With regard to use of surrogate markers, are there any limitations you see on that that you would only use those in cases where the mechanism of action is clearly understood or where the innovator product has already been approved using surrogate markers?

DR. BEN-MAIMON: Well, clearly, in an area where the innovator has been approved using surrogate markers I think it's totally valid to use them. I also think though in areas where they have not been, you can look at erythropoietin, for example, where they had to look at -- and the issue there was nobody really knew. I was actually a nephrologist at the time. Nobody really knew whether low hemoglobin, if you raised the hemoglobin, whether that translated into any real morbidity and mortality changes.

But today we know. Today we know people who walk around with hemoglobins of eight don't do as well as people who walk around with hemoglobins of 12 and 13. And so I don't think it's necessary to recreate the wheel and reprove what we already know from science. And so in those areas I think surrogate markers can very much be used.

White blood cell count, the issue of, you know, do you have to prove that it changes the

infection rates in things? We know that if you raise white blood cell count in people who have neutropenia, they do better. And so in those areas I think we could use surrogate markers appropriately because the science has advanced, and we don't really need to recreate the wheel.

DR. WEBBER: Okay, and contrary to what the slide says, this does not conclude our general panel yet. We have one more speaker, which is Sara Radcliffe, who is coming to the podium now.

Thank you very much.

MS. RADCLIFFE: Good morning. I believe it says on the agenda who I am, but it since it doesn't say it on the slide, let me just say I'm Sara Radcliffe, Managing Director of Scientific and Regulatory Affairs for the Biotechnology Industry Organization.

Good morning. Bio appreciates the opportunity FDA has made available to discuss scientific and technical issues surrounding follow-on protein products. Bio requested open and meaningful debate on these issues last year because of our concerns that any safety problems that develop as a result of such approvals could undermine the

confidence of physicians and patients in all biological products.

We welcome this meeting, and we look forward to the scientific workshop FDA is planning for January 2005.

Bio will present three general scientific and technical concepts that are grounded by the specific hands on experience of Bio member companies, experience that is crucial to understanding biological products.

First, protein products are more complicated and more fragile than most traditional small molecule drugs. Compared with the active ingredients of chemically synthesized drugs, proteins almost always have a much higher molecular weight and greater structural complexity.

Proteins may be modified by the addition of carbohydrates and by other post translational modifications. Also, protein products can be mixtures of many molecular species and can have unique impurity profiles which are invariably dependent on manufacturing process.

Second, the nature of a protein product is closely dependent on the starting materials and

processes used to make that product. Protein products are typically made in living systems which have inherent variability.

Minor changes made by a manufacturer to starting materials or to manufacturing processes can lead to changes that can alter the pharmacokinetic and pharmacodynamic properties of the protein product and ultimately affect the product's safety and effectiveness.

To insure consistency in the characteristics of the final product, the source material, manufacturing process, formulation, and storage conditions must be carefully kept within specifications and control limits that have been empirically determined by the manufacturer.

Importantly, we mean specifications and control limits that have been functionally validated as applicable to a unique manufacturing process. Many steps are involved in producing and purifying an active biological ingredient from starting materials, and these must remain consistent to insure the quality of the final product. The types of cells used and any modification of those cells are crucial to the characteristics of the final product.

The master cell bank is a unique entity comprised of living cells. The cell lines and cell banks that would be used to make follow-on products would never be the same as those used by the innovator.

The large scale cell culture required for commercial manufacture is highly dependent on the vessels used, the components of the solution, the type of fermentation process, and other conditions.

Sophisticated techniques are used for the purification of active moieties from cell culture, and the sequence and method of operation of these techniques are crucial to the final outcome.

Ongoing testing is essential during and after purification to rule out contamination and to confirm parameters, such as amino acid sequence, glycosylation pattern, molecular heterogeneity and isoform profile and potency, all of which may have an impact on a product's toxicology, pharmacokinetic and pharmacodynamic profiles, immunogenicity, and ultimately clinical safety and effectiveness.

Changes to a protein product cannot only render the product ineffective, but may also elicit an immune reaction which causes the body to attack

endogenous proteins. The potential for such immune reactions is extremely difficult to predict using analytical testing or animal models.

Third, protein products are difficult to characterize. Even a relatively small and simple protein product is difficult to characterize, and the molecular structure of many proteins cannot be characterized fully with current technology. Thus, significant changes to the product that may occur through even a modest alteration and manufacturing process might be impossible to detect.

While analytical and other nonclinical tests are becoming increasingly powerful and sophisticated, such tests remain limited in their ability to detect the differences in manufacturing processes and the changes in the final protein product that may affect clinical safety and effectiveness.

For small molecule drug products, a straightforward dissolution assay or a bioequivalence study involving a small number of patients may be sufficient to demonstrate sameness, but far more is required for a protein product.

Demonstrating that known and unknown changes are unlikely to have impacted on the safety or

effectiveness of a protein product requires substantial effort even on the part of an original manufacturer that is intentionally making a minor change to its own manufacturing process.

When innovator companies make changes in their own manufacturing processes, unanticipated changes in the product can and have occurred, and this is why FDA itself has regulated manufacturing changes for biologics so assiduously.

Yet regardless of scrupulous oversight, the complex nature of biological manufacturing methods means that the manufacturing process used by a follow-on manufacturer will differ from that of the innovator. To establish with reasonable certainty that process differences and changes have not affected a protein product's safety or effectiveness, both innovator and follow-on manufacturers must rely not only on testing and characterization of the final product, but also on extensive development experience with the product in process testing, toxicology studies, in vivo pharmacokinetic and pharmacodynamic studies, and reagents and reference standards that are not typically available to another manufacturer.

While science is able to tell us much

about some therapeutic proteins, this knowledge is inherently rooted in what is known about specific protein products. What is known about a specific protein product's safety and effectiveness relates closely to a particular manufacturing process and derives from the data obtained by the original manufacturer of the product.

This manufacturer isolated and purified the active protein from selected cells, developed and refined a manufacturing process that provided for consistency and structure, purity, and potency, and tested the product's safety and effectiveness with substantial clinical trials.

Where there is more than one product whose active component is a given therapeutic protein, each of the manufacturers separately conducted these activities and provided FDA with extensive data from clinical trials.

Because a follow-on manufacturer can never exactly duplicate the innovator's process, and because differences in process may result in differences in the protein product and its clinical effects, FDA must continue to apply consistent regulatory standards for all manufacturers and must insist on receiving the

full complement of data necessary to demonstrate safety and effectiveness.

A full complement of data is the set of data contained in the complete regulatory filings submitted by a manufacturer to the FDA sufficient to show safety and effectiveness. It includes all of the preclinical and clinical data needed to support the label being claimed.

Bio does not support any regulatory framework that incorporates requirements for unnecessary preclinical or clinical testing. Bio believes, however, that it is only through a thorough assessment of safety and effectiveness, including clinical testing meeting all ethical standards, that patients can be assured that initiating treatment with or switching to a newly available product will provide them with the anticipated benefits and safety of the treatment.

FDA policies for follow-on protein products must differ substantially from the policies applicable to small molecule generic drugs. This is true because of the inherent complexity of protein products.

The dependence of the final protein

product's characteristics and activity on its starting materials and on the processes by which it is produced, purified, formulated and stored, and of the difficulty of characterizing products with great molecular complexity and heterogeneity.

We reiterate our hope that this meeting and the FDA/DIA conference early next year will constitute the beginning of a truly deliberative public dialogue on follow-on protein products. The questions about future policy surely include scientific, technical, and medical considerations that will affect the outcome for patients, as well as legal questions impacting on the biotechnology industry's ability to sustain the innovation for which it is known.

We, again, ask that FDA expand its interactions with stakeholders to deal with nonscientific issues, especially the important legal questions regarding the agency's authority to consider for approval abbreviated applications for so-called follow-on protein products based on the data generated by pioneer companies and used without their consent.

We believe the principles governing the debate about follow-on protein products are simple and

clear, that regulatory requirements must be based in sound science; that patients deserve access to appropriately tested and competitively priced therapies; that industry's ability to make innovative medical products available through research and development should be promoted; and most importantly, that the health and safety of the patients served by both FDA and the biotechnology industry are preserved.

Thank you.

(Applause.)

DR. ROSENBERG: You and other speakers have made the point often that minor changes to product can dramatically alter product quality and potentially affect product safety and efficacy. Yet I think we at FDA are only aware of a very small subset of those changes.

And in previous industry meetings, we have asked for industry to share those with us on a more robust basis so that we can really understand the extent of that.

So is Bio committed to helping us to understand how some of these small changes can potentially affect product? Because this is key for our understanding.

MS. RADCLIFFE: Absolutely, and as I mentioned in our testimony, we called for open and meaningful public debate on this topic. Representatives of a number of Bio member companies are presenting today at this workshop, and I would encourage you to ask them in detail about those particular issues.

MS. BROWN: You had mentioned that there were some unique issues related to biologics, the master cell bank, things like that. But for post approval changes, manufacturers routinely change master cell banks. They may make formulation changes, and they demonstrate comparability without a clinical study.

How can you justify that a full blown clinical study would need to be done for like a follow-on biologic versus a post approval change for an innovator?

MS. RADCLIFFE: The innovator is able to rely on a significant body of knowledge that the follow-on manufacturer does not have access to. We do not imply that the follow-on manufacturer is any less capable technically than the innovator, but the innovator has the benefit of the full development

experience and relies on that when making manufacturing changes.

And that's why we have argued that the full complement of data necessary to show safety and effectiveness in the complete regulatory filing submitted to FDA would have to include a clinical trial.

DR. CHERNEY: Could you give us an example where that developmental data had a real impact on the type of change like a cell bank, that without that data you would never have known about it through any of your analytical testing or you comparability studies that you were proposing?

