

DRUG INFORMATION ASSOCIATION

FDA/DIA SCIENTIFIC WORKSHOP ON FOLLOW-ON
PROTEIN PHARMACEUTICALS

BREAKOUT SESSION E:
IMMUNOGENICITY STUDIES

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3:36 p.m.

Marriott Crystal Gateway
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M O D E R A T O R S

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P R O C E E D I N G S

DR. WOROBEC: I think we ought to get started. I'll be your moderator for this session. My name is Dr. Alexandra Worobec, and I'm from the Division of Therapeutic Biologic Products in CDER in FDA.

And this is Breakout Session "E," "Immunogenicity Studies." But before we proceed with our format, which will be a point and counterpoint format, I'd like to go over some of the ground rules. For those of you who have been at the session previous, just bear with me. I'm just going to run through these for the rest of the audience.

What we plan to do in the next hour and a half is to go through four different issues that we think are quite critical in evaluating immunogenicity, in order to address it in terms of follow-on biologics. And what we'd like to do is look at scientific issues; not looking at them from a legal or regulatory perspective, per se. So we really want to keep this a science-based

discussion.

Furthermore, the FDA moderator comments do not reflect agency policy, but reflect the individual scientific concerns of each individual moderator. Industry moderators should identify whether their comments are representative of themselves or of their industry organization.

As I stated previously, our format will be a point and counterpoint discussion, with four different discussion topics that will be given approximately 22 minutes per question.

Persons in the audience should speak to the issue by providing data. And no more than five minutes will be allotted per individual. You should speak clearly into the microphone. That was an issue with our last session. And please identify yourself by name and your affiliation.

The data presented should be submitted to the agency under Docket Number 2004N-0355. And eventually this will--We'll find out how this is going to be posted. And the moderators may present more specific questions to stimulate and focus the

discussion, especially if we're veering off the topic.

Without further ado, I want to have each of my panel members introduce themselves briefly and state their affiliation.

DR. LOZIER: Jay Lozier, at CBER, Division of Hematology.

DR. ROSENBERG: Amy Rosenberg, Division of Therapeutic Proteins, in CDER.

DR. STEIN: Katie Stein, MacroGenics.

DR. GERRARD: Terry Gerrard, TLG Consulting.

DR. WOROBEC: So we're going to go to the first topic, which is going to be related to immunogenicity and product quality attributes. And for the point, we'll have Dr. Stein present.

DR. STEIN: Immunogenicity of protein products cannot be predicted by biochemical analytical techniques alone. Comparative side-by-side testing is needed, and up-to-date methods should be used.

I would add to this that the data that we

have on the existing innovator products comes from a variety of sources. It comes from different clinical trials, patient populations, patients treated with various concomitant medications. The assays are all unique to the sponsor.

And we cannot compare across the board. Even if there are multiple products that have similar properties, such as two different antibodies to TNF-Alpha, you can't compare across the board, because the assays are unique to the sponsor.

So I think there's not sufficient data out there to allow us to be able to extrapolate from one to another. Side-by-side testing is needed.

DR. WOROBEK: All right. For the counterpoint, Theresa Gerrard.

DR. GERRARD: I agree that immunogenicity cannot be predicted by product attributes for a novel protein. But we're not talking about prediction; we're talking about a comparison. We're not in a vacuum. We're comparing product attributes of the innovator with the biogeneric.

And there are many factors that can affect immunogenicity: the population, the dose, the route. Those are all staying the same. So what we

need to control are the product variables.

Now, the biogeneric manufacturer, follow-on manufacturer, would have to do rigorous side-by-side comparisons. And they probably would have to use more up-to-date analytical techniques than were ever done for the innovator. And I think we've listed some of what we think are some of the important attributes to look at.

Sometimes the innovator didn't do these because the techniques may not have existed at the time of approval. They did what was appropriate then. But the biogeneric has to meet today's standards and test for product attributes by today's standards.

DR. WOROBEK: Do we have any comments from the audience with regard to the point or counterpoint?

DR. STEIN: I'll say this, as I did in the last workshop. While you are all running to the

microphones, let me add a point.

Many of the tests that Terry enumerated are done on drug substance where you have a high concentrated material. And I think it's very difficult to be able to pick up some of the impurities, some of the subtle changes, when analyzing drug product alone. And therefore, because the follow-on manufacturer doesn't have access to the drug substance of the innovator product, it is imperative that side-by-side comparisons be done.

DR. GERRARD: And clearly, when it comes to immunogenicity, the formulated drug product is what counts. That's what goes into the patient. I think that we can't underestimate the effects of formulation on things like solubility, aggregation, things that are important and might be associated with immunogenicity. So that's the appropriate comparison, is drug product to drug product.

DR. TANIGUCHI [In Audience]: Gary Taniguchi, BioMarin Pharmaceuticals.

I'll speak to what Valerie Quarmby

eloquently spoke to a little bit last session on the assay development validation site things, and reiterate how critical it is for the assays. And they are so complex that you really need to look at several different assays.

Also, side-by-side comparison is necessary because what you might see in a RIP you may not see in an ELISA [ph]. And I could go on and on about how the assays are very complex. It takes a very well experienced scientist and group to put these assays through development and validation. So I think it's really necessary to do a side-by-side comparison, and with a very good validated assay.

DR. GERRARD: I think we all understand the complicated nature of doing these assays. Do you think there's only one group that can do them? And they live in south San Francisco?

DR. TANIGUCHI [In Audience]: No, not necessarily south San Francisco. But over the past three or four--Yeah, Marin County.

[Laughter.]

DR. TANIGUCHI [In Audience]: No. Actually, you know, in the past four years there have been several meetings about just the

immunogenicity and how complex these assays are. I sat on a committee that wrote the paper where Tony Meyers [ph] lives. And even in that group of scientists, we had several discussions of how complicated these assays are.

And I think that you're talking about these biotech companies that have a multitude of experience with different types of molecules--antibodies, small proteins. And now you're going to have a follow-on biologic do a protein for the first time.

And I'm not going to speak for the processes. You know how complex those are, and those assays are, too. So, no, I'm not saying that no one else could do it, but it takes a lot of experience.

DR. GERRARD: I think it's rather insulting to say that they're making a protein for the first time.

DR. LISS [In Audience]: I make proteins every morning. May I?

DR. WOROBEK: Yes.

DR. LISS [In Audience]: Alan Liss, Barr Duramed.

This is the second session I've gone to,

and this is certainly the beginning of the IFEA,
the "Immunologists Full Employment Act."

[Laughter.]

DR. LISS [In Audience]: And it's clear
that we need it on both sides. And certainly, the
innovator's side has a lot of good scientists. And
I'm hoping, praying, having my background in
biotechnology, that those scientists are going to
generate some of these assays that we're not even
thinking of today. But the right assays are going
to come. And this has to be an imperative of this
meeting; not simply follow-on versus innovator.

On the other side, not all
biologics--Because not all generic companies will
or should participate in this new activity; only
those who understand the investment that needs to

be done and the science that we need to follow into. And certainly, there is a plethora of resumes flowing into my office of people from your companies, looking not to get out, not because it's a terrible situation, but looking for new opportunity to transfer what they're doing into a new venue to create new tests.

So I think this is what we're going to see. And certainly, it is a different picture. But the complexity of proteins will be handled by those few generic companies that are interested and willing and do invest in the right brains as well as the right equipment.

DR. WOROBEK: Alan, I have a question for you.

DR. LISS [In Audience]: Sure.

DR. WOROBEK: For those that can't develop those assays, or they're not sufficiently sensitive, what kind of an approach, if they still want to develop their protein, would you advocate? As a stand-alone, or what kind of a methodology would you suggest they consider using, if they

can't use the appropriate assays?

DR. LISS [In Audience]: Well, I think "can't" is too hard a word. And I think, as any innovator will do, and as certainly the biogenerics, we're trying to pick and choose from the best established assays, but also be innovative and create new ones for perhaps--And I think I certainly would vote for head-to-head comparisons.

And I think what, hopefully, we'll see is better assays from the whole spectrum of characterization to immunology; rather than solely resting on what exists today. And I think that'll be perhaps the biggest fruit that will bear from this whole effort, is these generations of brighter and newer ways of looking at the elephant, to carry over from yesterday.

