for us to keep in mind that these antibody responses need to be clinically relevant. I've seen some examples of companies who use this information I think maybe improperly where they say, well, our antibody only has a 2.7 percent HAMA. Yours has 2.8 or something like that. I think that that's clearly not appropriate and it needs to be something that is clinically relevant for us to be concerned about it. We shouldn't let the companies use that kind of information improperly.

DR. SALOMON: Yes. I think Dr. Auchincloss had made that point, and I agreed with that. That came up in

our pre-discussions about sort of things that we should get on.

So, let's go back to that specifically. If we agree that there should be an assay, to what extent should we grapple with the idea of standardizing the assay? Should there be standards for these assays? I know Dr. O'Fallon had made several times now the comment of specificity and sensitivity. So, to finish up this assay question, can we get some comments from the group on that?

How many different ways are there to do an antibody assay?

DR. SIEGEL: There are not only an unlimited number of different ways to do it, but for every one of them, you can choose your cut-point of positivity along what is usually a continuum so as to modify the sensitivity and specificity to your liking.

Unfortunately, these claims -- and this really is at the heart of question number 4 -- have induced some sponsors, we believe, to intentionally choose insensitive assays so they can then promote low rates.

DR. SALOMON: Right, but the question we're dealing with now, Jay -- we don't want to go on to question 4 yet -- is, is there anything that the committee can say constructively to the FDA regarding what we think should be done in terms of dealing with this sensitivity/specificity

issue up front?

So, I see a bipolar response here. One would be no. We can't tell you anything you could screw around with the assays in any way of a million ways and it's just impossible to standardize anything. So, we'll just have to take it on a one-on-one basis and insist on some sort of validation of sensitivity on that particular study, go on to the next one. Or that there's some way of standardizing this, some sort of molecular standardization that we could use or insist on.

DR. SAUSVILLE: Most of the time there is some sense of what concentration of biologically active substance is actually acting at a receptor or whatnot. I think as a minimum -- and I'd toss this out and get people's reaction -- putting it on the sponsor's shoulders to show why they can't develop an assay, that it would at least detect the drug acting as it's intended to. If they can't, well, then that's interesting, and that becomes then a set of biological realities. But most of the time you probably can. Then that then becomes by definition a bar that sensitivity is going to be addressed for each agent and becomes one way of comparing across agents. I toss that out.

DR. O'FALLON: If we were looking at the results of a randomized controlled clinical trial, we'd

demand that they'd quote us at least a p value and very possibly a statement of the power of the test that was designed. Yet, throughout the entire day, I've not heard a single number quoted as to the sensitivity of any of the assays that we've discussed or the specificity. I think at the very least we need them to document what those specific sensitivities and specificities are for those different assays.

DR. SIEGEL: Yes. The reality, of course, in most of these cases is there's no gold standard. There's no one who can say this specimen truly does have antibody to the product and that one doesn't. So, it's sometimes difficult to say which are the true positives and which are the false positives and what is the true sensitivity and specificity.

DR. O'FALLON: Precisely my point and some of the points I've made. You're talking an awful lot like everything that come out of these tests is the gospel, and yet it could be dramatically different from that.

DR. SAUSVILLE: I would simply respond by saying, ah, but one can say that you have an assay that would detect an antibody that would interfere with this substance acting in its biologically active concentration. So, that frames it more in terms of interfering with what you think the intended function of the biological is.

DR. SIEGEL: There's probably a lot more role -- and I think Dr. Zoon alluded to this -- to standardization and even quantitatization of neutralizing assays because for neutralizing assays, you're looking usually at an active molecule and a cell line that's responding to it, and then you're looking for the ability of serum to inhibit that. You can standardize what the molecule is, what the cell line is, a lot of the parameters, and that could be very useful.

For these ELISAs to detect binding antibodies or IRMAs, or whatever they are, the questions of standardization might be tougher. But that's a point well taken.

DR. BROUDY: But you can also know the standard curve. Every assay has to have a standard curve, and so you know the lower limit of detection on the standard curve. So, maybe that should be included, the standard curve and what the lower limit of detection is.

DR. SIEGEL: The lower limit of detection. You're suggesting again in terms of like mass units of antibodies.

DR. BROUDY: Right. Nanograms per ml or micrograms per ml or whatever because every assay has got a standard curve.