MS. RADCLIFFE: Again, a number of representatives of biomember companies are testifying today, and I think that question is best asked to those who really have had the hands-on experience and can provide you with the details.

We are also going to submit written comments to the docket, and so we would be happy to give more detail in that.

DR. KOZLOWSKI: I'll actually repeat a question, I think, that Dr. Rosenberg asked of a previous speaker, that although a lot of information

may be unavailable, certainly there's a lot of public information about a drug that's been on the market for a while.

Do you think that information has any bearing on changing what's necessary for a follow-on?

MS. RADCLIFFE: Certainly it has bearing. I mean, science progresses where the public science gives information to a follow-on manufacturer that is appropriate for the follow-on manufacturer to take account of.

But I think what we have argued, again, in our testimony is that a great deal of the information necessary to make a manufacturing change is information that is available only to the innovator in terms of its development experience.

DR. WEBBER: More questions?

Thank you very much.

And that concludes our general panel presentations. I would thank all of the folks who did come to present to us this morning.

We're going to take a 15 minute break until 11:05. The restrooms are, I believe, out to the left, and we'll reconvene at precisely 11:05 with the manufacturing panel.

(Whereupon, the foregoing matter went off the record at 10:52 a.m. and went back on the record at 11:06 a.m.)

DR. HUSSAIN: I think in the interest of time we would like to get started or you don't have a lunch break then.

(Laughter.)

DR. HUSSAIN: Are the presenters ready for this session? Well, Keith, I think we will just get started.

DR. WEBBER: We might as well get started, yes.

DR. HUSSAIN: Wait until this.

DR. WEBBER: Okay. This is will begin our Panel No. 1 or 2, however you want to count them, but this is the manufacturing panel in which we will hear some presentations regarding the issues of manufacturing and those things that need to be considered during the manufacturing process when making follow-on protein products.

And if we can bring up our questions just by way of introduction to the session, within the Federal Register notice we've put out a couple of questions related to manufacturing issues that we

wanted to use just really to stimulate discussion and presentations.

And the first question is: what aspects of the manufacturing process determine the characteristics of a protein product, whether produced through biotechnology or derived from natural sources?

And the second question is: what parts of the manufacturing process should the agency focus on when we're assessing similarity between protein products?

And before we bring up our first speaker, I think we should probably introduce the panel. Many of those here have already been introduced, but we'll go through it again for late comers, as well as for completeness.

I am Keith Webber, Acting Director of the Office of Biotechnology Products and lead for this particular panel discussion.

DR. FRASER: I'm Blair Fraser, Office of New Drug Chemistry, CDER.

DR. CHERNEY: Barry Cherney, Deputy Director of Division of Therapeutic Proteins, Office of Biotech Products, CDER.

DR. HOLCOMBE: I'm Frank Holcombe, Office

of Generic Drugs, CDER.

DR. JONECKIS: Chris Joneckis, Senior Advisor for CMC Issues, CBER.

DR. HUSSAIN: Well, I think we'll invite the first speaker. Each speaker in the session has ten minutes, and before we get started I took some time off to arrange a room, a quarantined room for those with cell phones. So when the next cell phone rings, stare at that person.

(Laughter.)

DR. HUSSAIN: And give me his or her name and I have a quarantined room available for them.

The first speaker, please.

DR. WEBBER: The first speaker will be Art LeBlanc.

MR. LeBLANC: My name is Art LeBlanc, and I'm President of SICOR Pharmaceuticals, Inc.

In my presentation I'm going to address a couple of questions. They're a little bit different than what has been identified. However, the question that I intend to address is: can a biopharmaceutical generic manufacturer make a product that has the same safety and efficacy as the innovator?

And second, can different manufacturing

processes yield the same product?

Bio and PhRMA have argued that for biogeneric or biotechnology products which can be complex proteins the process is the product. One of the arguments against biopharmaceutical generics is that one cannot change the process without changing the product.

In addition, it has been stated that one cannot adequately characterize biopharmaceutical generics to assure that it is the same as the innovator.

In reality, this is not the case. The process is not the product. Manufacturers of well characterized biologicals can change the manufacturing process and still have the same product. FDA allows innovator manufacturers to implement changes to the manufacturing process without new clinical data if the products are comparable.

FDA addressed the question in the early 1990s. In the past, FDA policy was that if a manufacturer made a manufacturing change, they would have to do a small clinical study to demonstrate that the product made by the old process was similar in safety and efficacy to the product made by the new

process.

In the early 1990s, the policy changed for biotech products and other well characterized biological products. This policy was not applicable to the more traditional biological products, such as vaccines that were not as well characterized.

That was the understanding by both FDA and the industry, and the request for a small, clinical, comparative study could not really address product differences.

In addition, advances in analytical technologies allowed for better characterizations of proteins.

The comparability policy required manufacturers to show by extensive testing that the new product was comparable to the old product. Comparable did not mean identical since minor differences are allowable.

The comparability policy was officially documented in a 1996 policy paper, but was practiced for several years prior to 1996. This comparability policy has implications for the biopharmaceutical generic industry. The process does not define the product.

FDA has accepted for more than ten years that manufacturing changes to biotech products can be assessed by analytical characterizations. Technology exists to assess possible protein changes.

Changes to the manufacturing process, including changes in site, master cell bank, fermentation, purifications, et cetera, are implemented all the time by innovator companies. These changes are assessed by extensive analytical characterizations. There are similar scientific issues for both comparability and biopharmaceutical generics.

FDA and industry have accepted that one can change the process and still have the same product. FDA has accepted that we can adequately characterize biotech products by analytical tests to demonstrate comparability after the manufacturing changes. An adequate analytical characterization generally negates the need for clinical data.

Regardless if a product is an innovative biotech product or biopharmaceutical generic product, certain features of the manufacturing process need to be maintained in order to insure the identity, potency, purity, quality and safety of the

pharmaceutical product. These features include robustness and reproducibility, validation, controls, and testing.

Our company manufactures protein products that have been demonstrated analytically to be similar to the innovator's product, and Dr. Naktinis will present these data later in the presentations today.

There's a strong relationship between analytical characterization and these features in the manufacturing process. Fortunately, technological advances and analytical methods and validation have provided companies with scientific capabilities for evaluating biopharmaceutical generic products. Combining data from the manufacturing process with the analytical characterization gives us greater confidence that the final product is similar to the innovators.

We have been manufacturing one of our products, interferon alpha-2b, for over 14 years. At least nine million doses have been given in 17 countries, and our company has a long history of manufacturing and distributing a follow-on product that is safe and effective.

Without a robust and reproducible

manufacturing process an out of control situation exists. Each step of the manufacturing process, both drug substance and product, must be controlled to assure that the final product will meet specifications. Quality, safety, and effectiveness must be built into the process. Final product testing assures that quality goals are met.

Preformulation and formulation studies evaluate the impact of the manufacturing process on the biopharmaceutical generic product. These include excipient compatibility, order of addition, temperature, mixing time and rate, pH, solubility, stability under varying conditions, adsorption, impact of shearing, freeze-thaw, autoclaving, stopper compatibility, effect of metal cations, oxygen effect, overage, light, et cetera.

Critical control points in the manufacturing process are identifies. Acceptance parameters are determined, specifications established, and in-process data generated during manufacturing to verify and control the manufacturing process.

In addition, process validation includes the validation of the cell tanks, cell banks, fermentation, recovery, formulation, and fill/finish

manufacturing process. It goes without saying that these are done with validated analytical methods.

Analytical methods for identity purity and potency of the API and final product to release stability should be sensitive, quantitative, and validated.

Addressing FDA's question on what parts of the manufacturing process should the agency focus on when assessing similarity between products, each manufacturing process must be evaluated as a unique process. The manufacturing process will be different for each product, as biopharmaceutical generic product manufacturers do not have access to the details of the manufacturer of the innovator's product.

Manufacturer's should submit a full CMC section for their application to insure that FDA has the ability to determine from data that the final product is safe, pure, potent, and of high quality. The CMC section will include full analytical characterization, a description and a manufacturing process and stability data.

Analytical characterization should include a molecule to molecule comparison to the innovator's product to demonstrate similarity.

The biopharmaceutical generic manufacturer need not perform the same analytical tests as the innovator. Improved analytical methods may have obsoleted original tests, and the same analytical methods as the originator may not be performed.

In summary, current analytical techniques allow characterization of possible changes in biotech products and comparison between biopharmaceutical generic and innovator.

In addition, combined with modern concepts of quality management, reinforced by in-process controls and validation allow for a high confidence that a biopharmaceutical generic product is similar to the innovator's and safe for distribution.

Thank you.

(Applause.)

DR. WEBBER: Thank you very much.

I just have one question before we move on to the rest of the panel. With regard to processing product-related impurities, oftentimes those are critically dependent upon the manufacturing methodology that's used, and so my question is how much should we take those into account as we evaluate follow-on biologics or follow-on proteins.

MR. LeBLANC: I think that what we have to do is we have to look at the impurity profiles and determine exactly what it is showing us. In doing the comparator or the comparative study with the innovator's product, we get some kind of idea as far as the differences, and in negotiation, discussing with the agency will determine exactly what are the needs that we have to do as follow-up as far as those individual impurities might be.

DR. WEBBER: Other questions from the panel?

DR. CHERNEY: Yes. I have a broader based question. I know we're talking about manufacturing mostly, but the comparability document that you quoted says that comparability can be established by analytical tests, nonclinical studies or clinical studies, and in many cases it's determined solely by analytical methods, but that document also says that testing may be complementary, in which case independent of the results of that one level tier testing, you may be required to do others.

I guess really what we're trying to discuss here is the situation of follow-ons. Where are we in this type of testing hierarchy? What

testing needs to be done? And what are the bases for that testing?

I know you weren't talking much about that, but --

MR. LeBLANC: I think Dr. Naktinis will cover that in a little bit more detail, but I think it does depend upon actually what the data that you generate and actually what you do see.