DR. WOROBEK: Thank you.

DR. SUBRAMANIAN [In Audience]:
Subramanian, from Barr Pharmaceuticals.

For those of you from the [inaudible] side, I have a question. What comparisons does the bio do when you do encounter significant change,

like a cell line change, whatever you do? What kind of a side-by-side comparison do you do prior to launching your new process?

DR. WOROBEK: Anybody from the panel?

DR. ROSENBERG: For significant manufacturing changes, we've asked for immunogenicity studies, and sometimes clinical safety and efficacy studies.

DR. SUBRAMANIAN [In Audience]: These are head-on, prospective, side-by-side comparison type of studies done ahead of time?

DR. ROSENBERG: Certainly, some of them are side-by-side. I don't know about the full range, but certainly some of them are side-by-side studies.

DR. SUBRAMANIAN [In Audience]: Immunogenicity studies, done in tens of thousands of patients?

DR. ROSENBERG: I don't think we've ever asked any company to do a 10,000-patient immunogenicity study. We've certainly asked for high-risk products to do a thousand patients, but I

don't think we've ever asked for higher numbers than that. And we're not likely to ask for higher numbers of that up front. That's not practical.

We might consider, if there was a good reason to do so, to ask to test a substantial number of patients pre-market or pre-release of a new product; and perhaps then to do a phase four commitment to look at more. But we try and exist within reality and what's possible to get in a reasonable period of time.

DR. GERRARD: But this is part of risk management. Certainly, other people have made changes and done just analytical characterization without necessarily doing any clinical studies.

DR. SUBRAMANIAN [In Audience]: Could we then reasonably say that follow-on generics can come into the market with sufficient physical characterization, PK/PD characterization, all types of characterization, and can have a sufficient pharmacovigilance once the product gets to market; and having done some amount of clinical studies, some amount of immunogenicity studies? Would that

be a right pathway to go?

DR. STEIN: I don't think the FDA is prepared to comment--

DR. ROSENBERG: Yes. I think those are regulatory.

DR. STEIN: --on standards today. The purpose of this meeting is to have a discussion and gather data about that.

DR. ROSENBERG: Yes, I--Go ahead, Alexandra.

DR. WOROBEC: No, I agree. This becomes a regulatory question. And I had one, a point of clarification. When you asked your question, were you referring to post-marketing changes, or before licensure, when you talk about cell line changes, etcetera? Or both?

DR. SUBRAMANIAN [In Audience]: With reference to the new innovator drug, I did ask about the post-marketing changes.

DR. WOROBEC: Okay.

DR. BADER [In Audience]: I would just like to make a point that there is a discussion

here that kind of says that we are no longer product by process, and we can go totally analytical. That is not the world that we live in today.

We have to file all changes with the regulatory agencies. Some of those changes require very little, because they're fairly simple. Some require fairly extensive things. Some can require clinical studies. And that's the world that we live in. Because as we live and breathe right today with the innovator products, we have to control our processes, we have to make amendments to the processes and make sure that the product is safe.

DR. WOROBEK: I'm sorry, sir, but could you identify yourself?

DR. BADER [In Audience]: I'm Fred Bader, by the way, from Johnson and Johnson.

DR. WOROBEK: Okay.

DR. BADER [In Audience]: I'm sorry. When you look at changes, we certainly make lots of changes that don't lead to clinical studies. I can

just name a couple that have happened recently.

One is a supplier to DuPont that made a change in their process in a chemical which basically didn't look any different. But then DuPont uses that to make their Teflon, so they notified the pharmaceutical industry that the Teflon they were making was slightly different. And if you happened to be using a Teflon-coated stopper in one of your put-ups of one kind or another, or whatever, that's a change. And so you have to have a discussion with the agency about that.

Any of these changes, by the way, in a company, it really means you go to your regulatory people, your quality people, your analytical people, your scientific technical people, your manufacturing people, and you take a look at this change and say, "Okay, how could that potentially affect our product one way or the other?" And you come up with whatever kind of additional studies you can do.

Another one is a manufacturer of protein

"A" in their fermentation process to make protein "A" changed one of their ingredients in a fermentation broth from an animal drive to a vegetable drive material. Therefore, that could lead to some change in the protein "A," although they couldn't see any difference in it.

Bringing that resin into the company, you had to do extensive studies, laboratory studies, to show equivalence. You have to redo your validation on protein "A" removal and how much might be coming off the column, etcetera; and go through discussions and whatever appropriate filing with the FDA on something like that.

If you look at something like a change in scale of purification, typically changes in chromatography columns, for example, can be done in a linear way. So from the aspect of the molecule, nothing has changed. They see exactly the same environment in the column. That would also be a change that would have to be put forward; although I think the agencies are generally fairly lenient. If you can show you really are linear, you're not

going to get into additional clinical studies.

On the other hand, it's very clear, a cell line change, which doesn't happen very often--I know very few have been done in the industry. But a cell line change, we've had a discussion with the agency on one that we were looking at at one point in time.

The initial discussion is, we start off, this is a new product. If you can demonstrate that it's comparable to your existing product, okay, then we can bring it under a comparability. But you are going to do clinical studies to look at safety, efficacy, and immunogenicity. That's just the way it is.

So I think when you look at the world as it is today, and if the follow-on pharmaceutical protein producers want to play by the rules that the innovators are playing by, and no different, then that's the rules we actually play by right today.

DR. WOROBEK: Thank you. Valerie?

DR. QUARMBY [In Audience]: Quarmby,

Genentech.

I'd like to endorse the point that was made by Dr. Stein at the start of this session; and also, comments made by the previous speaker. I think it's really important to understand that, at least the way that analytical biochemical stands today, it's not possible to predict absolutely the likelihood of an immune response based on analytical testing results.

For that reason, I think it's really important that we pursue immunogenicity studies. I think these need to be done head-to-head to compare innovator products with follow-on biologics, using the same current, sensitive, validated methods. And I really believe that this works needs to be done prior to the approval process; as opposed to in a post-marketing setting. Thank you.

DR. WOROBEK: I have a question for the audience and for the moderators. Do any of you know of instances where there were two products--Interferons, whatever--that were marketed, where they looked extremely similar in

terms of analytical testing, or comparable, and yet they had very different immunogenicity profiles? In other words, was the analytical testing not able to detect something specific that was then seen on immunogenicity testing?

DR. QUARMBY [In Audience]: If I could just comment on that, certainly, when we looked at our Protropin or methionol [ph] growth hormone process early on, material that went into rhesus monkeys, and into clinical subjects as well, elicited a fairly high sero-conversion rate. We modified our process and managed to manufacture material that was ultimately less immunogenic. But we were never able to chemically define the reason for sero-conversion in the early batches of material; despite looking very rigorously with a range of methods.

DR. GERRARD: But that was 20 years ago. I guess you'd have to ask, using today's methods--

DR. QUARMBY [In Audience]: Right.

DR. GERRARD: Today you would have to ask some of that same--I mean, perhaps those methods

were appropriate for the mid-'80s. But I think, you know, you hate to keep bringing that up when, by today's standards, the first thing you'd have to ask is, did that change get rid of aggregates, or something like that.

DR. QUARMBY [In Audience]: Yes. We actually characterized the material very rigorously; went way beyond the standards at the time.

DR. GERRARD: At the time.

DR. WOROBEK: And I think that brings up an issue of what was done in the past. And I was thinking of an example of Avonex and Rebif Interferon-Beta, where they did have different immunogenicity profiles but by characterization were very similar, really could not find any--

DR. GERRARD: Wait. You know, that's often cited as an example where there was reduced immunogenicity. But those two, where one was made in Germany and one was made in the United States, that was done in a different clinical trial. And

that's not a valid comparison. They were done with different assays. That makes it not valid. And they really were done at that point by different companies.

So it may truly be less, but there was a lot of motivation at the time to have--You know, it's a marketing advantage to have lower immunogenicity, clearly.

DR. ROSENBERG: Yes. I could just speak to that a bit. We carefully evaluated those assays, and they were very, very close. So, you know, was it exactly 24 percent-4 percent? There might have been a couple of percentage points difference. But we're very confident that there was a reduced immunogenicity with the product that was subsequently made.

