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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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OFFICE OF PHARMACEUTICAL SCIENCE

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SCIENTIFIC CONSIDERATIONS RELATED TO DEVELOPING FOLLOW-ON PROTEIN PRODUCTS

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PUBLIC WORKSHOP

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WEDNESDAY,
SEPTEMBER 15, 2004

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The workshop was held at 8:00 a.m. in the Germantown Room of Building II, University of Maryland's Shady Grove Conference Center, 9360 Gudelsky Drive, Rockville, Maryland, Dr. Ajaz Hussain, Deputy Director, Office of Pharmaceutical Science, moderating.

SPEAKERS:

DON BAKER, Ph.D.
HAL BARRON, M.D., FACC
FREDERIC G. BADER, Ph.D.
MURRAY P. DUCHARME, PharmD
THERESA L. GERRARD, Ph.D.
DAVID GREEN, Ph.D.
JAMES D. GREEN, Ph.D.
JOHN GREENWOOD
JOHANNA GRIFFIN, Ph.D.
KENNETH B. SEAMON, Ph.D.

FDA REPRESENTATIVES:

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STEVEN KOZLOWSKI, M.D.
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MERCEDES SERABIAN, M.S., DABT
MARJORIE SHAPIRO, Ph.D.
ELIZABETH SHORES, Ph.D.
MARC WALTON, M.D.
ALEXANDRA WOROBEC, M.D.

C O N T E N T S

P-R-O-C-E-E-D-I-N-G-S

8:01 a.m.

DR. HUSSAIN: Well, it is eight o'clock. And I think we should get started.

The Panel #4, addressing immunogenicity issues, is already seated.

And just a quick reminder, cell phones are off. And if the cell phone rings, I think somebody who is the neighborhood should turn and give an FDA inspector look to the person. If you don't know what the FDA inspector look is, maybe an FDA reviewer look.

I think the two most important topics that remain now are immunogenicity and preclinical and clinical issues.

We have some flexibility in time and yesterday Keith mentioned that we would like to use this to give you an opportunity to speak. I don't know how the logistics will work but let me suggest that for that half an hour or so you have an opportunity to make some general remarks.

I'll request the general panel that we had put together in Day 1 come back here for that purpose and maybe they can ask questions of speakers who may be there present because I'm not sure all of the

speakers will remain. But that will be an opportunity for you to make some remarks, general remarks.

With that, I'll ask Amy to introduce the panel and get started.

DR. ROSENBERG: Good morning, all. I would like to start by introducing the panel.

I'm Amy Rosenberg, Director of the Division of Therapeutic Proteins in Office of Biotech Products in CDER.

DR. SHAPIRO: Marjorie Shapiro in the Division of Monoclonal Antibodies.

DR. HIXON: Dena Hixon, Associate Director for Medical Affairs in the Office of Generic Drugs, CDER.

DR. WOROBEC: Alexandra Worobec. I'm in the Division of Therapeutic, Biologic, and Oncologic Proteins.

DR. SHORES: And I'm Elizabeth Shores but in this intimate setting here, please call me Wendy. And I'm Chief of the Laboratory of Immunology in the Division of Therapeutic Proteins.

DR. ROSENBERG: Okay. So the questions that were posed prior to the meeting are on the screen. How and to what extent should immunogenicity

be evaluated for a follow-on protein product? And number two, under what circumstances should comparative immunogenicity studies be conducted?

I think we already heard a lot of lively debate yesterday with two prevalent opinions out there. One was that there is nothing in biophysical or biochemical characterization or analytical techniques that would predict the immunogenicity of the therapeutic protein product.

And the second opinion was that one could use biophysical and biochemical characterization and analytic techniques to assure that the immunogenicity of the follow-on would be similar to that of the innovator product. So a slightly different twist on that.

In none of the presentations were any data presented that actually addressed the latter hypothesis. And being a science-driven agency, we certainly would love to see data.

So with that, with those preparatory remarks, why don't we get started. We have four speakers. Each speaker will be able to speak for ten minutes. And then followed by five minutes of questioning.

So we begin with Johanna Griffin, President of Procognia, Inc.

DR. HUSSAIN: Just a reminder, if you could speak closer to the mike, I think acoustics in this room are not ideal.

DR. GRIFFIN: Amy, thank you for the introduction. And thank you for the invitation to present here today.

The topic that I'd like to cover is glycosylation. Glycosylation is often thought to be implicated in immunogenicity but it's also a very difficult post-translational modification in many ways.

Number one, it is the most sensitive to any change in process; that is, cell type, clone, fermenter conditions, culture medium conditions, et cetera. And it's also one of the most difficult to analyze to allow monitoring and controlling of the process. And I'd like to tell you about a technology in which we can contribute to solving some of these problems.

Now the reason glycosylation is so difficult to analyze is because these are branched, complex structures that are added to the protein

backbone. Because they're branched, they're not linear and easy to sequence like proteins in DNA. And also, even though one percent of the genome is dedicated to glycosylating proteins, there's no template for the glycans themselves so you can't go back to see if the right glycans were put on a molecule.

Now the existing technologies are capable of analyzing glycosylation; however, the gold standard, which, today, I think is mass spec plus HPLC, is not amenable to allowing monitoring of the process.

It requires protein purification. It requires significant sample preparation. And often many days and up to many weeks to get a complete analysis. In addition, it is very difficult to analyze lots of proteins in parallel.

The technology that we have developed is a semi-automated process that allows us to analyze up to 20 samples in less than three hours. It's accurate to within plus or minus five percent of data that are obtained by mass spec plus HPLC.

No sample purification is required so we perform this analysis directly in fermentation broth

or culture medium or formulation. In addition, it's extremely easy to perform and someone with a very low level of technical skills can perform it. Even our CEO has been able to do it.

(Laughter.)

DR. GRIFFIN: This is a lectin array-based technology. Lectins are proteins that recognize features of glycans specifically.

We have also developed a proprietary database of lectin recognition behavior. So this allows us to analyze how different features of the glycan influence the lectin binding. We've also developed proprietary software and algorithms to deconvolute the lectin-binding data.

So we actually get two types of data automatically from this system. We get a scan of the chip, the lectin array, and from this we generate a fingerprint. Now on the array, we have approximately 30 lectins and each lectin is present in multiple replicates as well as multiple concentrations.

The fingerprint is a histogram of the normalized data for each lectin on the array. And you can see here in this picture there are fingerprints for two proteins compared with each other. These two

proteins were run at the same time, in parallel.

One of them, the one in periwinkle blue, is an IgG4 grown in NSO cells. The burgundy-colored fingerprint is the same protein grown in CHO cells. And you can see immediately that there are differences here.

This fingerprint itself is not quantitative data; however, it can be deconvoluted to generate quantitative data. And what you see in this chart is the features of the glycosylation that we are currently able to analyze. And what you'll note is perhaps that we can see things that other types of technology don't necessarily see.

If they're looking for them, sometimes they can see them but not necessarily. For instance, we always see O-linked glycans if they are present and we also see the epitopes that are added by non-human mammalian cells.

There are certain glycosyltransferases present in CHOs, BHKs, NSOs, et cetera, that humans don't have. So they produce an alpha 1-3 linkage for the galactose added to the glycans. This is assumed to be antigenic because humans don't make this epitope. And you can see that we have a very

sensitive assay for it. And I'll show you some more data in a few minutes.

In addition, we can very sensitively distinguish the number of terminal galactoses on the bi-antennery glycan present on the FC region of IgGs so we can see G0, G1, and G2.

In addition, we can even see if there are further truncations beyond the galactose if the terminal N-acetyle glucosamine that would be there in the absence of galactose is also missing. This is sometimes very difficult to see by mass spec.

So for each protein, we develop a specific assay and we optimize for all of these features including the lectin, concentration, the probe, the algorithms, the database, the linear range of accuracy for the sample concentration and quantity, and this often ranges from 20 nanomolar up to maybe 200 nanomolar, as well as the influence of any components in the culture medium or formulation that would influence any specific lectin's binding and we can correct for those variations.

So the data that are produced are highly reproducible, 99 percent from sample to sample run in different places and on different instrumentation. It

is validatable and this software are 21 CFR, Part 11 compliant. And the assays are run in GLP-compliant conditions.

Just to show you the reproducibility, these were two aliquots of an antibody that were sent to our facility in Israel and the other sent to our facility in England. They were run by different scientists. And you can see from this the degree of reproducibility that we are achieving with this technology.

So I'd like to show you some applications here. One of the applications, of course, is to determine whether or not and at what levels antigenic epitopes are present.

And here is a case in which we were looking for a clone that made more product but less of the antigenic epitope. And this is a fairly difficult protein. There were eight glycans and so the manufacturer of this protein was not able to analyze very many clones.

So I'm going to show you three representative clones that we analyzed. A is the parent clone. And B and C are two representative clones that they were analyzing that made lots more

protein. And you can just look at the fingerprints of these three proteins and see that they are relatively similar in their glycosylation patterns.

But if we look more closely at the alpha 1-3 galactose, which is thought to be antigenic because humans don't add that epitope, you can see that the levels among these three clones are really quite different.

In fact, Clone B has even less of the antigenic epitope than the parent or the Clone A, the original clone. And you can see that Clone C probably has unacceptable levels of the antigenic epitope.

So the power of this technology allows us to use a reference standard, which, in this case, is Clone A, the clone that was used for all of the early development, and compare it, in parallel, the samples run together in the same assay, to compare the results or the patterns of glycosylation among these samples.

Now if we deconvolute these data, again you can see that Clone B does, indeed, have very low levels of antigenic epitope and it has the positive features that this manufacturer was looking for.

It has lots of tri- and tetra-antennery structures and it has a lot of sialylation. Ninety

percent of the glycans are sialylated and about 60 percent of the antennae of those glycans are sialylated.

I showed you earlier that using this in clone selection or in cell type selection will allow you to choose --

DR. ROSENBERG: One minute.