DR. CHERNEY: So in some cases then you think analytical testing should be sufficient for a determination of similarity?

MR. LeBLANC: In some cases, yes.

DR. JONECKIS: Following along those lines, the document really talks about changes that are more related or somewhat discrete manufacturing changes, and they're all based on a comparator to a product that has been tested in clinical trials, and the document clearly indicates that one should take the impact of manufacturing into consideration.

With a follow-on protein product, one could have a radically different manufacturing process, as we well have heard. So how does one take that into consideration with just using solely analytical methods to make that comparison.

MR. LeBLANC: I think it goes, once again, to the actual data that are generated, and it's going to be very difficult, particularly depending upon the protein molecule that you're talking about. In some cases, it should be something that is fairly straightforward. In other cases it's going to be something that's going to be much more in depth, and I think that's going to be part of the negotiation process as far as determining exactly what's going to be necessary for the approval process.

DR. CHERNEY: You mentioned that you have a lot of clinical experience with the interferon alpha-2a, but do you actually have real clinical data and information on the efficacy and safety of that product?

I know it has been put into nine million people, but what data do you have to say that you have a similar safety and efficacy profile?

MR. LeBLANC: I think there is some ancillary information particularly relative to pharmacovigilance information that has been gathered over the years, and there's probably some additional, a certain amount of clinical data that has been generated relative to certain studies that have been

established with that molecule.

DR. WEBBER: Okay. Thank you very much.

DR. HUSSAIN: I request the panel to sort of limit the questions because we are already 15 minutes late on this session.

DR. WEBBER: Okay. The next speak is Dr. Robert Garnick.

DR. HUSSAIN: And I have invoked my authority to put a beeper on. So there will be a beep as you approach your time.

DR. GARNICK: I'm Dr. Robert Garnick, Senior Vice President of Regulatory Quality Compliance at Genentech.

And I'm going to try and make three points in my talk today. The first is to discuss Genentech's experience in the development of recombinant DNA products; discuss what we've learned; and highlight some of the surprises that we've had; and raise some key issues for FDA to consider when they're considering the issue of follow-on biologics.

Genentech was founded in 1979 Herb Boyer and Bob Swanson and is considered to be the innovator company in the development of recombinant DNA products. Genentech is also currently the largest

pharmaceutical protein manufacturer in the world. We have over the last 25 years manufactured 36 separate recombinant DNA products, everything from recombinant insulin to our most recent product, Avastin for colorectal cancer treatment.

We have received FDA approval for 13 recombinant protein products. We have three manufacturing sites at South San Francisco, Vacaville, which is shown in this slide, and we currently have 250,000 liters of cell culture in fermentation capacity.

Early on Genentech worked closely with FDA to define the preliminary standards for recombinant DNA products for insuring safety and efficacy. Genentech received the first FDA approval for a multi-use licensed facility for the manufacture of recombinant products, and we shared a strategic role with FDA in the development of comparability protocols.

To date Genentech has submitted and received approval for eight comparability protocols. Nevertheless, even in our hands with all of this experience, we have had a number of surprises that we consider directly applicable to the issue of follow-on

biologics.

Some of the things that we have learned. We have learned that biological manufacturing is a complex cascade of operational steps inherently susceptible to many forms of contamination, including viral, bacterial, microplasma, and prion. And we and others in the industry have had contamination, large scale contaminations, particularly viral ones, and have spent an enormous amount of time and money to detect and prevent these potentially catastrophic events.

The proprietary technology we have developed is not publicly available to follow-on biologic manufacturers. We've learned that the manufacturer of recombinant products requires highly specialized facilities in order to maintain the fragile mammalian cell culture systems which are the heart of the production, to control the highly complex manufacturing process, and to insure consistent production of complex molecules.

We have learned that there are absolutely no shortcuts that can be taken during this process.

To bring this example of complexity for the manufacture of recombinant products to life, in

this slide are two examples of two oncology products. One is the batch records for a small molecule oral dosage form product, and on the right is that of a protein product, in this case a monoclonal antibody.

For example, for the small molecule, the number of batch records required to produce this product is less than ten, where for the protein it's greater than 250. The number of product quality tests for the small molecule is typically less than 100, whereas for the protein greater than 2,000.

Importantly, the number of critical process steps, those that can and will affect the quality of the product, the small molecule are typically less than 100 and for the protein greater than 5,000.

And to bring this also to light is the fact that the batch process data entries used in the production of these products for the small molecule typically is 4,000. These are the opportunities to make mistakes, and in the case of the protein, greater than 6,000.

Again, in this case there are no opportunities for shortcuts.

We have learned that the manufacturer of a

recombinant product and the manufacturer of a consistent commercial product is based on the following: a well developed process and a well characterized molecule; appropriate validation of the process and assays; a process control system using a unique set of analytical assays that have evolved during the drug development by the innovator company.

And I should point out that these particular assays are specifically developed to measure key characteristics of that molecule which may have an important effect on the safety and efficacy of that product. They are not just picked out of a copy of Lenninger and decided to be adequate. They are based on what we know about the molecule that we've learned during our clinical trials. Again, there's no shortcuts here.

An important point is that the less you know about a particular molecule and what is important in that process, the more factors you need to control for.

A major lesson that we have learned over the last 25 years is to avoid making process changes that result in changes to the product; that different processes can and will produce different products.

This speaks directly to the case of follow-on biologics, where in the absence of the exact knowledge of an innovator's clinical experience and absence of the knowledge of their specifications and how they were derived and the characterization data conducted by the innovator on the molecule based on the results of their clinical trials, bioequivalent studies alone are not adequate to convert safety and efficacy for protein products.

My next slide is an example of just one example of what we have learned. In this particular case -- and I think we were asked before to provide some examples -- Raptiva, or efaluzmeb, is a monoclonal antibody which we just had recently approved for the treatment of psoriasis. Genentech originally developed the cell line and process for efalizumab and then transferred it to XOMA, who manufactured clinical grade material and performed the clinical trials for Genentech.

The XOMA material was used for the Phase I, II, and part of the Phase III studies, at which point Genentech intended to introduce its own Phase III material.

Based on the promising results of the

Phase I and Phase II trials, the same cell line and process were transferred back to Genentech for scale-up and commercial requirements. The materials manufactured at the 12,000 liter scale in Genentech demonstrated that the material, while it met the role of the original drug substance specifications and had a very similar characterization profile, there were some minor analytical differences.

However, and very importantly, even we with all of the experience during the manufacture and development of the drug deemed that those differences were insignificant. However, during a Phase III trial, we could not confirm that the materials produced by Genentech and by XOMA were indistinguishable.

We then, in consultation with FDA, performed human PK studies which highlighted a significant difference in the PK profile. Actually Dr. Andy Jones from Genentech and Dr. Hal Barron will talk about this example later today and tomorrow.

As a result of these differences, we decided that the only way to resolve this was through a third Phase III clinical trial, which we performed with a larger patient subset, and the approval of

efalizumab was based on the use of the Genentech material at that point.

Again, I think this is an excellent example of the type of thing that might happen with a follow-on biologic.

Thus, in the case of follow-on biologic manufacturers, it is certain that they will not have access to the innovator's cell construct and manufacturing know-how. Thus, any manufacturing changes that involve changes to the host cell and vector systems for protein expression and to the analytical and biological characterization profiles of the product and its impurities require reconfirmation of clinical safety and efficacy. Pharmacokinetic and pharmacodynamic surrogates are generally not sufficient.

It's important to recognize that a follow-on manufacturer does not have access to the same process and analytical systems that were used by the innovator. Therefore, the follow-on protein product cannot be considered therapeutically equivalent without meaningful and adequate clinical data.

For protein products, we've learned that consistent safety and efficacy of the complex protein

is really based on three pivotal aspects: clinical experience, manufacturing experience, and analytical experience, all of which are gained through the clinical studies used to evaluate the molecule, the manufacturing process, and the analytical tools which are also combined with this.

The question for FDA is: can the safety and efficacy of follow-on protein products be guaranteed if any of these segments are compromised?

And finally, I'll leave you with this last final slide and thoughts: that anything can be reverse engineered and copied, although some things are much safer than others.

(Laughter.)

DR. GARNICK: Thank you.

DR. WEBBER: Thank you.

(Applause.)

DR. WEBBER: In the agency, we receive and review information from innovator companies like Genentech for review and approval of your products. Is there something scientifically or based on the information that we receive from your company, is there something scientifically missing if we look at data from a follow-on company for the same product to

try to evaluate whether it is similar enough?

I mean, we would not have specifically what we would need from them, additional information that we would need from them.

DR. GARNICK: I think it's a good question. In the hands of FDA you certainly have available to you the information from the innovator in terms of what the innovator's product looks like. You have seen the results of the clinical trials, most importantly, and you also know from that information what we deem to be significant and what we don't need to be significant.

It's only on that basis; really in my view, it's really the absolute requirement that the materials made by a follow-on protein manufacturer will never be the same as the innovator. We know that the product will not be the same. It may be similar, but it will never be exactly the same. The impurities can never be the same.

The only way to deal with the questions of immunogenicity and clinical safety, long-term clinical safety, I think, are going to be based on a clinical trial and post marketing surveillance of material should you deem it appropriate to approve.

And I think the key thing is that's the standard that has to be set for both the innovator and for follow-on protein products, adequate clinical safety and efficacy.

DR. WEBBER: Any questions?

Thank you very much.

Okay. Our next speaker will be John Dingerdissen.

MR. DINGERDISSEN: Good morning. I'm John Dingerdissen. I'm Vice President of Worldwide Manufacturing at Johnson & Johnson in the Global Biologics Supply Chain.

On behalf of Johnson & Johnson, I would like to say that we fully support efforts to identify standards for follow-on biologicals as products.

