FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Thursday, May 25, 2017

8:00 a.m. to 11:39 a.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. RINI: We are going to go ahead and get started. Good morning. I am Brian Rini, acting chair for this meeting. I would like to remind everyone to silence their cellphones or other devices if you haven't already done so. I would also like to identify the FDA press contact, who is Angela Stark who is waving in the back of the room.

To start, we will go around, and I will ask the panel members to introduce themselves and where they are from and their expertise, and we will start with Dr. Gordon.

DR. GORDON: Gary Gordon, medical oncology. I am vice president for oncology development at AbbVie, and I am the alternative industry representative.

DR. MAGER: Don Mager, professor of pharmaceutical sciences at the University of Buffalo.

DR. ESTRELLA: Michelle Estrella, nephrologist, associate professor at University of California San Francisco.

DR. CRAMER: Steve Cramer, chemical engineering professor, bioprocess engineer analyticals.

DR. KARARA: Adel Karara, professor, University of Maryland Eastern Shore.

DR. LEWIS: Julia Lewis, nephrologist, Vanderbilt.

DR. WALDMAN: Scott Waldman, chair of pharmacology and experimental therapeutics, Thomas Jefferson University, Philadelphia.

DR. ARSCOTT: Karen Arscott, associate professor in medicine at the Geisinger Commonwealth School of Medicine, patient representative.

DR. ULDRICK: Thomas Uldrick, hematologist, medical oncologist, Center for Cancer Research, NCI.

DR. COLE: Bernard Cole, professor, statistics, University of Vermont.

DR. RINI: Brian Rini. I'm a GU medical

oncologist at Cleveland Clinic.

DR. TESH: Lauren Tesh, designated federal officer for ODAC.

DR. NOWAKOWSKI: Grzegorz Nowakowski, hematologist at Mayo Clinic Rochester.

DR. RIELY: Greg Riely, medical oncologist, Memorial Sloan-Kettering.

DR. KLEPIN: Heidi Klepin, geriatric oncologist, Wake Forest.

DR. HANCOCK: William Hancock, Northeastern University, analytical chemistry, HPLC mass spectrometry.

DR. KIRSHNER: Susan Kirshner, FDA, Office of Biotech Products, and I am doing CMC immunogenicity.

DR. LACANA: Emanuela Lacana, associate director for Biosimilar and Biological Products in the Office of Hematology Products.

DR. CHRISTL: Leah Christl, associate director for Therapeutic Biologics in the Office of New Drugs, CDER, FDA.

DR. de CLARO: Angelo de Claro, clinical

team lead, FDA.

DR. FARRELL: Ann Farrell, division director, Division of Hematology Products, CDER.

DR. RINI: Introduce yourself.

MS. PREUSSE: Courtney Preusse, patient representative, Fred Hutch.

DR. RINI: For topics such as those being discussed in today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place only in the open forum of the

meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing details of this meeting with the media until its conclusion. Also, the committee is reminded to refrain from discussing the meeting during any breaks or lunch. Thank you.

Now I will pass it to Lauren, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employee from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and

conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of the regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as

well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves biologics license application 125545 for the proposed biosimilar to Amgen Inc.'s Epogen/Procrit, epoetin alfa, submitted by Hospira, Inc., a Pfizer company.

The proposed indications, uses, for this product are, one, for the treatment of anemia due to chronic kidney disease, including patients in dialysis and not on dialysis to decrease the need for red blood cell transfusion; two, for the treatment of anemia due to zidovudine administered at less than 4,200 milligrams per week in HIV-infected patients with endogenous serum erythropoietin levels of less than or equal to 500 milliunits per mL; three, for the treatment of anemia in patients with non-myeloid malignancies

where anemia is due to effect of concomitant of myelosuppresive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy; and to reduce the need for allogeneic red blood cell transfusions among patients with perioperative hemoglobin of greater than 10 to less than or equal to 13 grams per deciliters who are at high risk for perioperative blood loss for elective, noncardiac, nonvascular surgery.