DR. MILLER: I just want to go back. I think

Dr. Schaible this morning showed us that these things actually can be done. You can quantitate an antibody, and then you can do a study to show that it is not clinically significant, which I think is what we really show. I think that should be done actually, as much as you can, before the drug goes to market, if there are neutralizing antibodies shown, that you need to know what the clinical consequences of those are before you put it to market because I think that's the best chance of finding out really the data. In a pre-marketing versus a phase IV study, you have a much better control over what you do. So, I would say that that should be considered maybe a minimum if you find something.

DR. CHAMPLIN: Yes. Well, again, it has to occur in some sizeable fraction of the patients to be relevant. If it happens less than 1 percent of the time --

DR. MILLER: Right, but if you see something more than 5 percent -- I mean, there's something, some cutoff.

DR. SALOMON: Dr. Stein?

DR. STEIN: I'd just like to ask Dr. Broudy. Frequently the standard curve is developed with an animal antibody. We have a human product or humanized antibody or some other product that goes into a rabbit and you develop a standard with a rabbit antibody. Does that bother you if

you see that the lower limit of detection if 10 nanograms per ml of rabbit antibody? That is frequently the way these are developed.

Unless you have a patient that had an adverse reaction, you went back and looked, and found they had a high titer serum, and you could use that antibody for the standard. But frequently that's a limited amount and not one that would be available again. So, it couldn't be used for a standardized assay over a long period of time.

There may also be monoclonal antibodies as well, and they have a limitation that they would only detect a single epitope unless you made a large cocktail to try to approximate a polyclonal.

So, I guess the question I have is would you be concerned if it were an animal antibody that were given as a specification.

DR. BROUDY: Well, I think those are concerns and I think we can't really get into that right here. But you'd have to look at the specific ELISA tests that were designed for each reagent and how it was set up and think about what curve they're using to call something a positive or a negative. And I think those are concerns.

DR. SALOMON: Kathy?

DR. ZOON: Just from some experience over the past 25 years with interferon, to kind of frame where we

evolved in the interferon field, because we have probably the most knowledge, and whether or not that's relevant to the broader cross section of therapeutics may be applicable in some cases and may not be applicable in others.

Over the years, it was recognized that having a standard assay for neutralization was very important for interferon. In fact, a great deal of effort was put into it by a Dr. Kuwadi, who's currently in Japan, to develop a standardized assay that everybody would adopt as an assay for determination of neutralization by interferon alpha and can be used for some of the other interferons. In general, that was picked up by most investigators and most clinical investigators.

It also became aware of the need to have a standard human antibody preparation. In fact, one was made and was actually viled and is used as a reference reagent by WHO.

Maybe one of the questions, as these products evolved, is it important that either WHO or FDA or somebody encourage the use of more standardized assays where appropriate and encourage the development of some of these reagents as a way to promote some standardization, recognizing that it may not be relevant in a lot of areas. The question maybe might be worthwhile discussing if the committee feels that would be relevant in some cases and

should that be supported and promoted to the level that is feasible.

DR. SALOMON: My comment would be from the way I see the committee going, I think some of this has already been discussed. I think what the committee is saying, again looking for consensus -- correct me if I'm not stating this properly -- is that just finding antibodies, even just finding neutralizing antibodies are not necessarily relevant. However, they could be. Where the committee's attention would become focused is when there's demonstration of a pharmacodynamic or a biological effect that then becomes relevant. Then the big question would turn back on is the antibody predictive of that. I think that that has been said a couple different times. If that were true, then I think the energy to develop standardized tests would be immediately appropriate. However, to use resources to develop those kinds of standardized tests in the absence of any correlative I think would be an unnecessary burden.

DR. CHAMPLIN: Yes. Interferons are so widely used now for such a broad range of diseases, but there's a need for that type of thing. But the assays for antibodies to the anti-CD40 ligand, who knows? It's a smaller spectrum of studies going on. So, when you really need the information is the very early point in development where

you don't have the standards. So, it's a catch 22.

DR. SALOMON: I guess the other thing I wanted to make sure the committee agreed -- I think that I'm hearing from everyone -- is that in the process of a sponsor coming forward to initiate the first clinical trials, probably a tremendous amount of results pre-clinically is not going to be relevant, and that a lot of this then should be the focus of the clinical trial period to establish these different elements. So, a lot of the assay design issues will be fluid during the run-up from phase I to the pivotal phase III trials.