I would also like to emphasize that the expanding access to safe and affordable medicines is critical to public health as an objective for our nation. Nevertheless, the standards and policies applied to follow-on biologicals must be built on the understanding of the complexities of the biological medicines in order to assure that they are safe and effective for patients.

As FDA has consistently recognized, the

scientific complexities surrounding biological medicines make them fundamentally different from chemically based drugs. A new set of standards and policies markedly different from those currently used for generic drugs must be established for follow-on biologicals. Patient safety must be of paramount importance.

Now I would like to turn to my main topic: the active agent of a chemically based drug product is a distinct compound with a relatively simple structure and relatively low molecular weight.

In contrast, the therapeutic protein is much larger, up to hundreds of times larger than the average chemically based drug. These proteins are chains of single amino acids in a specific sequence that then unfold elaborately into a highly complex 3D structure. Many therapeutic proteins have hundreds and thousands of amino acids, and even a small change in an amino acid sequence may dramatically alter how the product works in patients.

The protein can exist in different formations called isomers, and the chains tend to stick together in aggregate features that can dramatically impact their activity. The structure and

activity of some proteins is complicated further by glycosylation, the attachment of sugar molecules to the chains.

Here is a 3D model of the EPO molecule, a 1,000 atom molecule with a very specific structure that interacts with the receptor in the body. As you can see on this video, the effective interaction of the EPO molecule in red and blue and gray, that the receptor in green is dependent on many critical points of contact between the two. Any change in the surface-to-surface contact can cause a decrease in clinical efficacy.

Here we have a comparison of the EPO molecule in blue with the typical chemically based drug, aspirin, in red. Notice the dramatic difference in size and complexity. Here's a biomolecule that is 100 times larger than the chemically based drug.

The slides of the EPO molecule that I just showed you were just of the protein. Here in this picture you can see the additional complexity of glycosylation. In the purple you can see the sugar molecules attached to EPO.

I would now like to discuss the formulated product. A formulated chemical based drug product is

generally very well characterized, that is, well established methods are able to determine exactly what is in the product.

In contrast, a formulated protein product is a heterogeneous mixture of materials produced by the cells. This mixture contains the active protein, as well as other proteins that may contribute to how the product works in patients.

State of the art analytical methods using advanced instrumentation techniques do not always tell us exactly everything we need to know about the product. Biological assays using biological materials, such as cell cultures, are required to supplement analytical data, but even together these methods are limited in their ability to detect small variations.

Tomorrow you will hear from my J&J colleague, Fred Bader, who will describe our experience with erythropoietin in pure red cell aplasia. Erythropoietin is just one of the many biological products that have exhibited problems with immunogenicity as a result of a product characteristic that was not detected by routine analytical studies.

Today we will hear many people talk about

the importance of manufacturing as a process to the protein product. As a scientist who has worked on the development and manufacturing of biologics for more than 30 years, I say with confidence that the process used to manufacture a biological product is a significant determinant of that product. The process of manufacturing therapeutic proteins involves numerous complicated steps and is far more complex than that used for chemically based drugs.

Chemically based drugs are made by adding and mixing together known chemicals and reagents using a series of controlled and predictable reactions. This is basic organic chemistry.

In contrast, therapeutic proteins are made by harvesting the substances produced and secreted by constructed cells. This is genetic engineering coupled with elaborate fermentation, harvesting, and purification processes.

The complexity of biological manufacturing can be appreciated best by touring a manufacturing facility. That is not possible today, but I am able to share some pictures while I describe the steps of the process.

The first step is to develop a cell line

by isolating the DNA sequence that codes for the desired protein, selecting a vector to carry the gene, and then inserting it into a suitable bacterial or mammalian cell.

Types of cells and gene sequence used significantly influence the characteristics of the protein product. The unique master cell bank is then created using an established procedure. No two master cell banks are ever exactly alike.

The engineered cells are then cultured on a large scale under highly specific growth conditions to optimize cellular production and secretion of the desired protein. In this picture you can see the initiation of full scale media preparation.

The vessels use the components of the solution, the type of fermentation process used, and the physical conditions of the culture can impact the protein and alter its biological behavior in the patient. In these pictures you can see a typical cell culture reactor with a sophisticated level process control.

In addition to producing the desired protein, cultured cells also produce undesired proteins; altered forms of the desired proteins and

impurities.

Fractions containing the desired protein are harvested and isolated by a series of carefully selected and validated steps designed to optimize the purity and yield of the desired protein. A change in the purification process can alter the purity profile of the product and change its effectiveness and safety profile in patients.

After purification, protein molecules are analyzed for molecular uniformity, potency, and purities and contaminants. A wide variety of analytical tools, including physicochemical, and biological tests are used. These tests have become more sophisticated with time, but remain limited in their ability to detect all product characteristics.

The number of analytical tests can run between 3,000 and 5,000 per batch. Labor per batch will often run over 10,000 hours. The drug substance batch records can consist of thousands of pages per batch, as depicted in this example where we show Remicade on the right, a biological, and Grifulvin, a chemically derived drug, both J&J projects.

After analysis, the therapeutic protein is formulated. As with all the steps, the components of

the formulation and the process used significantly affect the product and its behavior in patients. Within each of these steps are numerous smaller steps that must be carefully controlled and validated. In order to insure batch uniformity, the steps must remain the same. Experienced personnel familiar with the subtleties of the process are essential for a consistent and productive operation.

The average manufacturing time from first cell culture to finished product is about eight months and can vary up to a year or more, whereas the cycle time for a small molecule can be on the order of three to four months.

Finally, I would like to show you some published data demonstrating the differences between various epoetin products currently marketed around the world. Eleven epoetin products here listed are available outside the U.S. and Europe, and they were obtained from eight manufacturers and evaluated.

These preparations were tested qualitatively for physical characteristics, such as general appearance, volume, pH, osmolarity, total protein, excipients, Western Blot, SDS-PAGE, and isoforms. One can see clearly that characteristics

such as the total protein concentration, as well as excipients and pH differ from product to product, all presumably the same.

Using a measure for protein content, one can see different EPOs have different content. Here one can see different isoform protein matters which are used to measure the uniformity and consistency with a production batch. The Eprex control is at both ends of the left-hand blot.

As you can see in this table, there is a wide variation among these products as measured in three bioassays. These data show that when manufacturers have attempted to copy a widely used therapeutic protein, such as a epoetin, using their own cell lines and process it resulted in significant differences in the characteristics of the products, differences that could affect efficacy, safety, and patients.

As you can see, the process for manufacturing a recombinant biological product is an exceedingly complex series of steps. The active bulk material is the basis for the efficacy, safety demonstrated in patients for that product made by those cells and by that process. Different cells and

different processes produce product variance, not copies.

The issue is not whether a new manufacturer has the scientific expertise to establish a complex manufacturing process. That's a given. The issue is whether any company can reproduce a protein product that is the same as another company's version of that product.

A new manufacturer must develop their own master cell bank, production system, and purification process without the benefit of the innovator's experience, historical data, process controls, and specifications. The new manufacturer must demonstrate the safety and effectiveness of their product in clinical trials.

In summary, the manufacturing process is a significant determinant of the therapeutic protein product. The principles and understanding of traditional generic products, even with respect to the terms used to discuss those products, cannot be applied to therapeutic protein products.

As this scientific dialogue continues, we must all remain mindful that patient safety must be the highest priority. We are pleased that the FDA is

pursuing a public process. We look forward to the next workshop in early 2005 where we will have an opportunity for more complete discourse among scientific experts, and I thank the FDA for this opportunity to participate in this dialogue today.

Thank you.

(Applause.)

DR. WEBBER: Thank you very much.

I'm afraid we don't have time for any questions at this point.

MR. DINGERDISSEN: Okay. Thank you.

DR. WEBBER: But let's move on to our next speaker, who is Suzanne Sensabaugh.

MS. SENSABAUGH: Good morning. I'd like to thank the FDA for giving me the opportunity to present today.

What I'd like to present this morning is a case study of a biopharmaceutical generic product. That product is human growth hormone. All of the information that I will present is information obtained from the approved labeling and FDA reviews and approval packages. So it is not confidential information and is in the public domain.

But I would like to reference what Keith

said this morning because I think it is very appropriate. Keith said we understand the world by the words we use to describe it. So I'd like to keep that in mind as we move forward.

Currently we have six approved human growth hormone products on the market today. These are immediate release products, and they were approved in late 1980s, mid-1990s. These are Humatrope, Norditropin, Saizen, Genotropin, Nutropin, and Tev-Tropin.

All six of these products were manufactured by different companies. Therefore, the manufacturing processes are all different as each company considers their manufacturing process to be confidential.

All of these companies use different master cell banks and cell lines. In fact, one of these products is produced using mammalian cell line or the other five are produced using a bacterial cell line.

Yet we find that all of these products are identical. All are 191 amino acids in length and have a molecular weight of approximately 22 kilo Daltons. Labeling for these products state that the amino acid

sequence is identical to pituitary-derived human growth hormone. At the time of approval pituitary-derived human growth hormone as a natural approved extracted product was on the market.

So, therefore, if these products are identical to the pituitary-derived human growth hormone, then we can extend this to say that they are identical to each other, and in fact, FDA recognizes that they are identical because they all have the same generic name with the somatropin.

So what we have here is we have the ultimate manufacturing change, and this ultimate manufacturing change has resulted in identical products.

The 1987 review for Humatrope, which was the first product to come on the market, stated that the product is structurally, physically, chemically, and biologically equivalent to pituitary derived human growth hormone. So even 15 years ago we had analytical methods that allowed adequate characterization not only of a protein product produced using biotechnology, but also of a natural protein extracted from human tissue.

FDA policy at the time of the approvals

were that safety and efficacy needed to be demonstrated in 50 to 100 patients for at least six months. FDA made this decision due to this protein being a simple protein that could be characterized, the identity, potency and purity was well established, and there was a product already on the market to which identity, safety, and efficacy could be compared.