This is a particular matters meeting during which specific matters related to Hospira's BLA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry

representative, we would like to disclose that Dr. Gary Gordon is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Gordon's role at this meeting is to represent industry in general and not any particular company. Dr. Gordon is employed by AbbVie.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. RINI: Thanks, Lauren. We'll now begin with an FDA presentation regarding the relevant regulatory pathway from Dr. Leah Christl.

FDA Presentation - Leah Christl

DR. CHRISTL: Good morning. What I am going to do first is go through an overview of the regulatory framework and FDA's guidance regarding the development and approval of biosimilar products in the U.S. This won't be product specific. This is a general overview about the regulatory pathway; get you familiar with some definitions, terminology; lk about the approval pathway and the standard; and then walk you through the development of biosimilars, talking about our approach to development and some specific development concepts.

After my presentation, we will have an opportunity for the committee to ask general questions, again, not product-specific questions. That will come later.

In looking at an overview of the BPCI Act, this was signed into law on March of 2010, and what it did is it created an abbreviated licensure pathway for biological products that are shown to be biosimilar to or interchangeable with an FDA-licensed reference product.

It states that a biological product that is demonstrated to be highly similar to an FDA-licensed biological product, which is referred to as the reference produce, may rely for licensure on, among other things, publicly available information regarding FDA's previous determination that the reference product is safe, pure, and potent.

This licensure pathway permits a biosimilar biological product to be licensed under what's referred to as 351(k) of the Public Health Service Act based on less than a full complement of product-specific preclinical and clinical data. That is where the abbreviation comes from.

A little bit more about what we mean by an abbreviated licensure pathway. This pathway doesn't mean that there's a lower standard for approval that is applied to biosimilar or interchangeable products than to the originator biological products. What it does mean in terms of the abbreviation is that there's an ability for the biosimilar sponsor to rely on FDA's previous

finding regarding the reference product to support approval of the biosimilar product. Then this allows for potentially a shorter and less costly drug development program.

This is what is meant by an abbreviated licensure pathway. It is through this reliance, and it is really an issue of the data package that is required for approval, which for biosimilar and interchangeable products is quite extensive.

You will hear later today product-specific information about the analytical and non-clinical and clinical studies to support a demonstration of biosimilarity with the reference product.

Once a biosimilar or interchangeable product has been approved by FDA, patients and healthcare providers can rely on the safety and effectiveness of that FDA-approved biosimilar or interchangeable product just as they would the reference product that the biosimilar was compared to.

To walk through some terminology and definitions that are outlined in the BPCI Act for you, the BPCI Act states that the biosimilarity

means that the reference product is highly similar -- or that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the reference product.

Both of these standards need to be met. Again, it needs to be highly similar and have no clinically meaningful differences. It is not one or the other. It is both for biosimilarity.

What do we mean by reference product? The Act states that the reference product is the single biological product licensed under 351(a) of the Public Health Service Act against which a biological product is evaluated in an application that's submitted under 351(k) of the Public Health Service Act.

An application that's submitted under 351(a) of the Public Health Service Act can be referred to

as a stand-alone application, and this application contains all the information and data that is necessary to demonstrate that the product is safe, pure, and potent. In contrast, an application that is submitted under 351(k) of the Public Health Service Act for a biosimilar or interchangeable product needs to demonstrate that the proposed product is biosimilar to the reference product.

Again, for licensure, the proposed product relies on, among other things, comparative data with the reference product as well as publicly available information regarding FDA's previous determination that the reference product is safe, pure, and potent.

While the application under discussion today is not seeking licensure as an interchangeable product, it is seeking licensure as a biosimilar product, the BPCI Act states a product can be biosimilar to or interchangeable with a reference product.

Interchangeability is described in the Act that the biological product is biosimilar to the

reference product. It can be expected to produce the same clinical result as the reference product in any given patient, and for a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the proposed product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

The Act goes on to state that the interchangeable product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the product.

Again, just to remind folks, the application under discussion today is not seeking licensure as an interchangeable product.