DR. GERRARD: But can you compare across different clinical trials with different assays?

DR. ROSENBERG: I think it's not easy to do that. And I think that you have to be very guarded about the results that you get. But we extensively evaluated the assays that were

used--you know, to as near as we can come. And I agree, we can't be completely sure, completely definitive. The assays were very, very close, and the patient population.

Also, we went back on serum samples. We went back and looked at serum samples from the original trial, and those results. We confirmed, in fact, that what was found back then was valid. So actually going back, having banked samples, was very helpful in that case.

DR. GERRARD: And that's a case where the product really--There were differences. They were comparable, but there were differences.

DR. ROSENBERG: Yes. There were some differences, but they were not deemed significant enough to be comparable. But that's where you get into trouble with comparability exercises. It's sometimes very hard to know what small changes mean. And in this case, it meant something.

DR. WOROBEK: All right. Does anyone else have any questions or comments for the immunogenicity and product quality attributes

question?

[No Response.]

DR. WOROBEK: If not, we're going to move to the second topic, which are animal studies.

DR. STEIN: Animal studies comparing immunogenicity are helpful in elucidating potential differences in product immunogenicity, but are not sufficient. Clinical studies are necessary.

So I would argue that comparative animal studies can tell you if there are differences between products. If a follow-on product reveals new antigenic determinants compared to the innovator product, then that might be something that would stop development right there. But if they are the same, that doesn't necessarily predict the human immune response. And clinical studies will be needed to evaluate this.

DR. WOROBEK: And counterpoint?

DR. GERRARD: Another possibility is that if you do animal studies, again, we understand that animal studies are not predictive of immunogenicity. But again, we're not asking to

predict; we're comparing "A" versus "B," the innovator versus the generic.

If they are not different, no change in titer, no antigenic determinants are seen, no new antigenic determinants--and this is with the caveat that you are using appropriate and sensitive assays--that would reduce the risk enough so that you can do post-marketing studies to follow immunogenicity. So we're not saying not do it, but to postpone it.

If you are going to do clinical immunogenicity studies pre-approval anyway, then why bother to do the animal studies at all? Whereas, I think it can add some value and minimize the risk, so that you then do it post-approval.

DR. ROSENBERG: Well, I think another thing that was mentioned with regard to that is that animal studies are helpful in terms of minimizing the risk in the clinic. So if you saw something in animals that was very different from the innovator, for example, you might think twice about doing a clinical study or further developing

the product. And so I think that has value from that perspective.

DR. WOROBEK: Yes. And actually, that's something we heard in the pharm-tox session yesterday; that irrespective of immunogenicity testing, that there are still toxicity issues for particular products that warrant further study; and that one should not just focus perhaps on the immunogenicity, but also explore those other toxicities, whether or not they are increased or decreased or there are new toxicities in the follow-on protein.

So it's some interesting information that's come out of this meeting that I think really gives us food for thought, in terms of what should be asked for in evaluating these products.

Okay, any questions? Okay. Could you please identify yourself?

DR. VAN DER PLAS [In Audience]: Thank you. Martijn van der plas, National Institute of Public Health, from The Netherlands.

I'd like to offer a counter-counterpoint,

also, from a European perspective. If you look at European guidance that's out there for several years now already, not specifically only on follow-on biologics, but on comparability in general, it says immunogenicity should be addressed by clinical data.

So this is a rather brief but very clear statement. It also seems to imply, more or less, that animal data--Well, there is no mention or reference to animal data. So it seems that the EMEA does not require you to do animal studies, and that results need not be submitted. So that this is only to be done for the manufacturer's own--how do you say?--the manufacturer's own idea, own process of decision-making. Thank you.

DR. WOROBEK: Is there anyone from the EMEA who might want to comment on this?

[No Response.]

DR. WOROBEK: No? All right. Valerie?

DR. QUARMBY [In Audience]: Yes. I'd like to endorse again Dr. Stein's point. I think animal studies evaluating immunogenicity are actually very

useful in elucidating potential differences between products in terms of immunogenicity. But I also feel that they're actually not sufficient.

Back in October of last year, the LC [ph] Health and Environmental Sciences Institute actually convened a panel of individuals from academia and industry and also the health authorities, to discuss this point. And I think one of the major things that generally was a collective opinion there was that animal studies do have utility, but that they do not predict sero-conversion rates or sequelae in absolute terms.

Therefore, I think it will be very risky to consider going into a post-marketing setting in the absence of clinical safety and efficacy data collected in concordance with sero-conversion information prior to marketing.

DR. LOZIER: Which panel was that? Excuse me?

DR. QUARMBY [In Audience]: It was the Health and Environmental Sciences Institute. It

was called the "Roundtable Discussion."

DR. WOROBEK: Right. That was in November.

DR. QUARMBY [In Audience]: Yes.

DR. WOROBEK: In Washington. And actually, I was at that meeting, and the conclusion, or consensus, was that animal studies would be useful--They have to be taken in context, but they could be useful for determining relative immunogenicity; i.e., with formulation changes, and so forth.

But this was actually extensively discussed in terms of non-human primates, lower animals--I don't want to reiterate everything. And actually, that summary is going to be coming out some time. We're going to be reconvening in March to write it up.

DR. QUARMBY [In Audience]: Yes.

DR. WOROBEK: But a lot of the same discussion that came in this meeting was echoed in that meeting. So it's interesting that we're coming to the same conclusions.

DR. QUARMBY [In Audience]: Yes. But I'd just like to follow that by saying that in fact I think it would be inappropriate to put a product

out into the marketplace on the basis of animal testing, in the absence of clinical data in a trial-based setting.

DR. GERRARD: But I think we only see the animal data as part of the picture. You know, this is one piece. You've done extensive side-by-side, the analytical characterization, and then you're doing the animal studies. So it's like a totality of the data.

DR. QUARMBY [In Audience]: Yes. I agree. I think you absolutely have to look at the analytical data, the pre-clinical data, and the clinical data, too, in their totality, before you actually try and put the drug through the registration process. I think it's very important to not skip the clinical side of things.

DR. WOROBEC: Alan?

DR. LISS [In Audience]: Certainly, I also agree with everyone that you can't use just an

animal study to be predictive of immunogenicity. And I don't think anyone, except certain people, thinks that that's what we're trying to do.

Just I was thinking from the previous session. In a previous life, in the world of vaccines, I've worked with proteins that were as characterizable as we could find, were identical. But only using a very crude, or a mouse model, just looking for general antibody, could we find differences that our analytical methods couldn't find.

And in one case, it was found only when used in adjuvant. And in another case with a similar membrane protein, it was found either way, with or without adjuvant. So I think, as a little test tube giving you some more analytical data, animals can be quite useful.

DR. ROSENBERG: Can I just remind people to please give their names and their affiliations very clearly, so our transcriber doesn't have to run all over the place?

DR. LISS [In Audience]: Sorry. Alan

Liss, Barr Duramed. Thank you.

DR. WOROBEK: And actually, one other point is if you have a business card, to leave it with the transcriber. Thank you.

DR. MAIA [In Audience]: Mauricio Maia, Genentech.

I want to focus on the portion of Dr. Gerrard's statement, or her counterpoint, that relates to the fact if no antigenic determinants are seen in the animal. I think the basic assumption there--And if you'll allow me, with all due respect, it's a faulty assumption to make the statement that an antigenic determinant seen in animal, no matter what animal that is, will translate into antigenic determinants that we'll see in humans.

DR. GERRARD: Well, and I think we all understand the caveats that a mouse immune response is not the same as a human immune response. But again, it's a relative comparison. You know, you potentially immunize with the new product and see are you generating anything that is not directed at

the old product. I mean, I'm not talking about the typical; just comparison titer.

DR. MAIA [In Audience]: That's a very dangerous comparison assumption to make.

DR. GERRARD: I think that provides useful information.

DR. STEIN: Well, I would just add that if you see new antigenic determinants by that kind of comparison, you have a warning signal right there. A negative in that doesn't tell you anything. It may allow you to do reduced immunogenicity studies, so a smaller number of individuals, but it doesn't substitute for the need for immunogenicity studies.