The results of the safety and efficacy studies were consistent qualitatively and qantitatively with previous clinical data in publications or submitted to FDA for pituitary-derived human growth hormone and other recombinant human growth hormones.

So FDA used their scientific judgment from data that they derived from publications from the literature, from the naturally derived protein product and from other recombinant protein products to make their determination of safety and efficacy.

This decision was first made 15 years ago, and to date the safety and efficacy profile remains the same for these products even with such an abbreviated clinical program.

Labeling for these products, the package inserts for these products state that the products are

therapeutically equivalent to pituitary-derived human growth hormone. So FDA already has criteria in place to make a decision on therapeutic equivalence for a protein product.

So what lessons can we learn from human growth hormone? There's already a biopharmaceutical generic on the market today in the U.S. This product has been on the market for at least 15 years. We know that even back in the mid-'80s science was in place to adequately characterize protein products.

The human growth hormone experience shows us that the ultimate manufacturing changes can yield identical products. These products were brought to market with a reduced safety and efficacy trials, and still today the safety and efficacy remains consistent. It also shows us that therapeutic equivalence can be established and that the decision making is in place in FDA, and the criteria to determine therapeutic equivalence is already in place.

So what I'd like to do is ask our esteemed panel today to please take a look at the human growth hormone situation, to take what we've learned from it, and apply this to future policy making in this area.

Thank you.

(Applause.)

DR. WEBBER: I think we have time for one question, two questions perhaps.

DR. CHERNEY: You call these six different products identical based on primary sequence. That typically is not sufficient to demonstrate identity between products. It shows that they're the same entity, but it does not show that they're identical product.

Can you elaborate on additional assays that were used to show that these are similar products?

MS. SENSABAUGH: The word "identical" was in the FDA approval packages and that's where I take that word from. As you know, the approval packages don't contain much in the way of CMC information. So I am not sure what criteria FDA used in the way of analytical methods to determine that these products were identical.

So I would suggest that maybe you can go back and look at the data that you have in house.

(Laughter.)

MS. SENSABAUGH: But look at that data, and what this is, what we're doing here is learning

from this lesson, and if we can already say that proteins are identical, which we have, then let's see what led to that decision making and use that in future policy making.

So I think that's fair.

(Laughter.)

DR. WEBBER: Any other questions?

(Laughter and applause.)

DR. WEBBER: Our next speaker is Mathias Hukkelhoven.

DR. HUKKELHOVEN: Good morning, good afternoon. Let me start by saying that my presentation should actually have been scheduled in the general section, and we did request that to FDA, but we do realize that there were a limited number of spots on the general panel.

Let me introduce myself. I'm Dr. Matt Hukkelhoven. I'm the approval head of Drug Regulatory Affairs at Novartis Pharmaceuticals Corporation.

I want to thank the Food and Drug Administration to give us the opportunity to represent the Novartis group of companies at this public hearing. The Novartis group is a world leader in the research and development of products to protect and

improve health and well-being. The group's success as a global leader in the innovator biopharmaceutical industry is demonstrated by the approval and launch of 11 new NDAs over the last four years, more than any other company.

As today's testimony reflects, FDA is hearing from industry representatives as well as many others who are presenting in many cases essentially two opposite ends of the spectrum on the issue of follow-on biologics. In such a polarized context, Novartis appreciates this opportunity to share an alternative perspective which we will detail further in our submission to the docket.

Our perhaps somewhat unique perspective is premised upon several bedrock principles: confidence in scientific progress; the capabilities and experience with biotechnology of our regulatory authorities, as well as the critical importance of patient safety with and public confidence in biotechnology based medicines.

We also believe it is important to encourage competitive landscape marketplace for biotech medicines, as well as chemical drugs, in order to facilitate patient access and continued investment

in our industry.

Based upon this foundation, Novartis believes it is time for a regulatory mechanism that encourages the development and approval of follow-on biologics. We define such products as second and subsequent versions of recombinant DNA derived protein products that depend on the same mode of action, are used in the same indications as the originator product, and are developed based upon an extensive and sound set of data generated by disposal and the demonstration of comparability with an originated product on all relevant levels, i.e., chemical, preclinical, clinical, and immunological, as we heard.

In suggesting such a new regulatory paradigm, Novartis merely is recognizing the next logical step in the evaluation of the biopharmaceutical industry. Its very success and creativity is what makes this step possible. With key patents expiring, the time is appropriate. In proposing that the development and approval of follow-on biologics should be authorized, Novartis is drawing on decades of experience, as well as its current capabilities and portfolio across the full breadth of the biotech and pharmaceutical industry.

While care must be taken and standards maintained, the dramatic progress in biotechnology now enables the development of the first follow-on biologic products.

I would state that the success of the biopharmaceutical industry deserves comparable regulatory progress. The biopharmaceutical industry has made phenomenal progress since the first biotechnology based medicine was licensed in the U.S. in 1982. Technologies to make and characterize protein products have progressed rapidly in the last two decades. In the same manner, regulatory requirements need to evolve in line with this development to reflect state of the art science.

Thus, as the first generation of biotech medicines mature, it is time for a mechanism that encourages the development and approval of biologics.

Biotechnology medicines have the confidence of the public. It is essential that high standards for safety and efficacy the patients expect and that the biopharmaceutical industry has always provided in collaboration with FDA are maintained through appropriate and consistent regulatory requirements for all biologics.

These standards have been achieved through the application of science based regulatory requirements. Just as the science has progressed in leaps and bounds over the last two decades, so regulatory requirements need to evolve in line with this development to reflect state of the art science focused on the most appropriate criteria.

As recognized by the FDA leadership, it is not appropriate to use outdated regulatory requirements just because those parameters were considered useful historically.

Dr. McClellan's, immediate past FDA Commissioner, emphasized the importance of FDA now advancing to promote health. Under Dr. McClellan's leadership at the FDA, the critical path report was published: "Innovation Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products."

It highlights our opportunity to turn the art of drug development into the science of drug development, Dr. McClellan's own metaphor. As stated in the report, in many cases, the developers have no choice but to use the tools and concepts of the last century to assess this century's candidates and,

quote, unquote, the power to market for even successful candidates is long, costly, and inefficient, due in large part to the current reliance on cumbersome assessment methods.

These themes which apply to both innovative products and follow-on biologics highlight the necessity of revisiting all aspects of the progress made with medicinal biotechnology. The time has come to fashion the regulatory paradigm that will apply rigorous scientific criteria to continue insuring safety and efficacy while minimizing unnecessary or unethical duplication of preclinical and clinical trials, which raise resources that are needed for continuous innovation and that contribute to artificially high drug costs.

We should not be continuing to accumulate regulatory requirements and doing studies simply out of tradition. Industry can and should join now with the agency to achieve state of the art regulations that correlate with industry's state of the art science, stimulate and reward innovation across the full breath of the biopharmaceutical industry. The regulations for follow-on biologics should be designed as a series of science driven requirements that

stimulate the industry to become yet more creative and more efficient and thereby give the most innovative companies the greatest success.

Just as the scientist not staffing our expectations for regulations should not be carved in stone. Biologics are complex molecules that raise specific questions where the science today is not where it will be tomorrow. We cannot and should not design regulatory paths that circumscribe creativity. Instead we should create straightforward appropriate hurdles that assure the safety of the patient, give some predictability due to development and then show the availability of effective medicine through biotechnology.

Some biologics will be easier to make into follow-ons than others, others which may remain actually forever irreproducible.

Old models and mantras are inhibiting progress. The product is no longer the process. The process is important, but the product is no longer the process.

Choosing worst case scenarios and invoking always the precautionary principle to defend the status quo is disingenuous. Regulatory paths need to

be as dynamic as the products they oversee. The proven capabilities of our regulators must be stimulated to find new mechanisms, revisit old ones, and discard those that no longer contribute to the safety and efficacy of products.

The industry which relies on the confidence FDA approval gives the consumers of our products can demonstrate confidence in our regulators and work with them using the joint experience of all the stakeholders to design an appropriate route forward.

For this reason, the FDA initiative embarked by Dr. McClellan to publish a draft guidance on follow-on biologics should be completed as soon as possible. The draft guidance will reflect the best current thinking of the agency and such guidance is the best foundation for continuing the public debate.

The development of new regulatory requirements must be transparent and fair. For the select few products regulated under the Federal Food, Drug and Cosmetic Act there already is an existing pathway under Section 505(b)(2). Whatever regulations ultimately are adopted to enable and encourage follow-on biologics that are regulated outside of Section

505, they must come about through an open process.

Biologics are not drugs, and we should not try to force feed them into the generic drug paradigm. Instead we should enable discussion of all the issues, from access to innovation, from patterns to data exclusivity, and from sponsor obligations to regulatory commitments, and perhaps create a, quote, unquote, facilitated BLA or some such appropriate, entirely new regulatory entity.

All of these issues can best be addressed in the most open public process of all, the legislative process of the U.S. Congress. Novartis envisions a win-win solution whereby a follow-on biologics industry is enabled. Innovators receive regulatory relief from arcane requirements, and patients get access to high quality and improved biotechnology products at competitive prices. This is not a zero sum game.

In conclusion, we must capture the confidence appropriate to the creative and successful biotechnology industry and invite the cumulative experience and ideas of the best and brightest of our legislators, regulators, researchers, industry, and consumers in order to devise appropriate legislation

to enable a new regulatory mechanism for follow-on biologics.

We should expect all regulatory processes to be concurrent with scientific progress and not risk leaving patients waiting for life saving medicines due to unnecessary regulatory demands. Instead we should think ahead together as to what is needed for all biologics.