DR. GRIFFIN: Okay. I'll talk faster.

I've already shown you the data here. Another area that you will see this could be very useful is in tracking a single protein through a process.

And here is an anecdotal situation in which we were given two samples of a commercially-available product from a hospital and two batches from two different manufacturers. Here are two batches from one manufacturer. Here are two batches from another manufacturer. Now you can see that there are changes. There are differences here. And this is a perfect technology for comparing those differences.

So to conclude, I'd just like to point out that this technology is not intended to replace existing technology. But it does provide a tool that allows you to monitor, in real time, the glycosylation

of multiple clones and to run those clones or those proteins in parallel so that the data are much more comparable.

Thank you very much for your attention. I'll be happy to answer any questions.

(Applause.)

DR. ROSENBERG: Questions from the panel?

How significant are antibodies to carbohydrate moieties in therapeutic proteins?

DR. GRIFFIN: Well, there are a lot of controversies in the literature regarding that. A lot of people think that gee, the terminal galactose is very important and certainly bisecting antennae and core fucose are all very important for the effecter functions.

But as you know, the glycans on the FC region of IgG are concealed normally and are not exposed until antigen is found. So whether or not there were be antigenic prior to exposure to antigen is a very valid question. And whether or not they are absolutely required for effecter functions is somewhat debatable although I think that the jury is in for certainly bisecting antennae and core fucose being very important.

DR. GOLDING: You know the classic immunology is that sugars have to be spliced at regular intervals in order to induce a response. Does your technology allow you to look at the splicing of the sugars on the surface of the molecule? And there has to be many determinants.

In terms of sugars and immune responses, it's the splicing and multiple determinates that usually induce the response.

DR. GRIFFIN: Are you referring to the sugars on the target, on the antigen or on the protein itself -- on the antibody?

DR. GOLDING: On the antigens.

DR. GRIFFIN: Actually that's an interesting question as well. There are a number of tumor antigens that probably have glycosylation in the antibody-recognition site. And we're currently working on one of those.

Whether or not the sugars are necessarily involved in the antigenicity of other proteins, it probably is a protein-by-protein dissection.

DR. ROSENBERG: Yes, but what he's referring to is the fact that if you have a multivalent ligand, that's very good at triggering

immune responses and the spacing of those antigens has to be such that it optimally ligates B-cell receptor. That's what that is referring to.

And I think most of our therapeutic proteins, we hope, unless they're aggregated, don't have a -- are not multivalent in that sense.

DR. GRIFFIN: Yes, okay, I'm sorry. I didn't understand your question.

DR. ROSENBERG: Other questions?

(No response.)

DR. ROSENBERG: Well, thank you very much.

DR. GRIFFIN: Thank you.

(Applause.)

DR. ROSENBERG: Okay. The next speaker is Dr. Fred Bader, Vice President of Process Sciences, Global Biologics Supply Chain for Centocor.

DR. BADER: Well, thank you. Good morning. I am Fred Bader, Vice President, Process Sciences, Global Supply Chain of Johnson & Johnson.

I am pleased to be here today to talk about immunogenicity as part of the dialogue on the potential approval standards for follow-on biological products.

A recent experience with epoetin and pure

red cell aplasia, or PRCA, provides a prominent example of the challenges associated with managing the immunogenicity of protein products. This example also reminds us how difficult it can be to identify the cause of immunogenicity and how poorly understood immunogenicity remains today.

I'd like to start by explaining some basic facts about the immunogenicity of proteins and some of the causative factors.

One common type of immunogenicity associated with therapeutic proteins is the formation of antibodies against the protein. Nearly all therapeutic proteins induce antibodies in some percent of patients who receive the product.

The frequency of antibody formation against therapeutic proteins varies or the formation varies by both frequency and severity of the impact on the patients. Some of the causative factors are patient related and some of them are product related.

All antibodies are produced by B cells, a type of white blood cell. IgG antibodies are a common type of antibody produced against proteins. IgG antibodies are problematic because they are long lasting and increase with multiple exposures. In the

production of IgG antibodies, there are four relevant factors.

First, the protein which acts as the antigen, which is the target for the antibody.

Second, the B-cells, a particular B-cell population has to have a receptor that can recognize and bind to the protein.

The third are T-cells, a particular T-cell population has to be able to bind to a short peptide sequence of the protein.

And fourth, an adjuvant has to be present that can activate the antigen-presenting cells that present the short peptides to the T-cells.

B-cells and T-cells are patient specific. The B-cell and T-cell receptors are randomly generated during early development.

Under normal circumstances, we delete B-cells and T-cells that recognize cell proteins through a process called tolerance. Otherwise we would form antibodies against our own cell proteins. However, most immunologists believe today that tolerance can be leaking.

Immunogenicity can be stimulated by the

actual form of the protein being administered and by the presence of the adjuvant or immune stimulant in a product. These are classified as product-specific factors that can effect immunogenicity and can vary between two different forms of the same therapeutic protein. In fact, for the same product in different put ups, which we will talk about.

These effects of the protein and adjuvants on the formation of antibodies in humans can only be determined by clinical studies. If the protein is not identical to the normal human protein, then there is a risk that it may be immunogenic as it will no longer look like a self protein.

For example, a minor change in amino acid sequence, misfolding of the protein, improper post-translational modifications such as carbohydrate addition or deletion, damage to the protein or aggregation could change the immunogenicity of the protein in unpredictable ways.

The presence of adjuvants in the process of making the protein or from materials used to formulate the protein can also increase the immunogenicity of the protein. Although these factors can be studied in animal and cell-based models, their

effect on humans can only be determined in human clinical studies.

Now I'd like to turn your attention to our case study Eprex in PRCA. Epoetin alpha is a recombinant human erythropoietin produced in CHO cells in a biopharmaceutical manufacturing facility. It is used to treat red blood cell deficiency or anemia in patients.

Eprex is the brand of epoetin marketed outside of the U.S. by Johnson & Johnson. PRCA is a severe and rare form of anemia characterized by an almost complete absence of red blood cell precursors in the bone marrow.

Between 1998 and 2002, an increased incidence of PRCA outside of the U.S. has been linked to epoetin products, particularly the Eprex brand. This increased incidence of PRCA was linked to an immunogenic response by the patient resulting in antibodies that bind to erythropoietin and prevent it from stimulating production of red blood cells.

These antibodies inactivate both recombinant erythropoietin administered to the patient and any erythropoietin that the patient produces naturally causing the patient to lose the ability to

make a sufficient number of red blood cells. The patient has to receive red blood cell transfusions and immunosuppressive therapy to maintain their hematocrit.

Our efforts to find the cause of PRCA were extensive. There were more than 100 people involved, working many long hours, particularly comparing current product with historical retained samples to look for changes. In addition, an immunogenicity advisory board was created to provide expert input. We also worked closely with many health authorities and deeply appreciated their help and support.

As you may expect, the cost of this investigation was considerable.

Our efforts to find the cause of PRCA were extensive. Every possible cause was investigated. Thanks to these extensive efforts, the mechanism of PRCA is now understood and we have increased our knowledge of the mechanisms of immunogenicity.

I just point out on this slide there is a wide range of things we looked at. Looking at the equal molecule, we were unable to find any change in the molecule over the last eight or nine, ten years that could be at all related to this particular

phenomena.

We also looked at multiple adjuvants. And as you can see in the blue there, that the leachates is the one thing that we found that basically fit all of the data. And we'll talk about that a bit now.

In our investigation, we were particularly looking for something that had changed in the product around 1998 when the increased frequency of PRCA first occurred.

While developing some more sensitive analytical methods, one of our scientists detected some non-protein-related peaks. These are on the right-hand side of these chromatograms. These peaks proved to be organic molecules that came from the rubber stopper in some pre-filled syringes of Eprex. These organics are technically called leachates.

By comparing with other forms of Eprex, we are able to determine that a formulant, polysorbate 80, was extracting these leachates from an uncoated rubber stopper that was used in a particular set of syringes. This combination of polysorbate 80 and the uncoated rubber stopper occurred beginning in 1998 when HSA was removed.

A different form of the product, which

used a FluroTec-coated stopper, that was launched in 2001 did not show the presence of these same leachates as shown in the blue line on this slide.

So if you look at the red line on this slide, you'll see a number of peaks, one through ten, which do not belong in the chromatogram. There's an EPO peak and there's two small polysorbate 80 peaks that are always present. And if you look at the blue line, that's basically the coated stopper. And what you see is none of these extra peaks exist in that.

We established a set of criteria against which we tested all hypotheses for the cause of the increase in PRCA and only the leachates met all the criteria shown above.

The most critical data here were the timing of the combination of polysorbate 80 and the uncoated stopper that occurred in 1988 and resulted in the leachates.

The second critical one was animal studies that confirmed that these leaches could act as adjuvants.

That the third was that we were able to demonstrate through close market surveillance that the frequency of PRCA cases associated with the uncoated

stopper syringe were much higher than with the FluroTec-coated stopper syringe as both were on the market at the same time in different strengths.

As the scientific dialogue and follow-on biologics continues, it is important to remember that patient safety must be of paramount importance. Any company marketing either an innovative or a follow-on protein product must be prepared to respond appropriately to thoroughly investigate unexpected adverse events.

Clinical trials are an essential component of assessing immunogenicity potential in patients. In this case, the incident of PRCA was rare, probably too rare to have detected it in a normal-sized clinical trial. This has prompted some to argue that clinical testing for a follow-on EPO or any follow-on biologic could be minimal, leaving the assessment of immunogenicity to post-marketing pharmacovigilance.

We do not agree with this view. A rare incidence of immunogenicity triggered by one factor related to one protein product does not guarantee that the incidence may be just as rare when triggered by another factor related to another protein product.

Furthermore, such rationale for minimal

clinical testing of immunogenicity would leave the true testing to after marketing. While rigorous post-marketing surveillance is essential for all protein products, it cannot replace the scrutiny that is applied to testing done in clinical trials.