DR. WOROBEC: Identify yourself, please?

MS. SENSABAUGH [In Audience]: Suzanne Sensabaugh, Sicor Inc., a subsidiary of Teva Pharmaceuticals.

And Amy, I have an answer to your question. I'm not from the EU, but I do have the exact quote from the EMEA guidance document on comparability of medicinal products containing biotechnology derived proteins as drug substance.

The annex [inaudible] non-clinical--

DR. ROSENBERG: Can you tilt the mike down to you?

MS. SENSABAUGH [In Audience]: Oh, I'm sorry. Okay. I have the exact quote from the EMEA document regarding comparability, and for immunogenicity. It says [reads]: "Immunogenicity must always be addressed by clinical data, unless clinically relevant immunogenicity can be excluded by other means." So just to provide you with that information.

DR. WOROBEK: Any other comments? I'd just bring up something that was mentioned this morning in the talks, just if there are any participants in the audience who think these are actually good animal models, are the immune-tolerant transgenic mice. Or it wasn't brought up, but also the whole neonatal immune-tolerant mouse model. Does anyone here see a role for that, in terms of testing? One comment? Any one of the moderators?

DR. STEIN: I would say it could be useful

if you have the mouse model. But I think asking somebody to generate a transgenic mouse for the purpose of immunogenicity studies would be a little far out there.

DR. ROSENBERG: Yes. Well, that's why Alexandra was bringing up this idea of the neonatally tolerant mouse. But to my knowledge for that--and Huub and Robin and Minu [ph], maybe you can comment, and Wendy--in order to sustain tolerance in those models, you have to have continual exposure to the protein. So you may lose tolerance after a time. But that would be sort of the poor man's transgenic.

I think, personally, that those kinds of models could be very useful in giving you a more sensitive read-out than a normal mouse. And Huub's data spoke to that very nicely, that if you then generate an Interferon transgenic mouse, human Interferon transgenic mouse, and you treat that animal with Interferons, it's less likely to generate the kind of response that you see in normal animals.

By the same token, you have to be careful with transgenic models. Because even though it may be a transgene under the endogenous promoter, the

copy number is important. Whether you're seeing actually physiological levels of the product needs to be documented very carefully.

And moreover, proteins such as Interferons have inherent immunomodulatory activities which, because of the species specificity issue, you're not going to see with the human Interferon in a mouse. So in fact, some of those studies that were done in the late '90s on Interferon, they injected the animals with mouse Interferon concomitantly so that they could mimic the immunomodulatory properties of Interferon.

DR. GERRARD: Actually, I wanted to turn it around and say if it's decided that clinical immunogenicity studies are always needed, is there any added value of the animal models? Because why do that if you're going to have to do the clinical studies anyway?

DR. STEIN: Right. Good point.

DR. ROSENBERG: No, but that gets back to your point, Alexandra, about needing to do animal studies so that you can be sure that before you go into the clinic and any patients, that you have an acceptable safety profile; or that some big alarm doesn't go off because you see a very different

pattern than you see for the innovator.

DR. WOROBEK: Right. It's more than just immunogenicity when we're talking about also a follow-on protein.

DR. STEIN: It may help to determine the size of the immunogenicity drug, if nothing is seen, if there are no differences seen in animals in a setting where you know the products are immunogenic.

DR. WOROBEK: Valerie?

DR. QUARMBY [In Audience]: Yes, Quarmby, Genentech.

If you put recombinant human growth hormone into a mouse model, it very rapidly sero-converts, and your ability to interpret data from that model, as you know, is very limited. So

recognizing that, a while back we actually generated a mouse strain that was expressing recombinant human growth hormone.

Expression levels varied somewhat, but that was actually quite a useful model system to look at growth hormone that had been through various stress situations, aggregates, different kinds of formulations, and so on and so forth, to enable us to tease out better and worse ways of formulating, for example, growth hormone.

So I think in certain circumstances, under very limited situations, you can get useful information from that kind of model. But I don't think in any way that you can extrapolate from the transgenic mouse model what you will or won't see in the clinic.

DR. FISCHER [In Audience]: Stephan Fischer, from Roche Pharma.

If one talks about usefulness of animal studies regarding immunogenicity, I took away from this morning's presentations that we have to be very cautious. And one speaker questioned whether

that makes sense at all.

Now, if I look into experiments where you are trying to raise antibodies with one antigen, you make the observation that immune response in mice, for example, is extremely different. You see differences in different animals with the same antigen.

So I am asking the question, how do you want to make a comparability assessment between two products if an immune response to one, or the same, product can vary a lot in animals? Where is then the use of doing these studies?

DR. WOROBEC: So what you're saying is there's a lot of variability in response in animals, in mouse models?

DR. FISCHER [In Audience]: At least that is an observation you make if you want to raise antibodies in animals.

DR. WOROBEC: Comments?

DR. ROGGE [In Audience]: Mark Rogge, ZymoGenetics.

I think this follows on with actually a

few of the different comments that have been made. You know, antibodies can cross react with other proteins and tissues and in other organs in the body; not necessarily only with the drug product or some element within these drug products. And there can be safety consequences that go along with that. So animal studies can actually provide a lot of value in understanding at least the potential outcome of immunogenicity if it should occur in a human setting.

DR. WOROBEC: Any additional comments?

[No Response.]

DR. WOROBEC: I'm actually going to ask to take a vote, because I'm very curious about how the audience feels on this topic. It's come up over and over. How many of you feel that animal studies should be part of a package to study immunogenicity for a follow-on product? Raise your hands.

[Pause.]

DR. WOROBEC: How many do not?

[Pause.]

DR. WOROBEC: Well, someone's not voting

here. All right. Most people seem to think it should be. Okay.

If there aren't any more questions or comments--Any comments from the moderators?

[No Response.]

DR. WOROBEK: No? Then we'll move on to the third question, which is moving into clinical studies.

DR. STEIN: The design of immunogenicity studies should take into account product and patient factors that bear on immunogenicity, including immunogenicity history of the innovator, probability of immune response, as well as the potential consequences of anti-product antibody formation.

Consequences would include effects on safety, and the loss of effectiveness of the product, as well as the duration of the immune response, there is evidence of possible tolerance, and a diminution of the anti-product response over time. This might be taken into account. And then products that have little risk of hypersensitivity

responses.

DR. WOROBEK: Counterpoint?

DR. GERRARD: And I note the slide says, "Regardless of the immunogenicity of the innovator product, most immunogenicity data could be collected post-marketing," but it really should be "Because of the immunogenicity data of the innovator product."

Again, we should be focused on antibodies; not immunogenicity alone, but immunogenicity with clinical consequences. And that actually is not a common event. Although most, I guess, or a lot of therapeutic proteins can generate antibodies if you look hard enough, those with clinical consequences that are severe are actually very rare.

So we have to take into account the history of the product. Remember, the patient population, the dose, the route, those things will stay the same with the follow-on protein. What is changing is--you know, it's a variation of the product. And those factors that could potentially change can be assessed analytically, so that most

of this can be done post-marketing.

DR. STEIN: Well, I would argue that where immunogenicity has caused a safety concern, we're aware of that, and that's been investigated by companies. But if immunogenicity causes loss of efficacy, and it's a product where only a small proportion or a minority of patients treated respond, you may not have any idea about what the correlation is between immunogenicity and efficacy, unless it's a major effect.

But if you're treating a population of cancer patients, and 30 percent of the population has a good response, you'd have to have quite a large difference to be able to see that in a small study. So that the data are not really out there as to whether immunogenicity correlates with lack of efficacy. And I think only when there are major problems do we really know this.

DR. GERRARD: And I think sometimes when there has been a loss of efficacy, it is transient; that there is a temporary period where patients do lose efficacy, and whether it's induction of

tolerance, which is probably what is likely going on because you're continuing to administer the product, you can either dose through or the antibody titers go down.

DR. LAWTON [In Audience]: I just wanted to comment.

DR. WOROBEK: Could you identify yourself?

DR. LAWTON [In Audience]: Sorry. Alison Lawton, from Genzyme Corporation.