The BPCI Act discusses some general requirements for a biosimilar. The application needs to include information showing that the product is biosimilar to the reference product, that it utilizes the same mechanism or mechanisms of action for the proposed conditions of use but

only to the extent that the mechanisms are known for the reference product.

So it's not incumbent on the biosimilar applicant to determine the mechanism of action in isolation, but they do need to provide information that where this is known, that it does utilize the same mechanism or mechanisms of action.

The conditions of use proposed in labeling for the proposed product need to have been previously approved for the reference product; needs to have the same route of administration, dosage form, and strength as the reference product; and where it's manufactured, processed, packed, or held, that facility needs to meet the FDA standards to ensure that the product continues to be safe, pure, and potent. And those standards are no different for a biosimilar or interchangeable product than they are for a stand-alone biological product in terms of the manufacturing standards.

The types of data that we would expect in a 351(k) application for a biosimilar or interchangeable product are also discussed in the

Act. In general, the data elements would include information demonstrating biosimilarity based on data derived from analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; animal studies, including the assessment of toxicity; and a clinical study or studies, including an assessment of immunogenicity, pharmacokinetics, or pharmacodynamics that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar product.

The Act does state that FDA may determine in its discretion that one of the data elements that are described above is unnecessary to support a 351(k) application for a proposed biosimilar or interchangeable product.

The PHS Act, as I said, defines reference product for a 351(k) application as the single

biological product licensed under 351(a) of the PHS Act against which the biological product is evaluated. However, FDA has taken a regulatory position that data from animal studies and certain clinical studies comparing a proposed biosimilar product with a non-US-licensed product may be used to support a demonstration of biosimilarity to a US-licensed reference product.

However, the sponsor does need to provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the US-licensed reference product. So there has to be an acceptable essentially three-way bridge between the products to support such an approach.

The type of bridging data would include direct physical chemical comparison of all three products in these three pairwise comparisons. It would likely include a three-way bridge and clinical PK and/or PD data as well, and all three pairwise comparisons should meet the prespecified

acceptance criteria for analytical and PK and/or PD similarity to support such an approach.

Again, it is incumbent on the sponsor to justify the extent of comparative data needed to establish the bridge to the US-licensed reference product and to support the relevance of the data that is generated using a non-US-licensed comparator to a demonstration of biosimilarity with the US-licensed reference product.

When looking at an overview of the FDA's approach to the development of biosimilars, FDA's published a number of both final and draft guidances in different scientific areas to support the demonstration of biosimilarity and how it is that we would look at how the data should be generated and also what would be needed to support a licensing application.

It is a little easier, instead of walking through individual guidances, to talk about some key development concepts. The first concept to understand is that the goal of the stand-alone development program and the biosimilar development

program are different. The stand-alone development program, its goal is to establish safety and efficacy of a new product.

The type of data that you would be expected to see in an application coming from a development program would include analytical information; chemistry manufacturing controls information about that product; non-clinical data; animal studies; an assessment of toxicity; any other animal studies that would be necessary; clinical pharmacology studies looking at exposure response; dose-ranging studies, those types of things; and then clinical safety and efficacy studies ranging from phase 1 to phase 3 studies.

We would look for a phase 3 clinical study typically. It could be one with justification that would support the demonstration of safety and efficacy in each condition of use for which they're seeking licensure.

In contrast, for the 351(k) pathway for proposed biosimilar and interchangeable products, the goal of that development program is to

demonstrate biosimilarity or interchangeability to the reference product. You'll see the same types of data in terms of the analytical and non-clinical and clinical pharmacology and additional clinical studies, but these are all going to be comparative studies in general.

The weight of these studies and how it is that we use these studies is different because, again, the purpose of the development program is different. It is not incumbent upon the biosimilar to independently demonstrate the safety and effectiveness of their product. They're demonstrating biosimilarity through their program. So this does have an impact on the development programs and the generation of data.

This next key concept is this concept of stepwise evidence development, and that supports that pyramid approach of how it is that we look at the data and the data generation.