Patients taking marketed products rightly assume that the risk associated with their medicine has been comprehensively evaluated by the testing conducted before approval.

In closing, I would like to say that we are pleased that the FDA is pursuing a public process while they consider the standards for follow-on biologics. And we look forward to the next workshop in early 2005 where we will be able to discuss the scientific details.

I thank the FDA for this opportunity to participate in this dialogue.

(Applause.)

DR. ROSENBERG: Thank you.

Questions from the panel?

DR. SHORES: Can you envision any direct type studies with leachates prior to using a particular container closure system that could help address this in a more global fashion?

Would immunogenicity studies with leachates from a particular container system be useful? Or is it too product specific? How do you see it?

DR. BADER: Well, my assumption would be that certain leachates, if it's an adjuvant for one protein, would probably be an adjuvant for other proteins. I think the example was given yesterday that thalates, for example, have been implemented as immune stimulants as well.

So having an understanding of some of these would be useful. However, one issue you get into there's so many different types of stoppers and formulations for stoppers that whether we would be able to come up with a good understanding of all those would be somewhat problematic.

And another issue that you get into is that some of the normal testing we do under USP or EP requirements are not necessarily the same as for the product.

And in this particular case, if you looked at fresh material that had just come off a filling line, you would have never seen these leachates. And, in fact, they were at relatively low concentrations

for the first ten months and then accelerated.

And so you would really have to look at these at end of stability. And that would depend on the formulation because the same stopper with HSA did not show the leachates.

DR. ROSENBERG: Is that why you didn't see it initially when you did your initial comparability analysis?

DR. BADER: That's basically a reason why would not have seen it initially, yes.

DR. ROSENBERG: So you did the same extended tryptic peptide mapping and you did not see --

DR. BADER: Actually we had never -- we did not look for that. We did the usual USP/EP methods. We never really did a thorough study with the actual formulation, which is one of the things that needs to be -- would need to be done in the future.

DR. ROSENBERG: Alexandra?

DR. WOROBEC: Yes, could you elaborate on the design of your animal studies, meaning what species were used? And how long the studies were done?

I'm assuming that the endpoint would be looking at antibody to erythropoietin but were animals followed long enough to necessarily pick up, you know, all of the animals that may have expressed an antibody response.

DR. BADER: Okay, the animal studies were primarily done with BALB/c and pdf1 mice. And, again, we spent quite a bit of time working with animal models with our expert immunology advisory board.

The most telling study that we actually did at their recommendation was we basically tested these leachates with ova-albumin in a mouse model because it's a well-established, well understood model. And we were able to show a dose-dependent increase in response to ova-albumin with the leachates.

We did a lot of studies with erythropoietin itself. One of the issues there is the mice respond to human erythropoietin so it effects their hematocrit. The other issue you get into there is if they start forming antibodies, these mice still produce EPO and they'll try to compensate.

So trying to measure the antibodies in the presence of mouse serum, which is full of mouse EPO,

became problematic although we had some very interesting results showing decreases in hematocrit over time as in mice it looked like they potentially might have had antibodies.

DR. ROSENBERG: Marjorie?

DR. SHAPIRO: Can you just clarify? Are you saying that even if you had done this stability out for several months or if you had done accelerated, you still would not -- since you weren't looking for those particular leachates, you would not have detected them at that time?

DR. BADER: Right. That would be correct. You know we did -- we had -- and, again, you don't what -- you can't look for what you don't know is there, I guess, is sort of the problem. So we had no particular assay to look for these particular leachates, you know, up front because we didn't know that they existed.

DR. ROSENBERG: I have a more general question which is so if you look at differences in either incidence of antibody responses or in titer of antibody responses, both binding and neutralizing, what would you consider to be a significant difference between one protein product and another, assuming the

assay is equally sensitive towards picking up antibodies to both products?

DR. BADER: This would be in patients?

DR. ROSENBERG: This would be in patients.

DR. BADER: In patients.

DR. ROSENBERG: Or in animals potentially.

DR. BADER: I mean that's an interesting question in a way. You know in the world of erythropoietin where these antibody responses generally were very rare, less than one per 10,000 patient years, our rate went up to, in a particular patient population of sub-cu administration to chronic renal failure patients, went up as high as 4.6 cases per 10,000 patient years. And that was considered by all regulatory agencies that we dealt with as a significant difference.

DR. ROSENBERG: Right. So that's for neutralizing antibodies for mediating a disease.

DR. BADER: Right. And in general with erythropoietin, the vast majority of antibodies are neutralizing.

DR. ROSENBERG: Yes, okay. So what about for binding antibodies just for other therapeutic protein products? If there is a difference in binding

antibodies, which seem to have no clinical effect, do you think that that is telling you something about a difference between the products even though it's not telling you anything -- that there is anything clinically significant?

DR. BADER: I guess I would assume it might be telling you something about the products. I'm not that much of an expert on -- I'm mean a lot of products have fairly high frequencies of antibody formation of one kind or another, particularly in non-neutralizing, up in the multiple percentage-type of range. And I guess those would have a higher percentage, probably are more susceptible.

But if the clinical data says that you get a large number of non-neutralizing antibodies but you don't get neutralizing antibodies, I guess medically it would be kind of an irrelevant argument. So each situation would have to be evaluated accordingly.

DR. GOLDING: Could I ask? The actual leachate, did you know what it is chemically? And something you alluded to is very interesting is the possibility of taking the leachate itself and using non-antigens and to seeing what is the level of adjuvanticity that it has.

And I think the most important lesson that you've taught us is, I think, that if you take an adjuvant and even with a protein that as far as we can tell is in its native structure, you can still break tolerance with it.

DR. BADER: That's right. Right. I think that's one of the biggest conclusions I think we've taken from this is if you have an adjuvant in the product, you know, over some period of time you're going to break tolerance in some number of patients most likely.

The question on the actual -- yes, we did identify nine of the ten peaks and basically eight of those peaks are related to the same material. It's a teriary amylphenolic material that is connected by its sulfurs. It's actually a vulcanizing agent used in the rubber. And so a number of those peaks are just different forms of that same material.

DR. ROSENBERG: Okay. We need to conclude here. Thank you very much.

Our next speaker is Dr. Terry Gerrard, President of TLG Consulting.

DR. GERRARD: Good morning. I'm Terry Gerrard. And I'm going to be talking about

immunogenicity concerns.

I guess one of the big questions that we heard yesterday and continue to talk about today are immunogenicity concerns a hurdle in the development of biopharmaceutical generics, the real questions being will a biogeneric cause greater immunogenicity than the originator? And can immunogenicity concerns be addressed either through analytical characterization or through clinical trials prior to the approval of biogenerics?

Well, regarding the first question, will there be greater immunogenicity than the originator? I think what we should be asking is will a biogeneric cause a clinical consequence as a result of immunogenicity, remembering that the presence of antibodies is not always harmful.

And I think sometimes we've heard in the past day and a half and in other places that immunogenicity is always bad. And we have to remember that's not true. Many therapeutic proteins generate antibodies in patients with absolutely no clinical consequences.

Now this is not to minimize the presence of antibodies and certainly antibodies to therapeutic

proteins can be a concern. And that's when antibodies can effect PK of the therapeutic protein, when antibodies diminish the therapeutic efficacy of the protein, and perhaps the most serious, when antibodies cross-react with the endogenous protein. So these are, you know, certainly something that we want to be watching for.

But the generation of antibodies to a protein should not always be an issue, remembering that antibodies with serious clinical consequences are actually very rare. Many antibodies are transient. And that there are many patients with antibodies to the protein that continue on therapy with no clinical consequences.

Now the second issue is can immunogenicity concerns be addressed through analytical testing prior to the approval of a biogeneric? Well, we might consider taking a risk-management approach and focus the resources on assessing product factors with the greatest risk of immunogenicity.

Now we've dealt with therapeutic proteins now for 20 years and have had lots of experience. We know that aggregation is probably the main product factor associated with immunogenicity.

With some of these other things like novel epitopes, impurities other than aggregation, oxidation, glycosylation changes, these are sometimes minimal risks. And then sometimes they're purely a theoretical risk.

Getting back to aggregation. We now have approved methodology that's available to measure aggregates. And very often this methodology was not available at the time that the innovator product was developed.

We need to perhaps measure aggregates on stability and if it's a lyophilized product, after reconstitution. It's important to remember that the USP test for particulates was developed for drugs and may not be appropriate for a lot of the proteins that we're dealing with.

Now these issues, as far as focusing on aggregation as a way to minimize chances for immunogenicity, are not unique issues to biogenerics and really apply to all therapeutic proteins.

Now what about clinical immunogenicity studies? Can immunogenicity studies be addressed through clinical trials prior to the approval of a biogeneric? Can we have a really full, in-depth

understanding of immunogenicity and the clinical consequences?

Well, the answer is no. But neither can the originator. You probably cannot fully understand immunogenicity prior to approval for any product just because of the limited exposure.

It was proposed yesterday that the more information known about the chemistry and biology of the biogeneric, the less clinical data should be required. Well, maybe a corollary to that is that if extensive analytical tests demonstrate identity between the biogeneric and the originator, the chance for increased immunogenicity is minimized.

I think it's important to recognize the limitations of small clinical comparator studies in being able to detect true differences between two products with regards to immunogenicity. One has to consider what is the expected difference? What is the size of the trial needed to show that level of difference? And it just may not be practical.

Now this is -- again, I don't mean to minimize the testing for antibodies. I think that the assessment of antibodies in the development of any therapeutic protein is important and should be

included as part of clinical trials.

I'm not saying that clinical trials are always necessary for a biogeneric but as part of a trial that's asking a good scientific question. But clinical trials done solely to evaluate differences in immunogenicity may be of limited utility.