There is one set of clinical studies that you can do to compare the rate of antibody formation between two different products. One of the issues I want to raise specifically is about this issue of interchangeability and switching patients. And I think that it's a very different aspect to switch a patient from one protein to another. And I think that's a very important clinical study that needs to be done, if we're talking about being able to switch or interchange these products.

DR. WOROBEK: Thank you. Valerie?

DR. QUARMBY [In Audience]: Quarmby,

Genentech.

I realize that in some cases antidrug antibody responses are transient, and in some cases they actually lack clinical sequelae. But there are in fact really important clinical sets of circumstances where people sero-convert, develop neutralizing antibodies, and then lose essentially their capacity to respond to a therapeutic. And I believe that the incidence, or relative incidence, of neutralizing antibodies to the various Beta-Interferons is a case in point, where I don't think one can dismiss sero-conversion as a transient thing that's of little clinical consequence.

And I think it's really important to design immunogenicity studies to take into account product and patient factors. I completely agree with Dr. Stein's point here. But I'd like to say that I think it's also really important to acquire immunogenicity data within the context of clinical trials that are actually capturing safety and efficacy information, too; so that one can actually

look at antibody data along with PK data and PD data and a full safety database.

I think it would be a mistake to run a study solely for the purposes of acquiring immunogenicity data. And I further believe that all of those data should be acquired in an adequately powered study prior to registration.

DR. WOROBEK: Okay.

DR. GERRARD: So you do see any abbreviated pathway? Because it doesn't sound like any abbreviation.

DR. QUARMBY [In Audience]: I believe that the follow-on manufacturers should be held to the same standards as innovators in this regard, because I think that, again, the whole purpose here is to assure oneself that we're putting a safe and effective drug into the marketplace.

DR. GERRARD: But I think that raises a different issue, because basically you're saying that there can be no such thing as a follow-on protein--

DR. QUARMBY [In Audience]: No, no.

DR. GERRARD: Now we're deciding on what are the scientific issues for developing a follow-on protein. But if they have to do a full

clinical efficacy immunogenicity pre-clinical, I think that's called a BLA.

DR. QUARMBY [In Audience]: But I would argue that if you're putting a biologic out into the marketplace, you need to do due diligence on that. And there may be certain areas that you can streamline. I'm not sure. It's not my part to make a regulatory call on this. But I think it's very important, as you're putting something into the marketplace, to do due diligence and really assure yourself, as best as you can, of safety and efficacy. And I don't see any way around getting that data in the clinic prior to registration.

DR. LISS [In Audience]: Hi. It's me again, Alan, Barr Duramed.

First of all, I agree with many of the points that the last speaker had. And certainly, there is no attempt to, again, out of context, design a clinical trial without lots of preliminary

data that gives you the various uncertainties relative to the innovator. That allows you to ask the right questions.

And you know, it's really confusing doing the same as the innovator. Because in most cases, that's inappropriate, because the rules were different back then, and we know more. We don't want to go to the same low bar that was appropriate at that time, because the bar has to be changed due to the march forward of science.

And I think it's critical, again, that the message of trying to do something because we don't want to do it is certainly not in any of the pictures of the move forward. We want safe products. We want to learn as much as we can from the products already in the market, and try to ask the better questions. And really, I think it detracts from the whole moving forward, the continual notion that we're trying to abbreviate everything just for the sake of abbreviation.

DR. HARRIS [In Audience]: I'm Reed Harris, with Genentech.

And I wanted to follow up on what Katie Stein had said, that you consider the product and the patient factors when you make a decision about

whether or not immunogenicity testing needs to be performed. And I'm wondering if we should also consider the production host cell line.

You know, does the agency have greater or lesser concerns when things are made, for example, in bacteria that are in inclusion bodies that need to be refolded, versus periplasmic secretion, versus yeast or [inaudible] cell lines? Is there a greater or a lesser risk, I guess, based on the production code?

DR. ROSENBERG: Well, I mean, I think you're getting to general issues. And there are different issues when it comes to different cell substrates. And the adventitious agent issue is different. Issues about aggregates are different, because frequently with inclusion bodies you tend to have more aggregation. With E.coli you have no glycosylation. That has a whole host of issues associated with it. With newer transgenics--for

instance, plants, chickens--there's a whole host of other issues that are associated with that.

And so, yes, I mean, we certainly have issues even when a cell line from the same strains is changed for one reason or another, perhaps to adapt to serum-free conditions. So, yes, I mean, that raises a whole specter of issues.

But what are you trying to--I mean, how are you connecting this to a follow-on? Presumably, the follow-on would be using the same cell substrates as the innovator, and not doing an E.coli version to compare to a CHO version of something.

DR. HARRIS [In Audience]: So for example, if a follow-on manufacturer used E.coli production, they would have to use the same either inclusion body preparation or versus periplasmic, in order to be considered a follow-on? Or could you have two different ways of using bacteria for expression and still qualify?

DR. ROSENBERG: So you're talking about the situation in which one would use an inclusion

body and one would have actually soluble--It would be secreted into the medium? I mean, they're two different products. I don't know. You know, you'd have to look at--I don't think that those would be considered similar, but I would really need to look into that a little bit more.

DR. HARRIS [In Audience]: Okay. Thank you.

DR. FACKLER [In Audience]: Paul Fackler, with Teva Pharmaceuticals.

I just wanted to speak to the abbreviated process. Admittedly, if what is required for a follow-on protein is a full BLA, we've wasted two and a half days. I think what we're suggesting is that the same process that a brand company might use if they moved their site of manufacture halfway around the world, or if they changed their cell line, presumably they go through a somewhat abbreviated process to receive approval to launch a product after a process change like that. And I think that's the kind of abbreviated process we're suggesting might be appropriate for a follow-on

protein pharmaceutical.

DR. WOROBEK: Thank you.

DR. STEIN: Could I just address that?

DR. WOROBEK: Yes.

DR. STEIN: And say that when it's the same manufacturer you're dealing with the same reference standard, the same assays, and a whole history of analytical data on that product. And often, it's the same process. It may not be. There may be modifications. And so you have that comparator data which a follow-on manufacturer wouldn't have.

MR. GARNICK [In Audience]: Bob Garnick, Genentech.

I'm going to follow on a little bit with what the last speaker just said. In listening to this debate for the last few years, in fact, what strikes me the most is the highest similarity between a follow-on biologic and an innovator's product in this case is the comparison to the innovator who changes their cell line and process simultaneously.

The reason for that is that the follow-on would never have the same cell line as the innovator, because of legal issues; nor would they

have access to their recovery process. So they would produce a product which is different in measurable physicochemical and biological manner.

So let's take the situation, what if it was we, as an innovator. What would we do in that situation? And the answer to that would be very clear. First, as you remember my presentation at the first meeting and which was submitted to the docket, Genentech's position has been to not change the cell line if at all possible, period. And that's always been our mantra. Nevertheless, there have been times in which it has been done.

And in those cases, we would do a complete analytical characterization; complete biological characterization by every known methodology, including orthogonal methods, available to mankind today; followed by animal PK and PD. And if the animal PK and PD showed differences, we would assume we have a problem. If it didn't, we would

then continue on to a human clinical trial, looking at issues for immunogenicity. Because again, the impurity profile has changed.

The cell line change introduces extreme differences into those products that can be detected and measured. And we've done this a million times, so we have that experience. And I think others share that. So I think the mantra should really be, yes, it should be similar to what an innovator would do in the case of such an extensive change. And I think it's just as simple as that.

I would also add that I think post-marketing surveillance for rare adverse events is still appropriate, even after the clinical trial shows no particular change. And I think that would be an example of how we could actually move forward in this debate.

DR. WOROBEK: Yes, I actually think you bring up a very important point in the role of post-marketing surveillance and some of the sort of pitfalls that we fall into where the adverse event

reports come in, but the physicians or the clinics that see these patients haven't done a very good evaluation. And you know, how can we perhaps better that, in terms of trying to get levels of--look at immunogenicity in that context, and also maybe measuring serum levels of the protein? Because that would be invaluable information. I think a lot of times that's not collected.

MR. GARNICK [In Audience]: Yes, very important information.