DR. CHAMPLIN: And my guess is that in only a small fraction of the products coming forward is this going to be highly relevant. Most of the things that you showed have a low level of antibodies being produced and they're not often of biologic importance. So, to put a lot of emphasis on it before you know it's even a problem seems misguided.

DR. SIEGEL: That may be the case, but more and more of the products are moving from relatively acute settings into more chronic use.

DR. CHAMPLIN: Not to say that it shouldn't be looked at at all, but I wouldn't sort of make it a deal breaker for the pilot study.

DR. SAUSVILLE: And here is where collecting

the samples, having planned ahead of time to be able to go back and make some sense out of all this once you've got the clinical data put together, I think is going to be very important.

DR. SIEGEL: What I think I'm hearing is -- but let me clarify to make sure it's what I'm hearing -- in terms of the concerns about the clinical significance, as several of the speakers have noted, I think is something not far from or perhaps quite similar to what we're proposing. So, let me just go over that and bounce that off you again and see if, in fact, I'm sensing the committee right.

DR. AUCHINCLOSS: I was just going to jump in there because I was just going to make that point. I think what we've said is what you've written down here.

DR. SIEGEL: That's what I was thinking. What we've written in the second bullet is that if you're collecting the specimens from the start, that by the time of marketing, if you have a sensitive assay so you can pick up low titers, high titers, whatever, and neutralizing and non-neutralizing, that those data should be explored for suggestion of correlation between those findings and PK, PD, efficacy, or safety.

Now, of course, if half of the patients have antibodies and half don't, you're going to have some amount

of power such as another assay we always do, which is looking at effects in men and women. It's not likely to be sensitive to every significant effect, but it will be sensitive to large effects. If you have only two patients who developed antibodies, you're going to be guessing what to make of it. But on the other hand, what it means may be less important if only two people have identified it.

So, the approach would be to routinely do that, collect the data, routinely analyze the data for correlations, and then make a determination if those studies suggest either that an important effect may exist or inadequate to exclude an important effect where there's a particular concern for any of a number of reasons. That's when additional studies should be considered.

You're saying that is, in fact, your sense too of what the committee is saying.

DR. AUCHINCLOSS: I thought what you wrote down here was excellent. The only point was a minor one. In number 4, you got hung up on an antibody assay --

DR. SIEGEL: We don't always need an antibody assay if there's a clear clinical sign that can be used. Yes.

DR. AUCHINCLOSS: (Inaudible.)

DR. SIEGEL: Yes. Point well taken.

DR. AUCHINCLOSS: But I really do think that

what you wrote down is sensible and reflects what the committee has been saying.

DR. SIEGEL: It sounds like that reflects what I've been hearing.

DR. SALOMON: What I'd like to do -- there are a couple of people that are going to have to leave at 4:00, and I'd like to then take a small chairman's prerogative to jump over question 3 to question 4, the product labeling and promotion issues just because -- I may be wrong, but I'm guessing that might be a little more contentious than question 3.

I guess I'm being informed Dr. Goldsby is leaving already. Thank you.

So, question 4 is on product labeling and promotion issues, and again, everyone has it in front of them, so I don't see a point in reading it.

But it raises a whole number of different questions about what we feel is appropriate and not appropriate for sponsors to claim based on these data, albeit we've identified a lot of unknowns in the product, and if so, what kind of guidelines can we give the FDA on this?

Dr. Auchincloss?

DR. AUCHINCLOSS: You have completely changed my mind. I came down here, after reading this, saying, oh,

come on, just let the sponsors say whatever is true.

(Laughter.)

DR. AUCHINCLOSS: I must say, along with Julie, I've really changed my mind. The statement that my product has less of a HAMA response than your product is truly a meaningless response is what I think I've learned today and therefore should not be included in the promotional --

DR. VOSE: That's not exactly what I said. I said that they need to prove that it is meaningful for them to say that.

DR. AUCHINCLOSS: Fair enough.

DR. VOSE: And it might be, but most of the time it probably isn't.

DR. SALOMON: So, Jay gave us the guidance that the question for the committee is not to put immunogenicity data in the product labeling. It is going to be in the product labeling.

DR. SIEGEL: Well, wait a second.

DR. SALOMON: I thought you said that.

DR. SIEGEL: Somebody, I think Bill, may have said that.

DR. SALOMON: I thought you said it's required. I wrote it down.