A complete understanding of immunogenicity and the clinical consequences may not be possible until post approval. Again, this is true for any therapeutic protein. And it's not a unique issue for biogenerics. And it may require post-marketing surveillance.

In summary, I think only immunogenicity with clinical consequences should be a concern. We need to focus on analytical testing of product factors that are associated with immunogenicity. And of all the ones we know, aggregation is probably the biggest.

The more information we know about the chemistry and biology of the biogeneric, we minimize the chances of differences in immunogenicity and recognize that clinical trials have their limitations in being able to detect immunogenicity differences.

With that in mind, I think immunogenicity concerns need not be a hurdle in the development of

biopharmaceutical generics.

Thank you.

(Applause.)

DR. ROSENBERG: Thank you.

Questions from the panel?

DR. SHORES: Yes, I wondered if you would discriminate between those products that had a known immunogenicity rates with the innovator product, versus those that appear to have no immunogenicity, in your thinking on clinical trials.

And the second part, if I can just give it to you now so you can respond, is we often include a part in the package label, a section on immunogenicity, what would be your recommendation for how that could be approached? Would you suggest no labeling? Or inclusion of language citing the innovator's product? And I'd like to just hear your thoughts on that.

DR. GERRARD: Well, with regard to the first, if there is a known immunogenicity issue, I think that the emphasis should all the more be on analytical characterization.

And I think Dr. Bader gave a very good example. Could something like that be detected in

clinical trials? No, not at a 1:10,000 incidence. But through rigorous analytical characterization, they did identify the problem. So, you know, that's actually a good thing.

And if you know something to have a potential for immunogenicity, you need to focus on those factors that are potentially causing the immunogenicity.

As far as -- again, as far as clinical trial done to look at differences, depending on if they have been shown by analytical characterization to be identical, the expected differences, can a clinical trial really show differences? Probably not.

DR. SHORES: Just to clarify what you are saying then, would you recommend that either the innovator or the biogeneric go and investigate the reasons for the immunogenicity before going forward?

DR. GERRARD: Well, I think that's probably always a good idea as with regard to your --

DR. SHORES: Then you would recommend that that be in the hands of the innovator or the biogenerics?

DR. GERRARD: Well, if I were the innovator, I'd certainly want to investigate the

causes of immunogenicity, certainly. But I think here we're focusing on what's the responsibility of the biogeneric pharmaceutical. And, yes, they may need to do more, just because there are more rigorous tests available now that perhaps weren't available when the innovator was developed.

DR. ROSENBERG: Terry, one of the things you left off your list of adverse effects of antibodies is hypersensitivity responses. And as far as I know, there are no good ways to predict, even using animal models, the potential for a product to mediate anaphylactic-type responses. How are you going to get around the necessity for studying that?

DR. GERRARD: Well, I think actually because they're not -- my understanding is that some of these are not anaphylactic. We've always referred to them as anaphylactic-like. Are they true anaphylaxis? And this gets to the question, you can probably go around in circles --

DR. ROSENBERG: Well, even if they're anaphylactoid, they're serious adverse events.

DR. GERRARD: Yes, they are serious adverse events -- but since we have no means of predicting this, what should be done? I don't know.

I think we can only recommend that people do something when there has been shown to be a correlation as far as its utility.

DR. ROSENBERG: So if there is no way to predict it, do we need to do a clinical trial?

DR. GERRARD: Have clinical trials been useful in demonstrating or predicting anaphylactic-like reactions?

DR. ROSENBERG: I would say that they have. Any opinions here?

DR. GOLDING: Well, I think the point is -- you pointed out that the clinical trials are not very large --

DR. GERRARD: Right.

DR. GOLDING: -- for practical reasons and if the incidence of this anaphylaxis or IgG response is very low, you're not going to pick it up. But on the other hand, if it's very high, if it's an unacceptably high allergen, then we want to pick it up and we want to know about it before the drug gets approved.

So I think it is, like you said, a risk-management thing. And if you don't do the trial at least say for a hundred or a few hundred people, you

don't know what the acceptable risk is.

DR. GERRARD: And now we're going back to theoretical again because I don't know of protein therapeutics that have a high incidence of anaphylactic-like reactions.

DR. ROSENBERG: Well, there certainly are some foreign proteins which have a fairly high incidence. But let's move on from this topic.

Other questions?

Alexandra?

DR. WOROBEC: Actually, that brings up an issue in terms of post-marketing. Typically for some of the generic products, one of the issues I can foresee running into is that reporting may not specify which product is causing a problem.

And that may be also compounded, for example, we're talking about anaphylactic or anaphylactoid reactions, having a clinician see this patient and not necessarily doing a thorough work-up and being left with an adverse event report where you really don't know what the patient had.

And frankly, there have been examples, you know, at the Agency for other types of indications where when sorting through these reports, it's really

hard to make out what they're due to. And I think as far as immunogenicity is concerned, we really need to have great data to really make the link. Because if you have sloppy data, you might miss the link.

So how do you foresee or have any insights into how to try to, perhaps, get cleaner reporting post marketing?

DR. GERRARD: Well, actually I mean if that issue needs to be addressed, the question is, is that best addressed by the biogeneric manufacturer or is that best addressed by perhaps changing the adverse event reporting system?

DR. ROSENBERG: Okay. We need to move on from here. Thank you.

Our last speaker is Dr. Ken Seamon, Vice President of Global Regulatory Affairs at Amgen.

DR. SEAMON: Good morning. I'm Ken Seamon, Vice President of Regulatory Affairs for Amgen. At the Agency's request, I will focus only on the scientific questions raised by follow-on biologics.

However, as Amgen expressed in its testimony before the Senate Judiciary Committee, we believe that the myriad legal, regulatory, and policy

issues surrounding this subject also require careful consideration through a deliberate and transparent public process.

Amgen's technical experience encompasses the fields of molecular and cellular biology, target discovery, safety assessment, therapeutic delivery, and biotechnology process development.

We have seven marketed products in the United States including some of the most recognized biotechnology products, many of which are used for chronic administration to large patient populations. These include Epogen, Neupogen, and Enbrel.

It is from this perspective that I comment on behalf of Amgen on the science of follow-on biologics and specifically relating to immunogenicity and requirements for clinical data.

We believe that in developing any regulatory paradigm for follow-on biologics, the following principals must be adhered to:

One, follow-on biologics are unique products and must be held to the same high standards of safety, purity, and potency as the innovator to ensure patient safety;

Two, immunogenicity and other adverse

events, unexpected and expected, presents a serious concern for all biologics and should be studied through controlled clinical trials, pre-approval, and monitored with robust post-approval surveillance; and

Three, follow-on biologics cannot be considered therapeutically equivalent to the innovator product and will necessarily require unique labeling.

If these fundamental principles are maintained and innovator rights are fully respected, we believe that through a sound public process, Congress, FDA, patients, and the industry can develop a sensible roadmap for the approval of safe and effective follow-on biologics to provide additional treatment options to patients and healthcare professionals.

Indeed, Amgen agrees with the statements articulated by PhRMA and the other colleagues in BIO over the past two days concerning the impact of the manufacturing process on the identity of biological products and the limitations of current analytical methods for determining identity of these products.

These include the limitations that have been discussed relating to product characterization, product and process impurities, and the difficulties

in determining tertiary structure.

We believe that as complex mixtures of heterogeneous proteins and impurities, these products are difficult to characterize with precision. And impossible to characterize with certainty.

Because of these limitations, we do not think it is currently possible to demonstrate the absolute identity of a follow-on biologic of the reference innovator product.

This data was also shown yesterday and this concept is also supported by a recent paper by Dr. Hugh Shelliken which demonstrates that so-called generic epoetin alfas from other parts of the world are very significantly qualitatively and quantitatively distinct from the epoetin alfas that are approved in the United States and Europe.

Presumably these all represent erythropoietins made in mammalian cell culture but it's clear that they represent different glycosylated species with corresponding differences in in-vitro and in in-vivo activity.

Since a follow-on biologic cannot be determined to be identical to the reference innovator product, it needs to establish its own unique safety

and efficacy profile. From this premise follows what we believe to be the critical issue and the focus of our comments today.

How to ensure patient safety through appropriate preclinical and clinical testing for all protein products?

Importantly, as was discussed by the other speakers, toxicity with proteins often presents differently than toxicity with small molecule pharmaceutical drugs with less off-target specificity but with the potential for antibody responses whose consequences are unpredictable without study.

The toxicity or adverse events can be related to the pharmacology of a product or due to immunogenicity which is sensitive to low-level species such as product-related or process-related impurities. This concept of immunogenicity is central to the development and testing of a protein product and, therefore, to the discussion of follow-on products.

Immunogenicity is unpredictable and may effect a variety of essential biological functions, impacting not only the safety but also the dosing, clearance, and efficacy of the product. For example, subjects may produce neutralizing antibodies that

block the effectiveness of the body's own molecule or antibodies that bind to another receptor and perturb healthy tissue.

Other antibodies appear to be harmless while some may cause a dramatic increase or decrease in the administered protein's clearance and/or its potency. Even among proteins with identical amino acid sequences, immunogenicity results can vary dramatically.

Preclinical evaluation for immunogenicity is an important first step but it does not provide the unambiguous data with regard to immunogenicity in humans. Like other products regulated by FDA, in-vivo testing of a developmental protein product begins with preclinical animal studies, with considerable attention paid to the early detection of an antibody response in addition to the on-target and off-target toxicity.

An absence of immunogenicity in animals, however, does not ensure that immunogenicity will not present later in humans. In the earliest phase of clinical testing, it is important to assess the half-life and clearance of the protein in addition to looking for signals for immunogenicity.

Unlike with small molecule drugs, pharmacokinetic effects can vary greatly from product to product with the same protein class. For example, six companies do manufacture FDA-approved versions of human growth hormone, one of the oldest and best understood biotechnology products.