DR. WOROBEK: Yes.

MR. GARNICK [In Audience]: I think post-marketing surveillance registries, these are things where we have discovered many interesting clinical sequelae in our products which in the future may be the second-generation molecules which could address those particular issues.

Another point to make that I think people have said [inaudible] the follow-on biologic manufacturer, while they may wish to have an abbreviated pathway, has a tremendous advantage over the innovator. And that is that they have a

molecule they know works in man to go after. That's something we often don't have in our clinical trials. So the cost of the additional studies to ensure that their products are safe and efficacious in the patients who have another alternative is something that we should not try and decrease in any way, shape, or form.

DR. GERRARD: Actually, I absolutely agree with Rob in the pathway that you've laid out, as far as extensive physical, chemical, biological characterization, the animal PD. And then if you see differences, it might require a human PK/PD to see differences. It might require clinical data. I think that was proposed in yesterday's session by one of the plenary speakers, that that may be an appropriate path.

MR. GARNICK [In Audience]: I'd just point out despite the characterization, I don't think--I think maybe people have said that, and I certainly, as an analytical chemist, would say this. I wouldn't count too heavily on analytical or biochemical characterization. I think someone used

a pyramid approach, with clinical studies at the very top of the pyramid. I would invert that. I think the human clinical studies are the most important factor, in terms of the safety and efficacy.

And the analytical characterization is important, and it's clearly a great sign if everything looks great. But it should not be taken as the be-all and end-all. That would be a terrible mistake.

DR. STEIN: I'd just like to make a point that I've made a number of times before in the last couple of days. And that is that the final product is not the most sensitive way to look for small differences between products. And what the innovator manufacturer has as drug substance can be concentrated, which is where the bulk of the characterization is done when process change is made.

The final product is something you need to look at, and you need to know what's in the vial. You need to have a potency assay. You need to have

lot-to-lot consistency. But the bulk of the characterization is done on the drug substance.

DR. GERRARD: But with regards to immunogenicity, it's exactly--It's what's in the bottle that counts. Because that takes into effect, you know, the formulation issues that we know can affect the immunogenicity.

DR. STEIN: And that you can only determine in the clinic. In other words, you can't look at the drug product and compare that to the innovator product and find those fine differences, unless you go into the clinic.

DR. FACKLER [In Audience]: I just wanted to echo some of those same comments that were made.

DR. WOROBEK: Identify yourself, please.

DR. FACKLER [In Audience]: Sorry. Paul Fackler, Teva Pharmaceuticals.

Admittedly, the clinical experience is the bottom line for comparable safety and efficacy. The problem with a clinical study to determine that is its insensitivity to subtle differences between products. And I think we've learned that lesson

over and over, that analytical tests are so much more powerful to detect very minor differences that may have no clinical difference.

And that's not to say that analytical is the end-all for comparing two products. That's why I think all along we've been proposing that there be the full complement of CMC documentation in a follow-on program that there is in the original BLA; and that subsequent to that, one would do some pharmacokinetic comparison, which again is significantly more sensitive, I think, to subtle differences in products than clinical studies.

In the session just prior to this next-door, where we were talking about clinical studies, there was an example given for Raptiva, where the process was moved from one site to another, and the analytical characterization was identical, or comparable. And the biological comparability passed, but the pharmacokinetic comparison wasn't bioequivalent by the statistical criteria. Yet they went ahead and did a clinical study, and showed that the early process and the

later process had the same safety and efficacy. Which I think makes the point for us that the pharmacokinetic study is a much more sensitive or discriminating method, and one shouldn't rely solely, I think, on clinical studies.

Again, not to take anything away from the bottom line that a clinical study provides, but I don't think it has this discriminating power many of these other tools we've discussed this week do.

DR. ROGGE [In Audience]: Mark Rogge, ZymoGenetics.

You know, when I gave my presentation yesterday, I was trying to make a point that maybe PK can provide some discriminatory opportunity, but there are also times when it doesn't. I mean, I know this Raptiva example came up. And I wish some colleagues from a former company of mine were here, to see if I could have permission to talk about this, so I'll be vague. But I worked on a product at one time only a few years ago that seemed to be working fine, and the PK data looked fine. And we went to new cell process, and the new product was

five times less active. And that was at the end of a very large phase two trial when we found that out. PK didn't discriminate that. And in fact, I don't think the company still understands why that loss of activity occurred.

DR. WOROBEK: Thank you.

MR. GARNICK [In Audience]: Bob Garnick, Genentech.

I'd just comment on that, because I lived through it. The situation was that the processes were changed. By the way, the cell line was the same between the two processes. And they were transferred, and the product, by bioanalytical and analytical methodology, as well as animal PK, looked completely comparable. And in the phase three clinical trial there was a definite, significant difference in efficacy observed.

We then went to a human PK study, and we did find differences. We didn't know what they meant. We had no clue whether this was the vagary of the assay at the time. And we then immediately went into a full human clinical trial.

Those results came out such that that product was approved based on the process that was transferred to Genentech. It was that product, and

it was different--okay, slightly different than the original. So it's not exactly as how this has been twisted. Basically, the bottom line was, the only thing that resolved Raptiva was the human clinical trial.

DR. WOROBEK: Very interesting. We had another comment, question from the audience?

[No Response.]

DR. WOROBEK: No? All right. If there are no more comments or anyone from the audience, I'd like to turn to our last question, which is another aspect of the clinical immunogenicity testing; meaning what trial designs would be most helpful in determining whether the follow-on is comparable to the innovator in immunogenicity? And for the point, Katie?

DR. STEIN: Given differences in key attributes of antibody assays and reduced clinical testing overall for follow-on products, comparative

side-by-side testing is necessary to compare immunogenicity.

And I would just add to that what I've said a number of times, that the immunogenicity data we have on existing products is often from a diverse patient population, from patients who are on different, concomitant medications. And the assays are unique to the sponsor. So even two antibodies to the same target antigen will have different assays with different levels of sensitivity. And the only way you can compare is by doing side-by-side immunogenicity comparisons, and then measuring the resulting antibody, or lack thereof, in the same assay, with the same validated characteristics.

DR. WOROBEK: And the counterpoint?

DR. GERRARD: Now, it's not essential to compare immunogenicity of the innovator and follow-on directly. A single-arm immunogenicity study of the follow-on could be adequate in assessing safety.

Now, with that said, that is true, and we

certainly have a lot of "me too" products that do their own immunogenicity assays that are not compared to other very similar products.

On the other hand, I think it is sometimes advantageous for the follow-on developer to do a side-by-side, if only because they can compare the immunogenicity of the innovator and the follow-on in very similar assays. We know it's not valid to compare across assays. So if you do see greater immunogenicity, is it because it's the product that's more antigenic, or is it really your assay is more sensitive than maybe something that the innovator did 15 years ago?

So I think sometimes it's clearly--although maybe not absolutely necessary--it's to your advantage to do this, just so that you can compare similar assays.

DR. WOROBEK: Any comments from the audience? Valerie?

DR. QUARMBY [In Audience]: Yes. I agree with Dr. Stein's point. I think it's absolutely imperative, using the same methodology here. If

you want to get a meaningful assessment of sero-conversion rates from the different biologics, you need to be looking at those head-to-head in the same study, then running the samples pretty much concurrently in the same methods as well.

I'd like to also say that I think it's very important not just to look at sero-conversion rates and titers, but I think it's also important to characterize any immune response that gets seen, as well. Because I think that you might, for example, conclude that two biologics were similar and equivalent if they had sero-conversion rates of 5 percent and moderate titers in their screening and titering assays. But if in fact in one of those circumstances that 5 percent response is all neutralizing antibodies, and in the other circumstance it's actually a response without clinical sequelae, then I think you're in a rather different clinical situation.

So I would encourage people to actually consider looking at a full suite of methods to detect and also characterize any immune responses

that might come out of the studies such as this.

DR. WOROBEC: Are you at all advocating characterizing non-neutralizing antibodies, or just neutralizing?

DR. QUARMBY [In Audience]: Well, there are a number of things that one can do characterize immune response sequelae. One thing that one can do if one sees a positive response in a screening assay is to put that sample into a neutralizing antibody assay and determine whether it's a strictly speaking neutralizing antibody response or not.