DR. SIEGEL: Bill may have said that.

I think what will be on the product labeling is

anything we know about clinical correlates of immunogenicity. If we know that there's loss of efficacy or safety concerns, that will surely be in the labeling. But what we're left with is a long history of putting a lot of numbers, percentage numbers, in labeling whose ability to inform is uncertain and whose ability to misinform has in cases been demonstrated.

DR. SALOMON: Right. Yes. No, I agree with that.

So, the question is if we're going to discuss immunogenicity, what kind of guidelines are we going to make for discussions of immunogenicity. And I don't think we're really disagreeing.

So, again, we get back to should there be a disclaimer in the product insert in bold, much like we have on a pack of cigarettes --

(Laughter.)

DR. SALOMON: -- that says based on the current technology of these kind of assays, we cannot make any prediction on the relative immunogenicity of our product versus any other product in its class.

DR. MILLER: I don't think you should go that far. If you have a 90 percent immunogenicity, people need to know that. I think you can say mild, moderate, severe. You can put criteria on that so you can't compare. But I

think that if everybody is going to get an immune response to it, I think people need to know that.

DR. VOSE: But I think they also need to know if it does or does not make any difference to the patient.

DR. SAUSVILLE: Right. I mean, that's the issue.

DR. MILLER: Right. But I think saying that you're going to require that they have it, I mean, yes, if it has a difference, a clinical -- I think that we need to know that before you go to marketing whether or not it does have clinical correlation.

DR. VOSE: Right.

DR. SIEGEL: If it doesn't, are you still saying, though, the numbers belong in the labeling?

DR. MILLER: That's true. If it doesn't, it shouldn't be. I changed my mind.

DR. VOSE: I don't think unless it has a clinical correlate that people need to be putting those numbers on the label because what happens is it gets out in the community where physicians don't understand what those numbers mean and then drug representative X comes and says, oh --

DR. SALOMON: Look right here.

DR. VOSE: Yes. It's right here on the label.

DR. SAUSVILLE: It's immune. It's scary,

anaphylactoid, et cetera, et cetera.

Besides that, it then gets into this whole quagmire of how hard do you look basically. If you have an assay that tests one level of sensitivity and another assay that -- if we're going to start allowing claims to be made A versus B, it gets into this issue of how comparable these things were.

So, I actually like the idea --

DR. CHAMPLIN: I think this may be a unanimous thought here because I don't see anyone objecting.

DR. SALOMON: So, we're going to do the cigarette labeling approach? We make no claims.

DR. SAUSVILLE: Maybe in slightly less bold letters.

(Laughter.)

DR. SIEGEL: I think what I'm hearing is not to put a disclaimer but even to suggest that we may not need to put rates in at all if there has been some reasonable looking for clinical correlates and not finding any.

DR. SIEGEL: Well, I think seriously what I was trying to articulate is I think that what we're saying is if there is a clear immunogenicity, then it has to be specifically spelled out in the product. However, if at the time at which the drug is approved, the data is such that at the final data cut that experts do not agree that

this is significant, then we should not allow this kind of data to be there that then can be abused in marketing.

DR. MILLER: I'll go back to why I'm harping on this. I'm very concerned from a clinical standpoint about the precedent, a drug being approved and out there on the market with a known 90 percent neutralizing antibody at 3 months and the clinicians being left to decide whether or not that means anything, which is what state we are in now with a drug. So, in that case I think that that information needs to be there.

Now, if we know that based on this we're going to say that you have to know the answer, then I think you cannot have the information in there. In that setting, I think you need have it.

DR. CHAMPLIN: I think we all agree if there is clinical immunogenicity, where the immune response alters the response to the drug, that has to be in the label, and it has to be in the label if it occurs in most people or rarely.

So, I like the sort of the semi-quantitative terms which then prevent comparison of 23 and 24 percent by drug reps and still imparts meaningful information.

DR. SALOMON: Of course, we'd have to set numerical limits to define mild, moderate, and severe, which then of course could be repeated by drug reps. These

are like the 1 plus 2 plus 3 plus things we have all done in certain times in the dark areas of our careers.

(Laughter.)

DR. SAUSVILLE: Then maybe the fall-back position is to say something to the effect, here's the immunogenicity data. This has not been compared head to head with any other particular item, and that, therefore, to claim that item X is better than item Y based on this type of test hasn't been scientifically established.