Regular scientific criteria meeting the highest standards must be applied for both originator and follow-on products. The new regulatory paradigm must be flexible, developed in a timely manner, and be compatible with the phenomenal read of scientific progress of biotechnology. It will enable a robust, responsible follow-on biologics industry to develop, stimulate investment into innovation across the industry due to more predictable intellectual property protections, resulting in new therapies to meet patients' needs and enable greater access to a broad array of medicines by patients.

This is not a type for paralysis based on hysteria and fear, but it is an opportunity to use the creativity for which the biopharmaceutical industry is known to provide access to yet more safe and effective

medicines for patients as effectively and efficiently as possible.

Follow-on protein products that are safe and efficacious as we originate the product can be developed based on a comparability approach entailing all relevant levels, if the strategy is chosen correctly and if the science is done properly.

Based upon our extensive experience with both drugs and biologics, Novartis has very clear views on general scientific concepts for development and approval of follow-on biologics, and we expect to present those in the submission to the public docket and also at the meeting early next year.

In the meantime, we support the issuance of regulatory guidance and establishment of legal pathways that maintain the regular standards of insuring product safety and efficacy, while at the same time allowing competition after legitimate intellectual property protections have expired.

Novartis looks forward to working with FDA legislators, colleagues in the industry, and academia and the other stakeholders to constructively shape this next critical path for the biopharmaceutical industry. We will very actively support this process

to provide solutions that will maintain an incentive for the innovator while providing access to more affordable medicines for patients.

Thank you.

(Applause.)

DR. WEBBER: Thank you very much.

One question. In situations where the quality attributes of the product that are critical for safety and/or efficacy are difficult or impossible to really assess in the follow-on products, would you suggest that we maintain a stricter requirement for manufacturing similarity and/or additional clinical trials to evaluate those or just forget the whole thing?

DR. HUKKELHOVEN: Yeah, I think it came up earlier this morning that there is probably a spectrum of complexity and perhaps a conceptual way to distinguish in complexity would be between nongycosylated and gycosylated proteins, although that is only one level of complexity. But we could foresee a situation where perhaps the amount of clinical testing with a glycosylated product should be more elaborate than with a nongycosylated product, but that needs to be determined on a case-by-case basis, and

that is what we mean with flexible regulations.

We believe that the science is there to assess what needs to be done in order to develop comparable biologics, but it will be on a case-by-case basis for each product, and as I said, there may be proteins that may be very difficult to reproduce, but we believe that most of them are reproducible by some scientific methods.

DR. WEBBER: You don't suggest that we have a higher stringency for manufacturing similarity between the two companies?

DR. HUKKELHOVEN: Well, I would think I'm not an analytical chemist, but I would think that the amount of tests that you do on the more complex proteins is more elaborate than on the less complex proteins.

We will, as I said, detail more of our thoughts to the docket when we do the submission.

DR. WEBBER: Thank you very much.

Okay. Our next speaker is Robert Adamson.

DR. ADAMSON: Thank you.

I'd like to thank the panel and the FDA for allowing me to come here and represent Wyeth's philosophy regarding a case study for comparability

and efficacy. Specifically what I want to talk about today is our learnings for recombinant Factor IX.

What I'd like to do is present this as a case study where our recombinant product would represent follow-on biologic and plasma derived high purity Factor IX already existing in the mid-'90s would represent the innovator module.

As distinct from what was said earlier on about there being some shame associated with the term "follow-on biologic," I'd like to suggest we'll proudly wear the mantle of follow-on biologic and did so; given that we brought forward the fact that there was a profound advantage in the use of our recombinant product compared to the incumbent product or the plasma derived product.

And I do believe that that should be the responsibility of follow-on manufacturers moving forward.

Factor IX is a critical component in coagulation. It's necessary for the coagulation of Factor VIII and subsequent coagulation. A deficiency in Factor IX leads to Hemophilia B. There are less than 200,000 Hemophilia B patients in the United States, and so accordingly, products can fall under

orphan drug status.

Recombinant Factor IX, or BeneFIX, needs to be activated prior to activity, and this is done by a proteolytic event, which is illustrated here, where the central region of the molecule is excised leaving the light chain and heavy chain held together by a disulfide bond.

If you look at the molecule, it is a very highly modified molecule which certainly falls into the complex category. From the end terminus on, there are four domains. The first domain is the so-called Gla domain where there are 12 glutanic acids which all need to be or most of which need to be gamma carboxylated for biological activity, followed by an EGF domain and the activation peptide, and then lastly the serine protease domain.

You will see by the colors that there are numerous post translational modifications on this molecule. The gamma carboxylation I've already mentioned, but there are a number of N- and O-linked glycosylations. There is beta hydroxylation. There is sulfation and phosphorylation, and I'll talk more about some of these modifications and the critical nature of these modifications to biologic activity.

We had a number of release specifications where we had to apply science and technology in a parametric way to make sure that when we released product, potency, identity, safety, and quality were preserved. I won't read through this list of characteristics, but it is an exhaustive list, and it was supplemented by a substantial and comprehensive characterization program.

For this product and all of the other products that we make, we have a top-down approach to characterization where we start off analyzing the impact molecule by a number of physicochemical means. Physical approaches such as optical rotatory dispersion, circular dichroism are used, as well as peptide mapping and carbohydrate fingerprinting of digested product.

In addition and subsequent to this, we have structural analysis of domains of the product where fine structural detail can be established by a number of different procedures.

In conclusion of these characterization and analysis, we were able to basically compare the post translational modifications between plasma derived product and recombinant product, and I'll lead

you to some extent through this table.

You can see that the number of Gla molecules for the plasma derived product were 12 per molecule of plasma derived Factor IX, whereas essentially recombinant factor lacked the twelfth of the 12 molecules.

Going down the list, O-glycosylation at Serine 53 and 61 were in both cases unusual but preserved. Beta hydroxylation was preserved. N-linked glycosylation was somewhat different between the two molecules being that recombinant Factor IX was less complex in terms of N-linked glycosylation, i.e., less branched and less modified.

O-linked glycosylation in both cases was similar and partial at the immunoacids indicated.

And lastly, and most importantly, two very subtle modifications of the protein which in the mid-'90s were not seen as significant modifications were those of sulfation at Threonine 155 and phosphorylation at Serine 158. As you can see, there was a significant difference between the recombinant product and the plasma derived product.

Importantly, in addition to these post translational modifications, we also saw that the

amount of aggregation in plasma derived products of a number of different types was significantly different. So-called high molecular weight species was significantly higher in plasma derived product than it was in recombinant Factor IX.

Moving on then to the PK/PD data and our preclinical and clinical experience, we did find that there was a subtle difference -- I should say subtle but significant difference -- in bioavailability or in vivo recovery between the two products. That is that even though both products were injected IV, there was a significant reduction in the bioavailability of the recombinant product versus the plasma derived product.

So approximately 30 percent of the recombinant product was less available when recovery was observed. This is indicated here in the next slide where we compared the cohort, a small cohort of Hemophilia B patients and found that recombinant factor was, indeed, recovered 30 percent less efficiently than the plasma derived counterpart.

And as you can see, we were able to put together appropriate and correlate models in both the dog and the rat so that we could put together structure function studies with the appropriate models

in mind.

When we did this, and these are the results of these structure function studies, I want to make sure that I properly recognize the fact that all of the specification release and characterization methodologies that I talked about very fleetingly before were essentially brought to bear on this experiment.

So without prior knowledge and experience of the product and the methods through predevelopment, development and commercialization, we would have been unable within the time frame we had available to put this data together.

Having said that then, plasma derived product is represented in blue and recombinant product in green, and as you can see, going from the left in, there is a 30 percent drop in biological recovery between recombinant Factor IX and plasma derived material.

I apologize for the X axis, but I'll essentially read it to you. The next three lanes indicate subspecies of the BeneFIX molecule which we fractionated, which have different levels of gamma carboxylation. The one on the left has ten, and then

11 and 12.

And as you can see, there was no sign that increased or differential gamma carboxylation had anything to do with this effect.

In the next lane we isolated high molecular weight from plasma derived material and added it back to recombinant product and that had no effect.

In the next two lanes, called FT-1 and FT-2, these indicate different glycosylation patterns which we thought might be more relevant to plasma derived material, so basically taking more branch material and more sylated material from recombinant product and enriching for that, subpeciating for that and adding it back to the experiment, and again, that had no effect.

What did have a substantial effect, as you see, was fractionating the small quantity of highly sulfated material such that close to 100 percent of the fraction was sulfated and using that in the experiment.

So our conclusion from this experiment was that the highly charged, dense activation peptide in the middle of the recombinant Factor IX molecule,

which as you can see here is covered in negative charge with a sulfate, phosphate and a number of O- and N-linked glycosylation sites.

The charge density of this are of the molecule even in subtle terms, plus or minus one or two charges, has been seen to be very, very important in the biodistribution, the in vivo recovery of this molecule.

Once we were able to establish the critical moiety in structure function, we were able to make sure that this moiety or the degree of sulfation of the product was consistent from batch to batch, and you can see this is data over a two-year period where we did that.

So in summary, to conclude, we believe that comparability established between recombinant Factor IX and highly purified plasma-derived product was, in fact, established. The reduced bioavailability was observed for Factor IX and in vivo models, and attempted for by in-depth characterization.

On the basis of this, we ere awarded orphan drug status on the basis of improved biosafety, and we attempted for reduced bioavailability by

specifying a dosing regimen in the package insert.

Lastly, it should be made very clear that clinical studies that we did were very stringent and as comprehensive as those counted out for the high purity, plasma-derived incumbent.

Lastly, and very quickly if I can -- I've just got three more slides to make the same point as a number of people have made previously -- this we believe constitutes innovative company know-how. The ownership or being proprietors of the production cell line of clone, call it master cell bank if you will, but the important thing as far as we are concerned is to own the cell line. Critical raw materials, internal standards, and process, along with in-process controls.