But I think that in fact you can have responses that are technically not neutralizing but still have quite profound consequences. You could have an antibody that actually cleared your drug rapidly from the circulation, and it doesn't necessarily have to be a neutralizing antibody.

Similarly, you could have an antibody that actually sustained your drug in the circulation. And certainly, studies of Type-One diabetics who raise anti-insulin antibodies with a fairly high

degree of frequency, even when treated with recombinant human insulin, would show that in fact you can see all of those scenarios. You can see neutralizing antibodies, or not; you can see antibodies that have no sequelae and no impact on PK; you can see sustaining antibodies and clearing antibodies, as well. Generally, not all in the same person at the same time, but across a population. So I think it's really important to do characterization work.

DR. GERRARD: What you're suggesting is standard nowadays for the development of any protein therapeutic.

DR. QUARMBY [In Audience]: Yes. And so what I am suggesting then--

DR. GERRARD: I don't think we're expecting a lower standard.

DR. QUARMBY [In Audience]: Good.

DR. GERRARD: I mean, I think everybody nowadays has typically a screening assay, which is usually, you know, [inaudible] or something, and then positives from there are further followed.

DR. QUARMBY [In Audience]: Yes.

DR. GERRARD: I think that's standard; isn't it?

DR. QUARMBY [In Audience]: Yes. So I think to have a suite of such methods that one uses in a clinical study that's run prior to registration is really key.

DR. ROSENBERG: I think just one more thing to mention about binding antibodies is that they often, or they can presage the development of neutralizing antibodies. So even if they don't show any clear effect, they may actually, by epitope spreading, cause an induction of neutralizing responses. I think you see that with IL-2 and in some instances with the Beta-Interferon. So I think that's something that hasn't been explored, but is critical.

DR. QUARMBY [In Audience]: Absolutely.

DR. LISS [In Audience]: Alan Liss, Barr Duramed.

I certainly hope the innovators are doing some of these really important studies that they're

suggesting that everyone else do. Because I really do think we need to see some of these things from the products that are currently on the market. And again, we need to work with today's standards, not something that may have been used when a product was approved. Full panels.

I also would like to see, as was suggested, some information about long-term immunogenicity of some of these, relative, of course, to the risk and use, so that we get a firm handle of this whole class of molecules.

DR. ROSENBERG: I'm a little puzzled by your statement, because I've said in both sessions that when there has been a major manufacturing change we do ask for immunogenicity studies, and sometimes safety and efficacy studies.

DR. LISS [In Audience]: Right.

DR. ROSENBERG: And those are using modern, more modern, up-to-date assays. They're not using the same assay that they used 20 years ago. So, yes, they are doing that.

DR. LISS [In Audience]: I heard. But I'm

also hearing the fervor of having the follow-ons do some added testing. And if in fact it is a safety issue because of the wrong tests being used, then the innovators, without changes, should be instituting some new methods, to be sure that we have safe and effective products.

So even in the absence of changes, you know, which side of this picture--It may have been just hearing a confused issue of it. But if it's a test that has to be done, and that hasn't been done because you didn't change a cell line--smart move--and you didn't have a comparability protocol, are there tests today that should be done on marketed products, that aren't being done?

DR. WOROBEK: I think one point is we are getting clinical safety data for those products.

DR. LISS [In Audience]: Good point.

DR. WOROBEK: So, you know, we have that whole universe of important clinical data to look at. And if we're not seeing signals, then, you know, we're not seeing--

DR. GERRARD: But it's also important,

like, are we following today aggregation appropriately in some of the products that have been on the market for a while? You know, perhaps not. I mean, the standards were appropriate then.

DR. ROSENBERG: Yes. I think that, for obvious reasons, immunogenicity responses perhaps have not been looked at optimally. And then for the adverse event reporting, you're relying on physicians to report those data. And we've all realized, and very visibly in the press, the limitations of our adverse event reporting system. And I think that in circumstances under which it's appropriate, we've asked for enhanced monitoring and immunogenicity studies, certainly safety and efficacy studies.

DR. STEIN: I can think of at least three sponsors that were asked to improve their products because the initial products were not made with current technology and not as clean or aggregate free as they ought to be [inaudible].

MS. SHORES [In Audience]: Yes. I'm Wendy Shores, from the FDA.

And I would just echo what Katie was saying. It is that any sponsor that has come with insufficient assays is now submitting to us

post-marketing commitments. So innovators are not getting away with anything.

DR. WOROBEK: Thank you.

DR. THOMAS [In Audience]: Adrian Thomas, Johnson and Johnson.

I'd like to take the discussion in a slightly different direction, which is around the topic of trial design. And really, it's possible to apply some intelligent principles here. And in general, it depends upon whether you're looking at relatively high-frequency antibody conversion or whether you're looking at perhaps a very low frequency, rare antibody conversion where the history of the product shows that there is important sequelae resultant from that.

And so I guess when you look at trial design, if you have a high-frequency antibody conversion rate then you can probably get away with a fairly small trial. But if the historical

perspective of the product suggests that a very low-frequency conversion might lead to issues, then you might have to do some form of uncontrolled design out in the population-based study using antibody assay techniques. But having said that, patients don't present with immunogenicity; they present with consequences, most commonly loss of effect.

DR. WOROBEK: Good point.

MR. GARNICK [In Audience]: I'd like just to comment on the issue of what the innovator is held to. Having just gotten three biologics approved in the last 18 months, I can assure everyone here that we exhaustively evaluated these products with respect to clinical safety and efficacy, looking for immunogenicity throughout the clinical trials.

We do conduct post-marketing surveillance as well as registries in most cases on these drugs, and look for low-level adverse events, including the effects of immunogenicity. So I can say this is kind of a [inaudible] biologics. This is how we

normally do business. And state-of-the-art assays are something that we routinely use.

I want to make a point about the aggregates. I think Dr. Gerrard brought this up. No offense, but nothing has changed in aggregates [ph] in 20 years. We knew how to look for them then; we know how to look for them now. We knew how to control them then; we know how to control them now. I don't think that's necessarily the single biggest source of immunogenicity in these products. And I think that the presentations this morning confirmed that particular point.

There are a lot of opportunities for immunogenicity, and I don't think we know them all; nor do I think we know how to look at them all. And it's important to have this clinical monitoring, because that's the only way we're really going to be able to find them. And that standard should be the same for a follow-on product, as well as for the innovator.

DR. GERRARD: But when people were talking about FDA-approved products, innovator products, I

don't think they were talking about recently approved products, which are held to today's standards. I think we're talking about by the very nature, when you were talking about follow-on proteins, those things that are coming off patents that have been used many years that were approved maybe in the '80s, and standards really were different then.

MR. GARNICK [In Audience]: For aggregation and things like that, there's no significant change in methodology.

DR. WOROBEK: In your registries, are you doing antibody titer testing? And are you looking at PK?

MR. GARNICK [In Audience]: Yes.

DR. WOROBEK: Is that being monitored?

MR. GARNICK [In Audience]: For certain products. You know, of course, it's important to realize that in your clinical trials you will find whether or not the molecule has potential for antigenicity. And if you have that potential, certainly you're going to look for it.

There may be some molecules, as we saw this morning, that may show none. I'm not aware of any. Most have low-level antibodies with no

clinical sequelae. Others may have very serious clinical sequelae, and you need to monitor that carefully. And yes, both in registries and in the trials we'll look for antigenicity.

DR. WOROBEK: I think adverse events are easier to pick up. But when you have loss of efficacy, you know, and let's say a patient who is being treated with a growth factor or some other monoclonal for cancer therapy, and there's loss of efficacy because of immunogenicity, that becomes tougher. Because you don't know if it's disease progression or if your product is not working any more. So I think that is hard to pick up; something for us to think about.

MR. GARNICK [In Audience]: My only experience with that--I can state that growth hormone back in the early '80s did have--The first preparations of growth hormone did have neutralizing antibodies, and were a major concern.

That was the rationale for a major manufacturing change, to reduce the host cell impurity levels and other variants to the minimal levels possible.