DR. SALOMON: That's the disclaimer approach. Put the data there and then put the disclaimer.

I actually don't mind the mild, moderate, severe. I think the point is well taken.

DR. CHAMPLIN: I don't think anybody the disclaimers.

DR. VOSE: Yes. Nobody is going to read the disclaimer. They're just going to say, oh, 24 percent.

DR. SIEGEL: Well, actually if we put a disclaimer in that about -- well, there are two types that we might be thinking of here, one that the clinical implications are unknown, but a disclaimer about that these data should not be used for comparisons actually sends a message other than to physicians because it sends a message to sponsors that is up front in case they haven't heard it elsewhere or could claim not to have heard it, that any

claims they might make have been determined by the agency not to be appropriate claims. So, there is a role.

In fact, as you all know as practicing clinicians, label reading is not perhaps one of your major endeavors. But we're trying to fix that actually by making much more informative and better labels, and I hope we'll succeed. But labels are also used by lawyers, by promotional people, by patients, but there's a lot of consumers --

DR. SALOMON: But I think I would say many of us actually, the first time we use a drug that's as serious as some of these, would read the label. I don't think I would want to be tested on it later, but --

DR. SIEGEL: And importantly, what's in the label forms the basis -- that was the point I was making -- of what is or isn't considered acceptable promotional information.

DR. SALOMON: An issue that came up in our discussions was how does the process chosen to produce these proteins actually influence the immunogenicity. That has come up a couple times in our discussions.

DR. SIEGEL: Before we leave this topic, let me just make sure I understand. It sounds like there's support in this committee that the notion of just giving numerical rates that do not have clinical implications and

could be misused, the committee recognizes problems with that and supports it sounds like either of two approaches which might be either not to include those rates or to use a semi-quantitative approach with rates with perhaps some, if not disclaimer, information about what implications of those rates are or are not appropriate.

Is that a fair recapture, that you might see -- Dr. Miller, for example, in the case you might feel that it would be useful to say most patients developed antibodies. However, with the limited data available, no impact could be discerned on safety or efficacy or PK.

DR. MILLER: Right.

DR. SALOMON: I think that's important in that we can't exclude the possibility that at the time a drug gets approved, there might be 60 percent of the patients developing an antibody response even with a significant neutralizing antibody response. But still there's no evidence of a biological effect, and we therefore downplay it in the original product labeling, but we at least put it there. Then maybe three or four years later, talking about the doomsday scenarios that we were kicking around earlier on, all of a sudden there's a 20 percent incidence of some horrible event that took four or five years to emerge. At least it's in the package insert. Right? We can't always know all the downstream implications of what we're talking

about.

I wanted to get at the process thing a minute because it does relate in some way to the product labeling. It also goes beyond the questions here. So, before people left, I wanted to bring it up.

One of the things that concerns me is that we talked about identifying that there's an antibody response and how we would identify it and then how we'd even label it and advertise it. But what we haven't really talked a lot about is what energy should be put on determining what that antibody response is against.

So, if I make a product that I get an antibody response and we follow it down, if it's against an aggregate, shouldn't we identify it against an aggregate and then put pressure on the sponsor to develop an aggregate-free product? In other words, where do we stop being passive about insisting on assays and get more active in terms of saying what is the element of this? Maybe it shouldn't be given subQ. It should only be given IV. Maybe it should be given with corticosteroids, et cetera.

DR. SAUSVILLE: There we discussed the stepwise approach that Carole outlined, reverse binding and then neutralizing, then PK, then PD. I mean, it would seem the logical progression of that is that --

DR. SALOMON: Is next find out what it's --

DR. SAUSVILLE: Yes, because it's important enough to change the biological properties.

DR. CHAMPLIN: Although the aggregates usually are -- it's not just like it's binding -- the aggregate may stimulate the immune response but it will bind the soluble factor.

DR. SALOMON: Right. But then you would be -- perhaps if you could demonstrate that it was -- well, that is actually a fair point. It's easy to say. It might not be so easy to prove.

Certainly non-natural forms, denatured, disulfide bridge, broken forms that might expose cryptic antigens, those would be very relevant. The aggregate question is relevant but more difficult. That's a good point.