Although each of these products has the same number of amino acids, and very similar molecular weights, the terminal elimination half-life of each product varies tremendously from 1.75 to 10 hours. This is not a trivial distinction because the clearance of a protein product can impact the body's immune response to the substance.

Thus, large variation in pharmacokinetic data for different versions of the same protein not only render those products therapeutically nonequivalent, they also raise potential safety concerns.

As clinical testing progresses to large-scale studies, which often involve at least several hundred, if not several thousand, subjects, we continue to evaluate possible safety risks with specialized attention paid to the potential antibody and immunogenic toxicities.

This can be complicated because almost every protein or monoclonal antibody administered to humans will cause some sort of immunogenic response in some, if not most, patients. Furthermore, the same protein can cause different kinds of antibody responses when administered to different patients in different clinical settings.

As noted above, these responses cannot be predicted through analytical or preclinical testing alone.

In our own experience with developing MGDF or thrombopoietin, which was designed to mimic thrombopoietin, we did not observe an immune response that resulted in important safety concerns until Phase II testing and then promptly halted the clinical program.

The Phase II clinical studies identified several subjects that developed antibodies down to the drug, neutralized the drug, and neutralized the endogenous thrombopoietin. This resulted in the loss of platelet production in these patients. Again, this was a serious event that was determined using controlled studies in many hundreds of patients.

Because of the diversity of antibody

responses possible with any one protein, it is important to follow the subjects for a long time to determine whether an immune response will develop and what the clinical and safety effects of that response are.

This potential for rare events to occur requires that in addition to a robust preapproval safety study, a robust pharmacovigilance program must be implemented to assure patient safety. And this was very well presented previously.

As this brief outline demonstrates, the development of any one protein therapy requires many layers of testing, from basic toxicity studies in animals through comprehensive clinical trials in humans in order to assure the safety of the product. The data from these tests cannot be merely transferred to other versions of the same protein.

We know from our own experience that significant changes in the manufacturing process have the potential to lead to significant differences in the result of the protein.

However, we also know that it is possible to qualify discreet changes to the manufacturing process using a combination of analytical

methodologies that rely on process evaluations, comparison of release specifications to historical data, and the use of additional analytical characterization methodologies.

These types of changes, the discrete changes, are relatively defined and associated with discrete changes to a particular unit of operation such as site changes or scale-ups. These can be usually qualified with appropriate process characterization and CMC data.

However, even as an innovator, it is more difficult to qualify significant changes in the process that effect the fundamental production technologies such as significant changes to the cell line associated with changes in cell expansion.

Frequently we will qualify such changes using additional characterization that includes preclinical studies, pharmacokinetic analysis, and clinical studies to confirm safety and efficacy. These types of studies are carried out depending on the particular product, its intended use, and really what is known about its overall adverse event profile.

This type of evaluation takes place even when there are no obvious differences in the product

profile based on the analytical characterization. And this is consistent with the comparability guidance from the FDA.

I contrast this with the types of changes that would be associated with a second manufacturer such as a follow-on biologics manufacturer where the same magnitude of changes are implemented but without the process history of the innovator or the use of proprietary reference standards and methods.

In this case, again, similar to the innovator when we make a significant change, it is appropriate to generate the CMC data, preclinical data, and clinical data to establish safety and efficacy.

In our experience, significant changes can be implemented and in many cases there are no obvious differences in the product profile.

However, I want to stress that due to the significance of the change and our evaluation of the potential toxicities associated with the product, we may still conduct a significant amount of preclinical and clinical studies to provide us assurance that the product is safe and effective for its intended use.

The goal of any approval process for

follow-on biologics is to take advantage of the experience already developed by innovators and the regulatory experience with the use of a particular product class.

Biotechnology products are simply too sensitive to their particular manufacturing processes, however, and immune responses variable and unpredictable, to allow a follow-on sponsor to rely exclusively on the innovator's preclinical or clinical research to establish the safety of its own unique product.

This leads us to several recommendations. With regards to safety, we recommend that there be appropriate preclinical safety studies using as guidance the ICH S6 document, Preclinical Safety Evaluation for Biotechnology for Pharmaceuticals.

We also recommend that any approval should be supported by appropriately-sized clinical trials. And we recommend that the ICH guideline, Extent of Population Exposure to Assess Clinical Safety, be used as an initial guide in determining the scope and duration of these trials.

This guideline recommends patient exposure of 100 for 12 months, 300 to 600 for six months, with

a total exposure of about 1,500 patients.

We recognize, and I believe the guideline acknowledges, that these numbers should be evaluated with respect to the specific product and indication. And in some cases, a larger exposure may be warranted. And I am sure that in other cases, one might advocate for lower exposure.

A thorough assessment of immunogenicity should be provided as part of the safety database for the follow-on product. And finally, robust post-approval pharmacovigilance, including monitoring for immunogenicity and related events as well as other adverse events, should also be implemented.

With regards to efficacy, any approval should be supported by bioequivalence and controlled trials to establish efficacy using either well-accepted surrogate markers or clinical endpoints.

For products with multiple indications, it is important to establish that each indication is supported by data especially for those indications where the underlying biology or mechanism of action is unclear.

In conclusion, we reiterate what we believe are the core principles that should guide

discussions about possible approvals of follow-on biologics.

First, any such process must be transparent, public, and science-based so that the risks we've highlighted may be fully debated by the medical, scientific, and patient communities. This process should include a period of pre-market comment regarding the appropriate standards for approval for types of products or product classes.

We recommend that the National Academy of Sciences, Institute of Medicine, and other respected science-based organizations be included in the process.

For example, it seems obvious that preclinical and clinical data will be required to establish safety and efficacy of the follow-on biologic. However, it is not obvious what amount of data would be necessary or how information that is currently in the public domain can be leveraged to facilitate development.

Second, the potential risks of immunogenicity are very significant and can be devastating in their most extreme circumstances. Therefore, immunogenicity should be assessed with

appropriate preapproval clinical data so as not to put patients at undue risk when the product is introduced into the marketplace.

Robust safety monitoring must continue post approval but a significant attempt via large, well-designed clinical trials must be made to detect and assess adverse events and immune responses before approval.

Third, because proteins cannot be characterized and duplicated in the same way as small molecule drugs, follow-on biologics can never be considered true copies of the innovator products and cannot be deemed therapeutically equivalent to the innovator product.

Thus the current paradigm for determining therapeutic equivalents and substitutability of drug products does not appear to be applicable to these complex protein products. In addition, given the diversity of immune response and the degree to which proteins are tied to their manufacturing process, we suggest the need for original labeling for all of these products based on their clinical experience.

And lastly, as unique products, follow-on biologics should not carry the same nonproprietary

name as the innovator but, instead, should be denoted by an original use and name.

With these principles in mind, we believe it is possible to discuss the possibility of developing an approval pathway for follow-on biologics.

Amgen believes that there is no barrier in the abstract to the development of follow-on products to provide patients and healthcare providers with more treatment options so long as full respect for the innovator's intellectual property, such as patents, trade secrets, and confidential commercial information is maintained and patients receive safe and useful products.

However, we believe that extensive discussions are needed regarding what preclinical and clinical requirements could be abridged for follow-on biologics while still satisfying the approval standards of safety, purity, and potency.

Thank you for the opportunity to provide these comments as well as some more detailed written comments we will submit to the process to the public docket. And we look forward to participating further in the discussion.

DR. ROSENBERG: Thank you.

(Applause.)

DR. ROSENBERG: Before we start with questions, I just want to make one remark. I think there may have been some misleading information yesterday which is that we do, indeed, for some major manufacturing changes for our innovator products, we do ask for immunogenicity studies prior to them being marketed. So I just wanted to clarify that for the record.

With that, I will open this up to questions.

Dena?

DR. HIXON: I have a question. You had commented that the follow-on biologic needs to be held to the same standards as the innovator product and certainly a true generic would be interchangeable in order to get that AB rating.

And there are a whole host of products out there that could potentially be considered here, anywhere from the simple peptides to the proteins that are purified from a natural source to synthetic peptides or proteins and then, of course, the recombinant products.

And it seems that the majority of our attention has been put on the recombinant products and the real high-tech products. But we do have to consider with the follow-on products what we do with some of these older products that are purified from a natural source and also how we would approach the simple peptides.

And as far as holding a product to the same standard, obviously when we're thinking about the potential for immunogenicity, we may actually be holding a follow-on to an even higher standard than the innovator was held to in order to get that interchangeability rating.

And I just kind of wondered if you had any comments about the approach to the simpler products and whether there's any point at which you would make a cutoff between how you would handle a peptide and how you would handle a protein. And whether you have any comments about products other than the recombinant and really high-tech products?

DR. SEAMON: I won't make a comment specifically about a particular product class but I will advocate that when we look at a follow-on product or a particular product class, I think you do need to

evaluate its intended use, what's known about the patient population, what's known about the adverse events associated with that particular modality of treatment. And that will allow you to define how much data is necessary to bring a follow-on product to market.

With regards to the therapeutic equivalents, based on the ability to extrapolate safety data from the clinical data generated with a particular follow-on product, again, we feel that it is important for the physician and the healthcare practitioners to be aware of that body of data, which is why we recommend that they not have a therapeutic equivalence rating so that the physician can be involved in making the decision to move patients to that product.

And Amy, with regards to your one comment after my talk, frequently after making significant manufacturing changes, we are conducting preclinical and clinical studies not just for immunogenicity but also to make sure that the adverse event profile is consistent with what's known about the product as well.

DR. ROSENBERG: Yes, I was just correcting

the misleading statement of yesterday.

Wendy?

DR. SHORES: I know you recommended that a body of experts be involved in thinking about the degree of testing that would need to be required. I wondered if you wanted to comment a little bit further about the details of immunogenicity testing.

Would incidence of antibody rates be sufficient? Would immunodepletion studies with innovator versus follow-on product be something that you would encourage? And just, in general, what kind of detail do you think the immunogenicity testing should have?