We've outlined a stepwise approach in our guidance and in our advice to sponsors. There's an evaluation of residual uncertainty at each step of

the data generation beginning with that foundation of the analytical comparison. There's also a totality of the evidence approach in evaluating biosimilarity. There is no one pivotal study that demonstrates biosimilarity. Folks think for stand-alone program pivotal phase 3 safety and efficacy studies.

Here, there's no one study that demonstrates biosimilarity. There's not a single pivotal study. It's really this totality of the evidence, all the similarity data that's generated, these comparisons to the reference product that supports the demonstration of biosimilarity.

Because of that, there's really no one-size-fits-all assessment that's happening. The stepwise approach, you're looking at the evaluation of residual uncertainty. With any given development program, you're looking at the data along the way, what differences have been observed; what are those potential impacts of the differences?

What residual uncertainty do you see as data is generated based on the comparative data and

looking at those differences and the potential impact? Then what study or studies will address the residual uncertainty? You want to make sure that the study that's being conducted is going to adequately answer the question that is in front of you.

The third key concept is looking specifically at the analytical similarity data. As I mentioned, this is the foundation of a biosimilar development program. And this is where we see extensive structural and functional characterization of both the reference product and the proposed biosimilar product.

Folks are familiar in terms of hierarchy of protein structure. You've got primary structure, secondary, tertiary, quaternary structure, and all of this needs to be evaluated within this analytical assessment.

You have heterogeneity. These products are going to be naturally sourced or produced through a biotechnology or recombinant technology typically. So there will be some heterogeneity to that for any

biological product that's produced, but that also needs to be assessed.

For a given product, a given biological product through the manufacturing process in a biotechnology system, you will also have lot-to-lot variability. You'll have that for the reference product. You'll have that for the proposed biosimilar product. That also needs to be evaluated for both products as a part of the analytical assessment.

What it is that we're looking at in terms of the analytical similarity assessment, again, it's this comprehensive structural and functional analysis doing a comparative assessment of the attributes that include a number of factors that are listed here: looking at amino acid sequence, heterogeneity, bioactivity, impurities, and looking for any differences where they need to be assessed as to their potential impact.

Again, there is a functional analysis that is also done as a part of this, and where a molecule is known to have multiple biological

activities, where feasible, each should be demonstrated to be highly similar between the products.

So what you're looking for here is understanding the molecule, its function, and then identifying the critical quality attributes that play a role in the function of that product.

The biosimilar applicant would first characterize the reference product quality characteristics and product variability, and then they would generate a manufacturing process for their proposed product that is designed to produce a product with minimal or no differences in product quality characteristics compared to the reference product.

However, there may be some differences that are observed. Those need to be identified, and then there needs to be a subsequent evaluation of the potential impact of the differences that are observed and thought given again in that stepwise evidence generation of what study or studies will address the uncertainty that may stem from those

differences and assessment of what the potential impact would be.

Again, there needs to be a very good understanding of the relationship between the quality attributes and the clinical safety and efficacy profile. This aids in the ability to determine residual uncertainty about biosimilarity from the analytical data and then to predict expected clinical similarity from the quality data and think about what additional studies need to be conducted to support a demonstration of biosimilarity.

FDA has taken an approach regarding a statistical analysis of the analytical similarity data. Statistical analyses of the analytical similarity data are conducted in support of a demonstration that the products are highly similar. It is not a pass/fail system. It is an adding to the robustness of the analytical similarity assessment, and you will hear a discussion of that later today as well.

Quality attributes are ranked based on

criticality with regard to their potential impact on activity, PK and PD, safety, immunogenicity, and other factors. Then the data are analyzed by various testing methodologies based on this ranking and then what testing methodologies would be appropriate for a given attribute.

In thinking about animal data generated for a biosimilar program, toxicity data are useful when there are uncertainties remaining about the safety of a proposed product prior to initiating clinical studies, but the scope and extent of animal studies, including the toxicity studies, will depend on a number of factors, including the publicly available information about the reference product; what is known about the safety profile, the toxicity of that product; and/or data submitted in the biosimilar application regarding the reference product and the proposed biosimilar product; and the extent of known similarities between the two.