So, I don't know. Not acting as the Chair now, my own personal thing would be that we ought to keep that in mind, that if an antibody response is discovered, even if it's not so clear it's biologically relevant in my opinion -- just because I'm a little concerned about the time frame in which we're going to define biological relevance in a field as complicated as biologics -- but if we find an antibody response, that there should be a phase in this phased-in process that we identify what it is against and consider ways to minimize it.

Well, we can return from product labeling and promotion to this last question, and that is study of repeat or intermittent usage. I think to summarize that, the concern that the FDA had in our initial conversations was that a lot of these drugs could be brought to market with the idea that they'd be used once, and yet, once it's marketed, people will essentially start using it multiple times. So, how big a concern is that in the context of immunogenicity, and to what extent should that be considered in the plans the sponsors provide, phase II, phase III versus phase IV?

DR. SIEGEL: Let me just add as a background to that the agency -- those of you who have read the newspapers in the last year are aware that the agency has focused a fair bit -- Dr. Zoon could expound on this -- on the fact that a number of notable toxicities have come to light in the post-marketing period. Where possible, it would be desirable -- it's not always possible in a feasible manner, but where possible, it would be best to identify them prior to marketing.

In sum, I think the data you heard regarding Remicade, for example, about reuse was a case where the immune complex disease on reuse came to light essentially within the first few weeks after licensure of the product. This licensed product was used in people who had also

received it in clinical trials.

With that and as was pointed out with, say, imaging agents for cancer, which we know sometimes behave differently on reuse because of the development of HAMA, there's a reasonable guess that you could license them for single use, but that some people are going to want to use them a second time. And the question is should we be more routinely getting those data pre-marketing.

DR. CHAMPLIN: It's hard to think of too many things that you'd only do once. In a transplant, modifying a transplant maybe. But most things, imaging agents, anti-inflammatory drugs, almost anything you would at least have the potential to reuse, so that that should be explored in the initial studies.

DR. VOSE: I agree. I think once they've gotten to the phase II portion, they know what dose, and they're going to go on to do treatment, that they should have at least some retreatment information. Again, we need to know if it's clinically relevant, though, as far as that's concerned.

DR. SALOMON: Abbey.

MS. MEYERS: One of the problems is more and more we're seeing with the new biotech products, the manufacturers really don't make an awful lot and have it on hand and there's usually a shortage. Even if they give it

away under a treatment IND, they have a very limited amount. They only allow a certain number of patients to go through. So, I can't see, unless you tell them up front that you want some people to be rechallenged, because the people who went through phase II are dropped when they start phase III. That's it. Nobody else can get it.

DR. SIEGEL: Yes. This I guess will be an issue that we would take up at early developmental meetings with sponsors so that they could plan it into their plan in terms of drug supply. I think that's a point well taken because with the biologics in particular, as you well know, there's often an upscaling necessary to market. In that period between the small scale production for clinical trials and the upscaling, there are these shortages.

MS. MEYERS: And they don't want to invest in that until they get some sense from you whether the drug looks good or not.

DR. MILLER: I'm actually going to take the opposite. I think there are some situations where you're not going to be able to do that. I don't think to require it in all situations is -- I mean, like the one that is for the acute chest pain syndrome. You can't very well require people to be retreated because generally people get treated, they get PTCA. Until you get huge numbers, I think that it should be recommended you can get the data,

but I think that in some cases, especially if you have an agent that works, you may not need to retreat them for a year, two years. So, it may be difficult.

I think that if patients are getting, in the clinical trial, repeated doses, that you make it imperative that you don't only test the first dose pharmacokinetics, you test the fourth dose immunogenicity and pharmacokinetics as well. So, from that standpoint. But in all situations, I don't think you can reasonably expect them to say, okay, we're going to wait around till somebody relapses, has a second episode of chest pains so we can give them the drug again.

DR. VOSE: But I think if the sponsors know this that that's part of the overall plan and then they have a protocol that's already open and available, at least they'll get some patients that they can do that on and have a little bit of information. I don't think you have to have a huge trial at the time that you're considering that.

That even, for example, has been done in some of the lymphoma antibodies, that they had a retreatment trial that was open like two months after the treatment trial was opened, and it has actually worked pretty well.

DR. SCHWIETERMAN: It's more common to have open label extension studies following, say, a phase I or phase II for both safety and for even long-term efficacy in

some cases. So, we could easily include these sorts of things, measuring patients who went off the drug or had serial doses, whatever, or just measuring at the fourth cycle what the antibody levels were.