DR. SEAMON: I think the immunogenicity can't be viewed only in a simple context of what is the number. And I think we need to make sure that we don't fall into that trap.

I think for the use of these products in a particular indication, again, it's not just the rate of antibody production. It's really what is the consequences of the antibodies? What's known about the particular treatment? What's known about the potential adverse events that could be associated with a neutralizing antibody with regards to endogenous

molecules or non-endogenous molecules?

It's well accepted that in many product classes antibodies are generated. And they really don't appear to have clinical consequences.

So where I think a more open discussion bringing in outside, additional experts could be valuable is when one starts to try and determine how to evaluate the safety considerations with regards to a particular product class.

With regards to bringing in outside experts, I think it would also be valuable, because there is a lot of information that's in the public domain and I think we need to have broader discussions to figure out how we, as a public health community, can leverage that information to facilitate development.

DR. WOROBEC: So does that suggest then you would agree there could be sort of tiers of what we would expect for immunogenicity testing based on the profile of the innovator product if there were known consequences to immunogenicity versus immunogenicity that didn't have clinical consequences?

DR. SEAMON: I think that has to be considered. And I think when you look at generating a

safety database for any approval, the FDA and other regulatory authorities are always doing that.

The ICH guidelines actually talk about a database and they give numbers. But really that has to be qualified with regards to how the product is going to be used, what the population is, what the known and expected adverse events are.

And then based on that, you can then decide what type of a safety database would be necessary that would include immunogenicity testing. And what are you looking for in that immunogenicity evaluation.

But I think for any product approval, whether it is an innovator product for a new indication or another innovator product for the same indication or a follow-on biologic, those considerations have to take place in the context of the particular product class and intended use.

DR. WOROBEC: I just have one other question. It slightly changes the subject.

Sometimes things are compared and there are slight differences, whether in the protein or the carbohydrate. And a question is how do we know when those differences matter? You know I think we've seen

a lot of technologies saying that we can -- sophisticated technologies saying we can look at two different proteins or the carbohydrates. And we can tell how similar they are.

But the question is when there are slight differences, what tools do we have to inform us as to when those differences matter?

DR. SEAMON: Well, again, I think you have to look at the whole database of information. For example, I made reference to the fact that when we make very significant changes to some products even though we do not see analytical differences, we will generate a significant amount of clinical data before bringing that to market, bringing that manufacturing changed product to market.

That's because we know that there are examples where changes have been difficult to detect that have led to very serious clinical consequences.

With other products, we know that there have been examples -- we know that there is some level of antibody response.

We also know that the biology would predict that an antibody response against that particular moiety would not lead to a significant

therapeutic consequence. And we also have good, very good analytical data.

In those cases, the amount of clinical data that we would generate to qualify that might be different from the former case. So I don't think you can make a statement that will apply across all proteins.

What I do believe, though, is that when significant changes are made, it's appropriate to consider a certain amount of clinical data to qualify those changes.

DR. ROSENBERG: Let me just -- Dr. Hussain tells me that we have some more time for some general --

DR. HUSSAIN: No, I think we ran out of time.

DR. ROSENBERG: We ran out?

(Laughter.)

DR. ROSENBERG: Okay. So do we have any time for one last question?

DR. HUSSAIN: Sure.

DR. GOLDING: Yes, I just wanted to ask if you would care to comment a little bit more about the TPO. You mentioned that the TPO in the Phase II

studies was associated with immunogenicity in patients.

What did you learn, if looking back, what could you tell us that you learned from the animal studies? Was it in any way helpful in predicting that this was going to be immunizing?

DR. SEAMON: It was very difficult to predict. I think you actually have to look at the usage patterns. Clearly -- and this information has been published, but clearly these were patients that were receiving the drug sub-cu, not IV. The product was a pegylated product, which was somewhat of a surprise since we would have thought that that might have inhibited the potential for immune response. It was a small number of patients, maybe 10 to 15 out of 400 to 500, so it was still a relatively low frequency but it was a significant event.

So I can't say, I can't comment on whether there was predictability from the animal studies. But I can only comment that this actually, again, in our mind, reemphasizes the importance of looking at some type of clinical data to look not only at immunogenicity but at the consequences of that immunogenic event in the patients.

DR. ROSENBERG: I think to add to that, the fact is that TPO, the endogenous product, is present at such low amounts that we're not inherently very tolerant to it. So for some of those patients, it only took two to three doses to break tolerance.

DR. SEAMON: Right.

DR. ROSENBERG: So there's that factor. And the fact that it is highly conserved across evolution and so even species-specific TPOs broke tolerance, too, in the respective animal species. So we know that there are some proteins to which we're not inherently very tolerant. And those are particularly worrisome.

And many of them, like TPO, happen to subserve unique biological functions. And so it gets -- it can be very troublesome, just to add to that.

DR. SEAMON: Okay. And I think, Marjorie, to your question, you know, the comment that Amy just made is exactly why clinical data will be necessary and each product class needs a careful evaluation in its own right.

DR. ROSENBERG: Okay. Well, thank you very much all. And we'll be continuing these discussions. Thank you.

(Applause.)

DR. HUSSAIN: The last session will start at nine-thirty.

(Whereupon, the foregoing matter went off the record at 9:19 a.m. and went back on the record at 9:31 a.m.)

DR. HUSSAIN: Well, I think the crowd is thinning out already.

Before we get started, I'd like to sort of gauge the interest in making general remarks. Are there folks in the audience who would like to make general remarks after the last panel? If so, please raise your hands.

No? So that's good in one sense. We can end this meeting early. And I think looking at my colleagues here, they'll be happy to do so.

What then we could do is after this panel's set of presentations and panel discussion, we'll sort of close the meeting early. And I'll sort of provide some closing remarks in terms of some information on where to find the transcripts of this proceeding as so forth.

So let's plan for that. After this panel

discussion, we will close the meeting.

Don Baker is one of our speakers. And he has not registered with us. So we don't know whether he is here. If he's here, please raise your hand. Okay. So we have the speaker. All right.

So let's get started. Steve?

DR. KOZLOWSKI: Hi, I'm Steve Kozlowski. I'm Acting Director of the Division of Monoclonal Antibodies.

And this session will address when and how it would be appropriate to streamline or eliminate certain animal or human studies during development of a follow-on protein product.

And during previous presentations, we've seen suggestions that vary from follow-ons doing full ICH numbers and full ICH preclinical studies to those suggesting none at all.

And we've also heard a large variety of factors including things like redundancy of protein for immunogenicity, the utility of surrogate markers, and a variety of other factors, complexity of the molecule, that may play into all this consideration. So we have speakers to address these issues.

And I'd like the rest of the panel to

introduce themselves.

DR. SCOTT: Dorothy Scott, Branch Chief, Lab of Plasma Derivatives, Office of Blood, CBER.

MS. EL HAGE: Jeri El Hage, Pharmacology Supervisor in Metabolic and Endocrine Drug Products in CDER.

DR. SERABIAN: Mercedes Serabian, Chief of the Pharm/Tox Branch in Office of Cellular Tissue and Gene Therapies in CBER.

DR. WALTON: Marc Walton, Director of the Division of Biologic, Therapeutic and Internal Medicine Products in CDER.

DR. DAVID GREEN: Dave Green, Office of New Drugs, Pharmacology, and Toxicology, CDER.

DR. JAMES GREEN: Good morning. My name is Dr. Jim Green. It's a pleasure to be here today to speak to you.

I'm currently employed by Biogen Idec, which is the third largest biopharmaceutical manufacturer in the world. I hold the position of Senior Vice President of Preclinical and Clinical Development Sciences.

I'm trained as a toxicologist. And for the last 16 years, I've worked for two of the three

largest biotechnology companies.

During this time, I've been responsible for a large portion of the development sciences that have been conducted in these organizations and particularly those aspects of the sciences that deal with determining safe use conditions for new experimental therapeutics.

In addition, prior to working with biotechnology products, I spent eight years assessing safety aspects of traditional small molecule drugs in big pharma.

I'm a member of the Pharmaceutical Manufacturers Drug Safety Steering Committee, having served in the capacity of Chairman of that group for two years. And I'm currently Vice Chair of the BioSafe Group within the BIO organization.

First, I would like to state that Biogen Idec agrees with and supports the general concepts outlined by the PhRMA and BIO remarks. In determining the path forward, however, the devil is in the details.

I would like to speak to some of those details today. And my comments will involve minimum data sets.

In Europe, regulatory authorities have already adopted a case-by-case approach and have communicated their considerations in a comprehensive guidance that provides direction and enumerates appropriate considerations.

The directive recognizes that a product claimed to be similar to another one already marketed will require an extensive product comparability exercise. Furthermore, it clearly acknowledges that biochemical analyses of the drug, substance, or product are not sufficient to address all aspects of quality, safety, and efficacy.

Preclinical and clinical bridging studies are needed, the extent and scope of these studies to be determined based upon data submitted and individual circumstances. It is well recognized that the development of biologic therapeutics presents unique scientific challenges to preclinical and clinical scientists who are responsible for determining safe use conditions and efficacy.

The first challenge involves how the product is made and that is shown on Slide 1. As you can see, over time, the way the product is made evolves. A central element of this slide is the

existence of what I refer to as a product equivalence program. This is very different from small molecule drug manufacture and development.

In addition to how the product is made, there are several other unique considerations that are shown on Slide 2. Recognizing that a follow-on biologic will be manufactured by a process that is unique and very different from that of an innovator's, how can valid comparisons be made?

Since a follow-on manufacturer will not have access to any process information from an innovator or bulk drug, is there another approach?

I would like to comment on how a data set like this might be constructed under what I refer to as a product technical assessment program.

First, to briefly review. A product technical assessment program consists of the following key elements: biochemical characterization studies to confirm structural identity, biological activity studies to confirm potency and maintenance of mechanism of action, pharmacokinetic studies to confirm that dosimetry remains unchanged, toxicology studies to confirm the therapeutic ratio and safety profile remains unchanged, and clinical studies to

confirm the pharmacokinetics, pharmacodynamics, safety, and efficacy.