We'd like to emphasize in addition to what's been said previously that critical structure function studies like these illustrated based on innovator know-how are critical.

We'd also like to make the point that his is exactly the same list, we believe, that we have, whereas FOBs manufacturers will be unable to obtain, and so this is a very differentiate in principle.

Lastly, and to conclude finally, we do

believe as has been said before that FOBs manufacturers will and should be able to develop and manufacture follow-on biologics. But given the complexity of biologics processes and products, a detailed database will be required to insure safety and efficacy, and that database should include what's listed up here.

So basically, as I said at the outset, we were proud to wear the label of follow-on biologic or in principle we would be proud to wear the label of follow-on biologic manufacturer, bringing higher quality of product to the consumer. We think that follow-on biologics manufacturers should have the same responsibility so that in addition to bringing better economics to the product, they should bring equivalent at least safety and efficacy.

Thanks very much.

(Applause.)

DR. WEBBER: Okay. Thank you very much.

And that brings us to exactly 12:30, which is the endpoint for the manufacturing session. So I'm afraid we won't have time for questions in addition.

I'd like to thank the speakers for some very stimulating discussions with regard to

manufacturing, as well as overall issues.

We will be returning promptly at 1:30 after lunch to begin the characterization session. Lunch is on your own. So we'll see you in and hour.

(Whereupon, at 12:31 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m., the same day.)

AFTERNOON SESSION

(1:30 p.m.)

DR. WEBBER: Okay. I think it's time that we get everyone to take their seats so we can convene the afternoon session.

I hope everybody had good lunch or found good lunch somewhere in the area, got a chance to check all of your E-mails and voice mails and whatnot, which reminds me. If anyone has turned on their cell phone during lunch and it's still on, please turn it to vibrate or turn it off, one or the other, so that we don't disturb any of the speakers during their presentations.

Now, the next session is going to be a two-hour session. We have eight speakers to discuss or present their views on issues related to characterization, and at this point I think we should introduce the panel who will be receiving these presentations.

And again, I will ask the panel to introduce themselves just so that they can give their names as well as their affiliations in the most fitting manner.

Thank you.

DR. CHERNEY: Okay. I'm Barry Cherney. I'm the panel lead for the session on the characterization.

I don't think there's any question that in these type of follow-on exercises the physicochemical characterization is going to play a critical point in this process. So I'm looking forward to hearing what the speakers have to say on this topic, and at this point I'd like to introduce or have the rest of the FDA panel introduce themselves.

DR. YU: Lawrence Yu, Director of Science, Office of Generic Drugs.

DR. EGAN: Bill Egan, the Acting Director for the Office of Vaccines at CBER.

DR. MOORE: Steven Moore, chemistry team leader in CDER.

DR. CHANG: Andrew Chang, Acting Deputy Director for Division of Hematology, Office of Blood, CBER.

DR. CHERNEY: Okay. To frame the topic for this, we did ask several questions that were in the Federal Register notice. I don't know if Keith will put them on the board, but I'm not going to reiterate them other than to say that the questions

really revolve around the capability of analytical methods to characterize the product and to predict the safety and efficacy of the product.

And in addition, we were trying to get to see if there are new analytical techniques that might be useful in these types of exercises and some of the factors that are involved and what we should be looking for and what we should stress in these types of exercises.

So without further ado, I'd like to introduce the first speaker, which is Richard Zeid. Sorry. Robert Zeid. Sorry.

MR. ZEID: Thank you.

Good afternoon. My name is Bob Zeid. I'm the principal consultant with TLI Development, and I want to thank again the FDA for the possibility of the opportunity to present on this very critical and rapidly emerging topic.

The presentation that I want to talk about today is structure activity relationships and their uses and limitations in this follow-on paradigm that we're discussing. A number of people have already brought up excellent examples of both, but what I'm trying to do in the preparation of my presentation was

to focus on a methodology or approaches which would actually be useful to a regulator's mindset, which is a public safety mission.

And so with that in mind, I have tried to strike a balance and give some tools which may be or approaches which may be valuable.

With my first slide, let me just say there's no doubt that structure-activity relationships have a well established and useful and they are an integral part of any development program, and so it's a widely used aspect of both the follow-on paradigm as well as comparability protocols.

I'll just forego with the laser, but certainly what I wanted to point out is just a few examples of where structure activity relationships have been highly integrated into all of these programs.

Certainly one of the most notable things that we're discussing is any fast track or expedited program or expedited review, but the key question I have is: how much confidence can one have in comparing one product to another? And is the structure-activity relationship truly portable or not?

And that really comes down to the

quintessential question of multi-source biotech or therapeutic equivalent biotech, is there's no disputing that one can establish therapeutic equivalence. It's just a debate as to how much data is absolutely necessary to describe it without a doubt and to instill the public safety mission of safety and efficacy.

But my hope is that if SAR or if this concept is portable from one manufacturer to another, then it could be a useful tool to distinguish important or inconsequential differences in product profiles, and thus, it may actually help expedite development for both innovator as well as comparator companies because it would allow us to eliminate unnecessary or duplicative preclinical studies, as well as to focus in on the clinical program which is most relevant.

So I guess the key point is not so much what the differences are as much as what they bode for safety and efficacy, and that is the large, foggy area that I believe a lot of us are wrestling with, but my hope is that if we are able to actually establish a structure-activity relationship database for various product classes, that this can actually be a wonderful

foundation for general chapters in compendial monographs and can provide a useful tool for regulators to harmonize their assessments of manufacturing changes from one manufacturer or from several manufacturers of the same product.

Now, as the title denotes, there are limitations of structure-activity relationship, and I'd like to give credit to Dr. Davis of Lilly. I borrowed some of his concepts from a great presentation that he did, and to his credit, I wanted to bring out some of these.

The purpose of this presentation is to really highlight the fact that the limitations of structure-activity relationship do not preclude its use or its vital contribution to a multi-source or a follow-on program. It's just at one point or another what does the manufacturer have to demonstrate to the FDA's confidence that these manufacturing relationships and these structure activity relationships have been established.

What I have often considered in the whole realm of therapeutic equivalence is really this slide that brings up the tiered approach to testing for demonstrating therapeutic equivalence. These concepts

are well established in the ICH and FDA guidelines with respect to a tiered approach depending on product complexity, the nature of the change, the clinical indication, immunogenicity, et cetera.

But what I did want to highlight here is that by virtue of using some key novel technologies, we can integrate structure-activity relationships and an emerging database. We can link the physicochemical profile of the product to critical parameters that may be observed in manufacturing or those which might emerge in stability.

And also what was really brought out in startling detail and excellent review by Dr. Adamson from Wyeth-Ayers earlier is structure-activity relationships can often be detected in pharmacodynamic responses, as was shown with the recombinant Factor IX versus BeneFIX or versus plasma-derived Factor IX.

So the point being that these relationships exist, but it is incumbent upon a comparator company to explore them and develop this database so that they come to the FDA with almost a neural net approach in terms of what is a manufacturing process and in terms of optimized parameters, potency. What does your stability profile

look like compared to another product? And, of course, what does this bode in terms of bioassays and biological activity?

And in addition to the FDA questions, which I will try and address at least one or two of them, I have some of my own. Key among these is: are the analytical methods robust enough to actually compare critical parameters from one manufacturer to another?

In some cases, yes. I would like to point out an exception to the rule doesn't mean that the rule does not apply. Put another way, there are exceptions to the current generic manufacturing, generic ANDA mechanism that we have. For instance, topical antifungal creams require a bio IND, but that does not negate the value of the ANDA regulatory paradigm that we all routinely use.

What I'm saying is that even if structure-activity relationships do not appear or are not apparent in some product classes, they may be in others, and that this physicochemical profile is portable across different manufacturers.

A key question, too, is is this physicochemical data when it's correlated to

structure-activity relationship, does it allow for expedited development by someone else?

In certain cases, yes, but in other cases it appears to be an open question.

Is the comparability to a compendial standard or a precursor gold reference standard still applicable to multiple manufacturers as it is to the innovator, as was originally brought out in the April '96 comparability guidelines?

Here, again, I believe it is because the precedent is already there. A great number of innovator firms did a wonderful job of showing their product in comparable activity to NIST, NIBs, WHO reference standards, as well as a panoply of other products that were already approved on the market.

But the benefit to society is that these products were delivered sooner and faster, and society as a whole has benefitted by that.

Can the structure-activity relationship help address any observed differences in microheterogeneity?

And obviously, yes, this can, but in lieu of full comparative safety and efficacy studies, that appears to be a conservative approach that I'm sure

most regulators would say no; that unless you have some body of data to show the microheterogeneity does not impact the bioassay and that that bioassay is directly linked to some surrogate marker and safety and efficacy and you can make the connection that your structure activity shows you no difference as purported in the clinical trial, then I would say, yes, you can save yourself some clinical development.

But in large part, the structure-activity relationships are poorly understood and not fleshed out. So I would be remiss if I say that SAR could help deliver a package that was completely devoid of clinical safety and efficacy, but there may be some confirmatory testing as opposed to the full double blind, randomized, clinical trials or proof of principle studies.

And of course, all things being equal, can the structure-activity relationship help reduce or eliminate the need for preclinical testing?

As previous speakers have elucidated, yes, this can, but it is really dependent upon the product complexity, as well as the purported mechanism of action.

And I do believe the last question is

this concept can be used to facilitate manufacturing changes across multiple manufacturers or even large manufacturing changes within a single innovator. So here are some key considerations that I just wanted to bring to bear, is that if I were to advise a client, I would ask them or consider that they would want to perform side by side physicochemical analyses of several lots of their product to several lots of an innovator. They would also want to do force degradation profiles to assess what kind of rate and kinetics of impurity formation they have.

Are you seeing novel impurities or are you seeing different levels of the same impurity?