DR. SIEGEL: I think that we see the spectrum in terms of pragmatics. There are certain things like flares of multiple sclerosis or arthritis or Crohn's disease or whatever which occur reasonably regularly where you could collect some amount of data. Imaging of tumors where you could certainly image before and after therapy and people are interested in doing that where one could expect to be able to collect those data. I think waiting around to follow people for them to have an MI might be a more difficult situation. We'll tone that with some concern about the pragmatic.

Rejection episodes or organs is something where usually if you follow over the course of two or three years of development at least, you're going to get a second episode in a lot of people.

DR. SALOMON: Dr. Auchincloss?

DR. AUCHINCLOSS: Well, actually I think everything I was going to say has really been said. So, let me just go one step further, and that is, in your question you say you want us to discuss the nature, extent, timing, and role of these studies, which I don't know if

we've done that. Do you have something sort of in particular in mind? Because I do think in general, yes, studies of reuse should be part of percertification.

DR. SIEGEL: Well, no. That was just to open up broadly for you to provide input where you'd like.

There is one other aspect of this question which hasn't been touched on, though, which is there's one question which was raised in the presentation. There's this question of one-time use and then repeated one-time use. But there are also those drugs that are used chronically and the concern that although they'll then be studied chronically -- and we have guidelines and policies regarding how many patients for how long should be studied in different settings. One thing that happens, once they're out of the clinical trial setting, is rather than chronic continuous use, a patient may be on it for several months and then be off for a period of time and then be restarted.

DR. AUCHINCLOSS: I think intermittent use is a very important issue to cover, and you made that clear there. But that probably does happen in most clinical trials also. Again, if you've set up your protocol to look for those events and capture them when they occur, you probably see them, don't you?

DR. SIEGEL: Well, we've seen some drug

development programs which wouldn't have captured that information, in fact, failed to. But I think it can be if one plans to.

DR. SALOMON: Well, I think we'd all agree then, again trying to reach a consensus here, that there's no doubt with any immunogenicity experiment, whether it be in an animal or a human, that repeated dosing and the avenue of dosing are critical, but that repeated dosing, regardless, is a high risk factor for getting amplified primed responses. Right?

And certainly the clinical effects of a primed immune response can be profoundly different than that of the primary immune response, which is something that hasn't come up yet. But it's also true. Right? Usually much different, more specific, higher avidity antibodies frequently.

Anyway, so the bottom line is I think that we just need to make sure that a trial in which the intention is obviously to treat repeatedly, that that be from the beginning incorporated in the trial design.

DR. AUCHINCLOSS: I just wanted to ask the FDA for a little clarification. In a sense this is a little unusual. Right? Because you're basically asking the sponsor to come up with information that goes beyond their request for labeling.

DR. SIEGEL: Well, exactly. That's why it's not quite the no-brainer that Dr. Salomon --

DR. AUCHINCLOSS: No. I don't think it's a no-brainer at all.

DR. SIEGEL: Because in fact --

DR. SALOMON: I wasn't characterizing it as a no-brainer. I just thought this was appropriate policymaking.

DR. SIEGEL: Nobody would deny that repeat use could heighten those issues, but one potential response to that is, well, we'll just put it in a caution, don't use repeatedly. This is for one-time use only.

DR. SALOMON: No, but to me that's disingenuous. You're not going to tell someone with Crohn's disease that had a beautiful response to your reagent that, well, I'm sorry, we can't treat you again. I think that to me is a no-brainer.

DR. AUCHINCLOSS: I wanted to clarify that because I think the assumption with which I approached this is that reuse and intermittent use is such a given with all of these products that you have to assume that's it --

DR. SIEGEL: We should be collecting the data.

DR. SALOMON: Yes, and I agree with Dr. Auchincloss on that.

Are there any other comments on this?

(No response.)

DR. SALOMON: Then I think I'd like to thank everyone on the committee. I hope that we've addressed each of the questions.

DR. SCHWIETERMAN: Yes. We very much appreciate the input. Thank you very much.

DR. SALOMON: At this point, we are complete with the open committee portion of today, and at this point we'll take a 10-minute break and come back to the closed committee discussion, the update of the research programs and a site visit report.

Again, I thank also the audience for their attention today as well.

(Whereupon, at 4:08 p.m., the committee was recessed, to reconvene in closed session, this same day.)