One might be tempted to conclude that if a follow-on product is shown to possess the same physico-chemical characteristics and is shown to be bioequivalent against certain predetermined pharmacokinetic parameters, that is in a head-to-head comparison of the follow-on product and an innovator's product, it can be presumed to have the same clinical safety and efficacy profile as the originator's product for the purpose of its approval.

Although this approach works well for small molecule drugs with very defined characteristics, this conclusion would be erroneous for biologics. There are many examples where process changes were made and unintended consequences to the activity of the product were observed.

These examples, which include antibodies, proteins, and fusion proteins, showed unexpected changes in pharmacokinetics, pharmacodynamics, therapeutic index, and immunogenicity rates. You have heard innovator companies speak to their examples.

Biogen Idec, in particular, knows very well the examples of Alefacept and Avonex where cell

line changes were made during development and unexpected changes in key product attributes were observed. These unexpected effects were only detected in clinical trials and in extensive toxicology studies.

These examples are well known to you and details have been discussed in the scientific symposiums. These examples highlight the fact that it remains difficult to predict with certainty whether a detected product change will be important or not.

It is because of this uncertainty that all elements of the product technical assessment program are viewed as essential for the assessment of safety and biological activity of a biologic.

As previously discussed, it is now recognized by potential follow-on manufacturers and regulatory authorities that the approach currently accepted for generic small molecule drugs is not appropriate as a path forward for follow-on biologics. The path forward at this point in time can only be driven by data and clearly stated data requirements.

What should this data set consist of?

The follow-on manufacturer should be expected to provide a complete chemical,

manufacturing, and control dossier on their manufacturing process. This dossier would be expected to reflect current state of the art requirements, ICH compliance, GMP compliance, the number of batches, et cetera.

Beyond this, the key elements of a product technical assessment program can be used to guide the development of a data set that could be considered sufficient to support a regulatory authorization of a generic or follow-on biologic.

The approach would require head-to-head comparisons of the follow-on product to the innovator's product. A more detailed example of such a comparison is shown on the following slides and in Table 1 of the paper submitted to the docket.

For example, in the biochemical analysis assessment, a sampling strategy that involved a head-to-head assessment of samples collected from various lots over time and regions could generate a data set to assess statistical equivalents of what might be defined as key product attributes. I have attempted to provide in each slide a view of what is the likely probability of technical success might be in each area.

In this case, I would assign a low to medium probability of technical success because we are starting with two fundamentally different manufacturing processes. However, the data could show otherwise.

In the pharmacology and bioassay areas, a similar statistical approach could be used. In this case, there would not need to be a requirement that that assay used be identical to that of the innovator. The assay need only measure an important biological endpoint. In all likelihood, the assay formats will have evolved due to advances in science.

It would also be important to have comparative data generated in a relevant animal model of disease, if available.

In the pharmacokinetic area, statistical equivalents of important disposition parameters would need to be shown to support claims of equivalent dosimetry.

In the toxicology area, to support the use of a multi dose therapeutic, in this case, a 14- or 28-day repeat dose study in one pharmacologically-relevant animal model, could support the initial conclusions regarding projections for clinical safety.

Importantly, this study could allow the first assessment of whether or not a major difference in qualitative immunogenistic profiles between the two products are observed.

For example, a data set that showed a follow-on biologic's immunogenicity profile to be neutralizing and blocking compared to a non-blocking profile for an innovator's product or to induce an increase in glomerular hypertrophy at a rate or severity that is higher than an innovator's product should raise substantial concern early in the development program.

In the clinical area, a single dose bioequivalence and repeat dose safety, immunogenicity, efficacy study would need to be demonstrated. For a chronic use therapeutic, the trial should be at least six months based on consensus medical science opinion at the time.

Validated surrogate markers should be viewed as sufficient to support approval. And provided that the prior technical assessments were met, you could contemplate the probability of technical success for the clinical assessment as being on the order of medium to high.

Furthermore, it might be possible to further modify the data set required based on case-by-case considerations. These considerations would involve product quality and complexity of the product, the disease to be treated, product-specific clinical pharmacology or toxicology issues, and product-specific clinical trial design issues. And these considerations would be very product and situation specific.

The approach described is rigorous and the requirements are challenging to meet. The fact that the follow-on manufacturer is starting with a new cell line and process, new assays, new reagents, new procedures that are unique to their own product and facility raises, in my view, a high probability that numerous differences between the two products will be detected in head-to-head comparisons.

In a tiered approach, however, these potential differences can be enumerated and assessed as to their likely impact on safety and biological activity relative to the marketed product.

So in summary then, what I have hoped to have demonstrated in these brief remarks is that there are clearly unique safety issues that are confronted

by developers of biologics. There are safety issues ranging from the induction of unexpected target organ pathologies, infection, the induction of cancer, to just about everything in between.

The induction of an adverse immune response is a concern but should not be the only concern. Many of these issues are complicated by our limitations in current systems that are employed to assess and predict safety.

Because of these unique issues, compared to generic small molecules, the extent of non-clinical and clinical testing support to support a registration approval must be more extensive.

In addition, the historical significance of biologic case studies in which unanticipated changes in a product's key attributes were observed as the result of changes in the manner in which the product was made must be considered when defining guidance requirements.

And finally to help frame the discussion of this issue going forward, we have proposed for consideration a process for constructing and evaluating minimum data sets that should be considered adequate to support regulatory approval of a follow-on

biologic.

Thank you for your attention.

(Applause.)

DR. SERABIAN: Jim, I have a question.

I mean with regard to the toxicology studies, we all know there's potentially species-specific issues with respect to these products. There have been at least one, I'm aware of, product that's been approved based on preclinical studies using a homologous protein. How would you, when you talk head-to-head comparison, deal with something like that?

DR. JAMES GREEN: That's a tough question.

DR. SERABIAN: Yes.

DR. JAMES GREEN: And that's situation specific.

In that particular case, well, let's say where we are with the science today and construction, essentially, of animal models that are responsive is doable.

Now I think the thing that you have to trade off is that the onuses should be on the follow-on biologic manufacturer to prove safe use conditions. And if there are test systems that are available and

can be constructed that demonstrate those safe use conditions, they should be required to use those.

Whether or not they would be held to the same head-to-head comparison in that case with an innovator's product, I think that would be situation specific.

But in my experience, there aren't too many of those situations where that kind of a very unique narrow focus occurs. But in that case, I think you would have to have some active discussion.

DR. DAVID GREEN: Would you care to comment on whether the types of studies that you are thinking of should be confirming or exploratory? In other words, should they analyze whether certain unique features need to be verified? Or should they be more global in their emphasis?

DR. JAMES GREEN: I think they should be global. Certainly the time frame or the database that is available on a particular product-to-product class needs to be considered for considerations that would be designed into a particular study in a head-to-head manner.

But what I would be looking for essentially are important qualitative or quantitative

differences in a well designed head-to-head study. And depending on, you know, for example, if there was a -- I think the immunogenicity issue is a particularly good one to think about because contrary to many beliefs, all proteins aren't immunogenic in animals. The response is very highly varied.

But what you'd be looking for essentially here is how does this product compare to the innovator's product. And if signals showed up essentially in that comparison that showed marked differences, that should raise a significant concern, in my view, with respect to how vigorously this is assessed in early stage clinical studies.

Now if there were a target organ issue or a therapeutic ratio issue that was associated with a product class or a particular product, that should be rigorously evaluated in a head-to-head manner.

And if there was a large difference, a large and clinically or toxicologically meaningful difference in therapeutic ratios to this same target organ effects between the two products, that again, that should raise a significant issue that these products are behaving differently and they're looking like very different drugs.

I think what the tiered approach, in my view, provides you with are data sets on multiple levels, essentially, to make these comparisons. You don't really have to have an understanding of how an innovator's product is made. You just to have an understanding, essentially, in appropriate test systems when they are compared how similar or how different.

And if they build essentially on each other, and that's where I got to my assessment essentially of what's the likelihood of a clinical study being successful, moderately to high, well that presumes that on biochemical, assay, kinetic, toxicologic assessments, that you have concluded that there is reasonable similarity or you cannot detect meaningful differences.

Under those circumstances, I think that you may reasonably conclude or see in a data set that in a head-to-head comparative clinical trial, that again these molecules are behaving very similarly with respect to safety and therapeutic efficacy.

And if you can do that in one or two trials as opposed to the dozens of trials that an innovator does to support a registration approval,

that's where the economy is gained. That's also where the economy is gained essentially in the non-clinical toxicologic assessment.

DR. KOZLOWSKI: So in your tiered approach, I mean basically use something that's always attributed to the FDA which is case by case.

And I think how to make some general guidelines or a sense of what would be necessary for different products considering the wide range of complexity, how similar is similar, what do subtle differences impact on what's required later. Do you have any thoughts about whether or not such a set of principles could be set up?

DR. JAMES GREEN: In my view, yes. And I think although this example that is on these slides that I reviewed here describes essentially only one case, a multi dose therapeutic that could be under chronic use conditions, for example.

But I think it's really more the thinking along those lines, how you build a case, how you build a data set. And when you get into essentially the non-clinical and clinical realm, does the prior data set allow you to conclude that there can be economies essentially worked into the development of the

program?

And I would think that if, for example, no differences in target organ effects or non-pharmacological effects were observed, then why require more extensive non-clinical assessments if you have already confirmed on one level what has already been demonstrated?

And this information, for the large part, is publically available so it's available in labels, it's available in summary of basis of approval, it's available in publications that companies make or scientists make.

So I don't think personally that it's that difficult to get a data set both that you can generate or you can bring to bear from published or publically-available information to help support your conclusions.