This also goes with the microheterogeneity. Are you seeing a different glycosylation pattern versus the innovator, or do you see a glycosylation pattern of your product degenerate into something different even though they start off initially the same?

And once you have a single source of data in your hand of side-by-side comparison, I think then you can start to make a more accurate assessment of the next step, which of course you would want to evaluate bioassay activity. It's a regulatory

requirement that all biologics require a potency assay because of their complexity. The chemical composition, the chemical characterization is insufficient.

So the bioassay, actually we have a panoply of tools in front of us: tissue based, whole animal, ex vivo, human. So there are a variety of different methods by which we can explore this, and I would dare say I think rather than being limited in the scope, I think that their possibility, the potential is yet to be tapped.

So the key here is to summarize these data for the in-house observed changes and differences and what relevance they might have to safety and efficacy. Where you don't know, that should be also noted, and you need to try and summarize these structure-activity relationships, what you've observed in terms of the finished product as compared to how is this being integrated into the manufacturing process parameters and the stability and other key aspects such that you're not on an edge of failure in your manufacturing realm, and you have confidence that you're going to deliver a product which is well within the optimized criteria you want.

Let me just wrap it up here then. The conclusion and action items is that we really need to explore this more thoroughly, and I think it offers a wonderful scientific venue for a lot of opportunity here.

Once this is established, we can then integrate it into the scientific and compendial areas, regulatory decision trees, and perhaps legislative aspects.

Thank you very much.

(Applause.)

DR. CHERNEY: I think we have time for a question.

DR. YU: At a recent scientific discovery meeting, one expert made the following statement: "The SAR can provide useful and supportive information. However, it cannot provide definitive and conclusive information for scientific decision making."

I just wonder if this is still the case for follow-up protein products.

MR. ZEID: I would agree with that. I would agree that SAR is vital. It's a vital part of the foundation of the package, but you cannot make the

regulatory determination by that alone, and that the analytical comparability, the pharmacokinetics and pharmacodynamic studies in conjunction with SAR and the manufacturing process data should give you a very comfortable level for some of the simpler programs like insulin, growth hormone, and GCF.

But come of the more complex products, the heavily glycosylated monoclonals, even though these are complex and they have very specific activities, I think think that you're going to be looking at a single open label or a confirmatory clinical trial to look at immunogenicity and bioavailability.

DR. CHERNEY: Thank you.

At this time we'll have our next speaker, Arnon Chait.

DR. CHAIT: Good afternoon, and thanks for the opportunity. I would like to thank actually Robert for making such a good initial case for me.

I'll present basically technology that, among others, could actually help kind of unravel a little bit of the mystery, but maybe I should start off by saying that I'm not going to render any opinion on any particular site because really my role here, I think, is to more present perhaps kind of the new

frontier, if you wish. Frontiers in technology and science is dispassionate. Our technology, as well as some other people I know in the crowd, could easily serve both sides of the picture simply in proving both the safety and efficacy and repeatability of these products.

So, again, the key needs, to summarize it from a nonregulatory constraint, in simple English is basically to insure function, safety, and repeatability.

What I'll say really is more focused on the latter part, which is repeatability, but definitely if somebody would ask me again, I could definitely say something about structure pivotal relationship because the technology lends easily to the first two.

So basically when we talk about characterization of protein as a very complex product, there is many ways. There are hundreds of methods. People have done lots of careers just on one specific method.

One-D, 2D, physicochemical toxicology, PK/PD, et cetera, what's missing? And what's missing really is anything that has to do with the three

dimensional higher order structure because protein, as we all know, their function is obviously ultimately imbedded in the intermolecular interactions, which means that if you know how the other part of the molecule looks like, you are definitely much, much closer to function than any other techniques that look at the specifics of how the molecule is made.

So really, it lends you automatically to say that if we had a simple technique to see all of the atoms and where they are, then we'll be where small molecules are today because that's what we do in small molecules. It's a rigid structure, and then we simply ascertain that this is so, and therefore, it's an aspirin.

If we can do the same thing for EPO, we might be in good shape if we know all of the atoms, but we know that this is absolutely not true, and it's not true mainly because all products, as has been said before many times, are heterogeneous, especially with respect to glycosylation, et cetera, and we don't understand the structure activity relationship very well, and there is just too much data.

So we have data overload. A lot of it is meaningless. A lot of it actually contradicts the

study. So basically we're saying we give up, and it's exactly the truth. The detailed structural characterization, namely, knowing where all of the atoms are, is not very useful to satisfy the key needs.

It might be very useful to somebody trying to describe the molecule as structural biologists, but not for our purpose, but what is actually useful is if we can simply not give up on the idea of looking at the entire molecule, and instead let's talk about focus information of the three dimensional structure, and that could be very highly useful.

So instead of describing what all of the atoms are anymore, we simply are saying we're still interested in this function, which is related to the structure, but we'll describe it in application specific terms.

And that really lends us to the idea of a signature, and again, we're not discussing our technology in a moment, but there are the technologies looking, I know, specifically on glycosylation pattern, for example, which is quite unique and lends itself very well with what I'm discussing here.

So instead of talking about the structure,

which is complex and we don't care about too much, we'll talk about the signature of a structure. So it's very simple, should be simple. Otherwise nobody is going to use it, easy to obtain and can be constructed specifically for every need.

So instead of one structure where all of the atoms are that we don't care about, we're talking about perhaps ten, 20, whatever. Whatever is of interest to you, you can derive a signature of that structure with respect to that need.

So, again, conventional characterization versus signature, just to even drive it home a little bit better, basically tells you something about the molecule. It tells you what's the chemical make-up of this. It tells you the charge, molecular weight, alpha-beta, whatever you want. It tells you a lot of stuff about the molecule, where signature really talks more about the state of the molecule, typically in relation to a standard. it is not an absolute thing. It's not like a melting temperature of a protein. It is more if you give me a standard and say that this is okay, can you say something about by looking at how the molecule is constructed perhaps, some aspect of it on a 3D. Can you say whether it's related to that

standard?

And you can, therefore, derive signature for the degradation state specific for a molecule; aggregation including things that are very complex like aggregation and dosage form; confirmation, which is the holy grail, namely, does this confirmation look like the same as this confirmation after we expose it for 40 degrees for seven days, et cetera.

And of course, similarity to well characterized standards, and I'll discuss again one technology, and we have another technology here that easily could have been here instead of me saying the same thing, I think.

Again, our technology is Structural Signature Technology. That's the name of it, SST, and it's product and purpose specific, highly sensitive, and again, specific, and I said it twice again.

You can derive many signatures depending on what your needs are. It's very easy to use, very easy to acquire, which means it's useful, and if you ask yourself statistically could you say with any certain power that the answer is X, Y, and Z, given the sample that you use to derive your data sets, we can say in the same way that most other techniques are

couched in.

And more importantly, of course, because now remember if we claim at least that we had a method to look at the 3D structure, then obviously we should say something about the function even though I don't venture it. We have a lot of data that does correlate very well with aspects of functionality.

The scientific basis of it is basically the method response for 3D arrangement of the solvent exposed residues. We don't look at how the inside of the protein looks like. The business end of a protein is how it interacts with other protein or with outside, and what we do is we construct basically structures of solvents, aqueous based solvent and simply try to see what is the thermodynamic difference between interacting with a custom Water I and custom Water II.

It sounds very complex, but it's a very simple assay. It's again thermodynamically going back to the origin, and it's very easy to construct.

Some examples, these are just pictures. Usually it doesn't work with pictures in practice, of course, but you can look at it at the bar chart almost and look at the shape of these bars as telling you

something.

So the top left is, for example, maybe a particular signature that's responsive for your reference, and -- I don't know -- the one on the right a little bit next to it could be something that has a residue modification or oxidizer, deamidizer or whatever.

Actually, they're all real cases actually. The one on the far right compares a properly folded and unfolded protein. Very simple; it's intuitive almost to see between the dark and the light shades.

We can also look at the bottom left, for example. It's microheterogeneous. I know it's the buzz word; it's the key word. They are microheterogeneous; therefore, you cannot touch them.

That's not true. Every lot, and on the X axis we have a lot and on the Y axis is what we measure. You can put a bar on one below and above, correspond to products that are coming out of different lots, and you can place basically plus-minus three sigmas around there, such that if something that has reduced potency or creativity or whatever it is that you're interested in falls outside, that is fine, too.

And finally, on the right what we have is actually a study that is stuff that we can buy on the street. These are just ribonuclease A, for example, and we did an intervenor and intra-vendor studies of product consistency with respect to 3D structure.

And, again, nobody is buying anything here, but just to simply say there is a technology. It is automated. The chemistry is standardized. There is a statistical basis behind it.

And finally, the last two slides actually, I think that really more is better. You know, we kind of are thinking about, oh, you give us so much data, and then the data someone conflicts itself, but if you look at the data in 30,000 feet view almost, all data is good, and again, if the data could somehow combine using methods that I'm not going to describe now, but nevertheless describing the protein, then it's good.

So, for example, today if we use conventional characterization and functional data to describe, say, EPO, which is there on the right, then if you derive a signature based characterization, namely, remember we are not describing the molecule make-up anymore, but how it looks like on the outside, sort of the business end of this.

If we take signature based characterization and somehow be able to find not all the time, but some cases functional relationship between them, then of course what one can do is in the future simply work within the green box and be able to describe the molecule in both conventional characterization, which we do not displace; of course not, as well as things that represent the function or the structure, the high order structure of the molecule.

So finally as kind of my own understanding at least, is: is complexity equal to risk? And actually there have been in many other industries. When you fly your next plane, trust me. They are not doing anything except measuring 500 signatures continuously of what's happening there inside the engine, and if they see things that are kind of vibrating a little bit on and off, they know how to interpret it.

Even though they don't understand what it exactly means, that's sort of their all. And complexity, again, is not an excuse for not approaching forward the thing that science can answer today.