I think that was a point I also wanted to make. Host cell protein impurities, whether they're E.coli or CHO derived, are a major concern. Whether they act as adjuvants in affecting immunogenicity or not, I don't know that anyone really knows. But the real design of the industry has been to minimize these particular impurities to the lowest possible levels. And our recovery processes are designed specifically for that purpose.

So we try actively--and we spend an enormous amount of money doing that--to develop products, even though they're mixtures, to reduce those host cell impurities to as low a level as we can.

DR. BADER [In Audience]: Fred Bader, from Johnson and Johnson.

I just would like to raise one topic here which hasn't really been discussed, and I think it

may have some bearing on some of these questions about trial designs, etcetera. In the current role of innovators, for example if Roche came up with another indication for NeoRecormon, Eprex wouldn't automatically get that. They would have to do their own study to get that same indication.

And one of the questions that I don't think has really been addressed is for a follow-on pharmaceutical protein. When they do this study, what access do they get to, as far as indications? Do they do one study that would cover all indications? For example, something like Erythropoietin, you could do one nephrology study and now you get free dialysis and [inaudible] dialysis and all sorts of things. One oncology study, and you get all the various oncology indications at one time for a couple of those studies, or not.

Because one of the things we kind of get into is what do follow-on pharmaceutical proteins benefit? And my sense has been that they would do a smaller set of studies for a broader range of

indications. And if that's the case, then it's probably more critical, particularly doing side-by-side kinds of comparisons and things like that, because of the breadth that they're going to cover with a small amount of data.

Any responses from FDA, the follow-on protein companies?

DR. STEIN: I'm not going to answer the efficacy question, per se, but bring it back to the issue of immunogenicity. I think we heard Jay Siegel say this morning that patients who are, for example, cancer patients who have had multiple rounds of chemotherapy, or patients who are immuno-suppressed, don't always make antibodies to the product. And it's very difficult to extrapolate from one patient population to another. In fact, you can't do that. And so if one were going to look at the issue of immunogenicity or different indications, one would have to go into those different populations.

DR. ROSENBERG: But routinely, when products are tested in different patient

populations, we routinely ask for immunogenicity studies in those patient populations. And that's critical to do.

DR. KIM [In Audience]: Hello. My name is John Kim, from LG Life Sciences.

And I'd just like to have some clarification about the comment made by Genentech. Because I think, took that the earlier growth hormone has the higher immunogenic response, including the neutralizing antibody. What is the case whereas they have the [inaudible]. So what he is referring to is different from the widest combination where actually the protein structure itself was different.

DR. WOROBEK: Can you come up to the microphone? Thanks.

DR. GARNICK [In Audience]: My recollection is, even though the original product--In fact, there's an interesting analogue to that. The original growth hormone was Protropin, which had an end-terminal [ph] methionine that was expressed in E.coli. And we

were actually concerned that the end-terminal methionine was the cause for the antibodies. In the end, that didn't turn out to be the major cause. It was, we believed to be, the E.coli host cell impurities, as well as some of the other variants of growth hormones that were separated out in the revised purification process.

To my recollection, about 7 percent of the total antibodies--I have a good memory for insignificant detail 20 years ago. About 7 percent of that total antibody non-neutralizing population, I think, was due to the end-terminal methionine.

That product, by the way, remained on the market until just last year, when we removed it because we had developed a second generation growth hormone which is the natural human sequence material. And the interesting point is, even though this work was done 20 years ago, that really represents a cell line change, a cell line in-process change.

We went to periplasmic expression at that point. We did full clinical testing. We did

analytical characterization, biochemical characterization, the best we could at the time, PK/PD, and full human clinical trials, in order to have that product registered. So it's an exact analogue of what we're trying to deal with here today.

DR. WOROBEK: Any other comments?

MS. YAMASHITA [In Audience]: Elizabeth Yamashita, Bristol-Myers Squibb.

I just have a question of study design. We haven't talked about statistical power, what a good result is. Are we shooting for the 80 to 125, like bio-equivalency? I would just like to hear some people's thoughts on that.

DR. GERRARD: Well, I don't think we're talking about 80 to--We're not talking about bio-equivalence. I think when we're talking about doing immunogenicity studies, I think we have to be practical and balance that. With a study really designed to see a clinical difference in immunogenicity between two very similar products, it would have to be huge in order to see what would

be expected to be small differences.

So I think generally we trade off with what's practical in getting at least descriptive information about the product, so that you have some labeling information; and then rely on post-marketing surveillance.

DR. WOROBEK: I agree. For some of these adverse event rates--For Eprex it was quoted one in 10,000. To do a clinical trial to evaluate such a low incidence would be prohibitive. But I think where data can be captured would be in the post-marketing setting for that particular scenario. And I think, again, this is going to all be a case-by-case analysis based on what we know about incidence of certain adverse events for the innovator product.

DR. ROSENBERG: Yes. I think we have to make sure that the products that get out there on the market, whether they're follow-ons or stand-alones, are as safe as innovator products. I don't think it's ethical to do otherwise. And so whatever kinds of studies it takes to accomplish

that will be necessary. So I think that's sort of the underlying principle.

MS. YAMASHITA [In Audience]: So that would speak to specific product types, and sort of a case-by-case approach.

DR. ROSENBERG: Right.

MS. YAMASHITA [In Audience]: And I think the J&J person had said something, that that is known to be immunogenic. Definitely, it's a smaller study. But then what do you do with the compounds that you're actually probably checking to make sure the aggregates aren't going to cause a problem or, you know, other kinds of other process-related issues?

DR. ROSENBERG: You have to do sufficient immunogenicity studies to be sure that the product is safe and that, within the clinical context, you're not seeing adverse events resulting from that that differ substantially. And you can capture some of that up front, and you'll capture some of that post-marketing. And where that lies really is something to be decided on a case-by-case

basis.

MS. SENSABAUGH [In Audience]: Suzanne Sensabaugh, Sicor, Inc., a subsidiary of Teva.

I would like to follow on to Rob Garnick's comment about the Protopin, the methionated HGH. I think it needs to be remembered that the next six growth hormone products to come to the market that were immediate release--these were without the methionine on the end--were all brought to the market with an abbreviated approval process.

The FDA made the decision that the approval of these products' safety and efficacy could be demonstrated in 50 to 100 patients followed for six months. And we know that all of these products are manufactured with different cell lines, with different manufacturing processes. And the immunogenicity is very low, and it's very transient.

So I just want to put that example out to the group as a success story of where we do have these biotech products on the market, where they have different manufacturing processes, different

cell lines, abbreviated approval programs; and to date, safety and efficacy have remained consistent. So I'd just like to put that out to the panel for, perhaps, discussion--discussion focusing on immunogenicity.

DR. WOROBEK: Do you know what post-marketing commitments may have been asked for those?

MS. SENSABAUGH [In Audience]: Very, very limited post-marketing commitments. But all my knowledge comes from the public domain.

DR. WOROBEK: Right.

MS. SENSABAUGH [In Audience]: But very limited post-marketing commitments, is my recollection.

DR. WOROBEK: I think this will be our last question, since we're actually running a little late.

DR. GARNICK [In Audience]: I don't know that a registry that's gone on for 20 years is a limited post-marketing commitment. No, these products all went through clinical trials, just to

set the record straight. They did all go through clinical trials, human clinical trials. The only abbreviation was the duration of the study. And after all, how long does it take to show that people grow?

DR. CHIU [In Audience]: Yuan-yuan Chiu, from Genentech.

[Inaudible] and I review the growth hormone, almost all the six [inaudible]. So I do remember the post-approval commitment. There was a commitment to follow the antibody induction of all the patients who received the product.

DR. WOROBEK: Okay. Thank you. I think that will be our last question.

And I want to thank the participants for a very fruitful discussion. What our moderators are now going to do is go through all our comments, and come to a conclusion in terms of areas of consensus and disagreement. And tomorrow morning, we will present this in the morning session.

What we'd also like for you all to do, all those people who got up to the microphone, to give

your business card to our transcriber, Sharon, who is sitting on the right-hand side of me. We would appreciate it. It will help in the final minutes for this session.

And again, thank you very much for your participation.

[Whereupon, at 5:03 p.m., the session concluded.]

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