DR. KOZLOWSKI: And if things like, for instance, understanding the mechanism of action well play a role in how you develop this scheme, then clearly there need to be, you know, an understanding about what a well-defined mechanism of action is. And I think there are no criteria for necessarily assessing that in the same way as we assess other

things.

DR. JAMES GREEN: Absolutely. And I think just on first principles, a product that even a dozen years after an innovator product or products are now available and on the market and we still really don't understand how it works, but in that sense you've got a lot of clinical experience that you can judge, and if it works, it works.

But for some of these molecules that are pleiotropic, that have narrow therapeutic indices, we really should be probably more cautious with molecules with that kind of a profile than ones which appear to be relatively benign, innocuous under most conditions, and highly specific.

DR. KOZLOWSKI: Okay. Thank you.

(Applause.)

DR. BARRON: Good morning. Thanks very much to the FDA for the opportunity to talk today on the concept of follow-on proteins and the need for undergoing thorough clinical testing.

My name is Hal Barron. I'm the Senior Vice President of Development and Chief Medical Officer at Genentech. And today I'll be commenting on this question from a relatively purely clinical

perspective, given my background.

Before I start, I just want to make a couple comments that I think were highlighted yesterday and form the foundation for some of the conclusions drawn in this talk.

First, and these were brought up by a number of people speaking yesterday, including my colleagues from Genentech, and I think the first thing is that it's very clear that the manufacturing of proteins, the process of doing that is a very complicated one.

And what I think we heard extensively is that when we know what's important, we can measure it very well. In fact, extremely well and, in fact, the technology for measuring those things is getting better and better.

The issue that I think really highlights the need for clinical testing is the fact that we don't know what we don't know. And because of that, the product is the process. And those are sort of the guiding principles for some of the conclusions you'll hear me draw.

If we can't rely on basically preclinical evidence for therapeutic equivalents, then we're left

with human information, studies -- data from studies in patients. And the first question then comes up, can we rely on human PK and PD data? Or are we forced to consider information from clinical trials?

Well, first -- and these are conclusions that will be supported, I think, by the remaining slides -- first, bioequivalence is, in fact, inadequate. Pharmacokinetics are not a valid surrogate for the clinical effect for most biologics. And although I won't have time to go into too much detail about this, pharmacodynamic endpoints, while they may reflect biologic activity, are usually unreliable surrogates for clinical efficacy and certainly for clinical safety.

And thus, because of the points made, follow-on proteins need to undergo enough clinical testing to ensure that they are therapeutically equivalent to the approved protein.

Now in thinking about therapeutic equivalence, I refer back to the talks from yesterday morning in talking about terminology and using CDER's definition of therapeutic equivalence, we understand the bar that the follow-on proteins are being held to.

First, drug products are considered to be

therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. And this is a very high bar.

I'd like to just -- because I think we've talked around this issue quite a bit over the past day and a half and I thought I'd give you an example from a clinical experience at Genentech that I think may help elucidate some of the issues that I'm referring to, and the example is that with a drug called Raptiva or efalizumab.

Raptiva is a monoclonal antibody to CD11a, a beta-2 integrin expressed on leukocytes, which are involved in the binding of the leukocyte to the endothelium and transmargination into various tissues. And we studied this monoclonal antibody in moderate to severe plaque psoriasis.

Raptiva was originally manufactured by XOMA and used in the early Phase I, II, including the beginnings of Phase III trials.

The manufacturing was transferred to Genentech and we made manufacturing changes but our

intent was to preserve the distribution of molecular forms. So in some respects, although not a perfect example, this might be analogous to a follow-on protein.

It's important to note that we did observe what we thought were inconsequential analytical and formulation differences. We subsequently evaluated these differences in extensive analytical and biological animal studies and found that there was no effect on the pharmacokinetics of this new entity.

However, because of the process changes, we decided, along with guidance from the FDA, that further testing in a human bioequivalence study was important. In this study, we demonstrated, to our surprise, significant differences between the XOMA and Genentech material with the Genentech product having a higher area under the curve, again pointing out that you don't know what you don't know.

We actually tried to understand this observation and performed a second human bioequivalence study which investigated the Genentech antibody in the XOMA and Genentech formulations. And this study demonstrated bioequivalence, confirming that the formulation was not accounting for the

differences. And here's the data shown here.

You can see the ratio of the Genentech to XOMA material. When one looks at the area under the curve, you can see about a 30 percent increase in the area under the curve with 90 percent confidence intervals that exclude one suggesting this isn't due to chance alone.

And in the bottom of this data slide, you can see that when the Genentech antibody was put in the Genentech or XOMA formulations, you can see that the area under the curve and Cmax were essentially similar.

In a very, very simplistic way, one can consider this PK data to lead us to believe that administering approximately 70 percent of the dose of the Genentech antibody would have similar effects to the XOMA antibody. But, of course, we don't understand why the PK was different.

The unpredictable nature of these PK changes really forced us to consider repeating Phase III, repeating the entire clinical efficacy and safety profile before obtaining a license.

Interestingly, when we looked at the clinical data between the two molecules from an

additional Phase III trial, we saw trends for a lower PASI response. And I should point out that just to highlight this graph, on the Y axis here is the percentage of patients with the what's called PASI 75. And a PASI 75 is a way of scoring plaque psoriasis with a PASI 75 being a 75 percent reduction in the severity of the plaque morphology and distribution.

And as you can see here, although the placebo rate is very low at two and a half percent, the observation within the XOMA study was that the PASI 75 was almost 39 percent whereas the rate with the Genentech material trended it lower at about 27.

Now I should point out that these are not a head-to-head comparison. These represent two different studies because we didn't have the same material to do a head-to-head but it certainly raises the possibility that, again, the molecules have different activity.

And certainly the fact that the Genentech material had a higher area under the curve, this was surprising.

I should point out, and I don't have time to go into extensive detail, but we looked at the safety profile of both these molecules and, in fact,

were quite similar. But very important to be studied in a very large number of patients before making the conclusion that this is adequate for licensure.

So we've learned a lot from a number of examples at Genentech. This one, I hope, highlights some of the important things that we learned, that changes in manufacturing process that we believed, as the innovator, should not have actually significant effects on the property of the protein, in the case of Raptiva resulted in clear differences in pharmacokinetics.

Further, the higher drug exposure did not result in any greater efficacy. In fact, as you saw, there might have been a trend towards lower efficacy.

Given the complexity of therapeutic proteins, the impact of changes in pharmacokinetics and probably pharmacodynamics for many molecules, on the safety and efficacy cannot be reliably predicted.

Therefore, to establish therapeutic equivalents for follow-on proteins, it will be necessary to conduct controlled clinical trials to clearly establish efficacy and safety profiles rather than to rely on any preclinical data or even human PK/PD data.

There is a number of ways that I think we could discuss as to how to identify the size and the endpoints of clinical trials. But the key point is not if, it's how, we should do these clinical trials because it's very important as a patient or a physician prescribing these follow-on proteins, if the patients and doctors are going to believe that these are therapeutic equivalents, the data needs to support that.

So I'll end with that and I'd be happy to answer any questions.

(Applause.)

DR. DAVID GREEN: You mentioned that we shouldn't rely on pharmacodynamic endpoints but then you used the terminology or wording unreliable surrogates. Well, some surrogates, obviously, have been validated and might be considered pharmacodynamic markers.

So could you elaborate a little bit on what you mean by unreliable? Is that to mean that it's unassociated with a mechanism of action that would be predictive? Or is it unreliable in that it can't be reproduced in a definitive way and varies among tests?

DR. BARRON: I guess as a clinician, my perspective on surrogates is a little biased. But I think that pharmacodynamic endpoints, while there are some that are validated and I think can be used, in general, they are validated for a given molecule and a given mechanism.

I think it's challenging to extrapolate that. And even some of the surrogate markers that we've used in medicine even over the years have turned out to be less reliable than we had hoped for.

But I think that if the FDA and the clinical community all agreed that the pharmacodynamic endpoint was extremely predictive of the clinical efficacy, I still think we're left with wondering whether it's predictive of the safety experience.

And so when looking at pharmacodynamic endpoints, I think one has to take into account both safety and efficacy and it's sometimes very difficult to predict these safety events. And so I still think you're left with clinical trials to understand that component of the risk-benefit profile.

DR. KOZLOWSKI: In the case you presented, the pharmacokinetics had changed because of a change that you could not measure otherwise. But it was

picked up in this assay. So, in fact, the real worry would be something that wouldn't be picked up in such an assay and then have a clinically different outcome.

DR. BARRON: I think you're right. And that sort of points out maybe one of the flaws in this example in that there was a PK difference. But I think what I was trying to highlight is that we did pick that up and we could pick that up.

And that wouldn't be typically missed because of -- but because the changes were thought to be insignificant because the -- and I didn't go into significant detail on this, but the preclinical PK and PD data was identical.

There was really very little reason to, from our perspective, be terribly concerned that this human PK study would be different. It was important to do and it highlights the fact that when subtle changes are made, things can happen. And, in fact, even the PK changes, it isn't exactly clear what that means clinically.

One almost has to imagine a very robust clinical data set being regenerated with this new change. And, again, we don't even really fully understand what led to that PK change. So there's

probably a whole spectrum of other things that remain unknown.

DR. KOZLOWSKI: Yes. This is more of an analytical question but we've heard certainly presented here a lot of new technologies for looking at the differences between proteins, some signature-based, on -- I mean do you think there's potentially a way of further evaluating this difference with either technologies that you have or that are available?

DR. BARRON: Yes, I think that's a great question and, again, my background is clinical so I'll answer it as a clinician. I think these are extremely important in the sense their positive predictive value is very important. And when you see a difference, I think that leads to further testing that needs to be done.

The problem is when you don't see a difference, what else haven't you measured that might be important? It's somewhat circular in the sense that you can always use this argument but the process is the product. And when you make process changes, there are so many unknowns that it becomes very difficult to know whether these signatures being the same, what clinical significance that's going to have.