Again, looking at that initial analytical similarity data, identifying the differences and

considering the potential impact of those differences and whether or not animal studies would help to address those differences and support a decision about safely moving ahead with additional clinical studies.

For some products, a comparison of PK or PD in an animal model may be useful, but that really depends on the animal model, whether it is a relevant animal model, and it is going to be predictive.

The next concept is thinking about the role of clinical studies, again, moving through that pyramid and that stepwise evidence development. The nature and scope of clinical studies that are conducted for a biosimilar development program will depend on the extent of residual uncertainties about biosimilarity between the two products after conducting structural and functional characterization and where relevant, animal studies.

However, as a scientific matter, FDA does expect an adequate clinical PK, and PD if relevant,

comparison between the proposed product and reference product. Also, as a scientific matter, at least one clinical study that includes an adequate comparison of the immunogenicity of the proposed product and the reference product will generally be expected.

Then as a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there are residual uncertainties about whether there are clinically meaningful differences between the products based again on that structural and functional characterization, animal testing, and then now the additive human PK and PD data and clinical immunogenicity assessment. So again, this all builds on that stepwise evidence development in that pyramid that each piece builds upon the next.

In thinking about comparative human PK and PD data, the agency has stated that PK and/or PD is generally considered to be the most sensitive clinical study or assay in which to assess for product differences, should they exist.

In looking at PK, the sponsor needs to demonstrate PK similarity between the products in an adequately sensitive population that again is adequately sensitive to detect differences between the products, if they exist; for PD, looking for similar pharmacodynamics using measures that reflect things like the mechanism of action or reflects the biological effects of the drug because you're looking for that functional similarity.

PK and PD similarity data supports the demonstration of biosimilarity with the assumption that similar exposure and pharmacodynamic response, if it is applicable for a product, will provide similar safety and efficacy where an exposure response relationship exists.

If a comparative clinical study is necessary in a program, it should be designed to investigate whether there are clinically meaningful differences in safety and efficacy between a proposed product and the reference product. Again, these are all comparative studies looking at potential differences between the products.

In designing that study, there are considerations for the population, endpoints, sample size, and study duration, and these need to be adequately sensitive to detect differences between the product, should they exist.

Typically, we would expect an equivalence design to be used, but other designs could be justified, depending on the product that we are discussing and also program-specific considerations based on the data that we are seeing.

Again, there should always be an assessment of safety and immunogenicity in any clinical study that is conducted. So if there is a comparative clinical study that does need to be conducted, it would be expected that safety and immunogenicity would also be evaluated in that study.

The next key concept deals with extrapolation. There is the potential for a biosimilar product to be approved for one or more conditions of use for which the reference product is licensed based on extrapolation. However, it is not a given, and it is incumbent upon the

biosimilar applicant to provide sufficient scientific justification for extrapolation within their application.

Differences between conditions of use such as indications do not necessarily preclude extrapolation, but there are a number of factors that need to be considered in that scientific support for extrapolation such as the mechanism of action in each condition of use, the PK and biodistribution in different patient populations, immunogenicity differences in different patient populations, and differences in expected toxicities in each condition of use in patient populations. That scientific justification needs to address all of these factors and provide adequate support for extrapolation.

One way to look at it as what's shown here on this slide is looking at the stand-alone drug development. Again, you have clinical safety and efficacy data. We expect a phase 3 trial to support safety and efficacy in each condition of use for which licensure is sought. And that's what

the reference product would have done.

In considering extrapolation in a biosimilar development program, there is all of this comparative data that is generated comparing the proposed product to the reference product; the analytical comparisons; possible animal study comparisons; clinical pharmacology looking at demonstrating PK and PD similarity; and then additional clinical studies, which would include the assessment of immunogenicity, comparative immunogenicity, and then possibly data from a comparative clinical study in one or more conditions of use.

You take all of that data, and then you look at the concept of extrapolation from information that would be contained in the 351(k) application as well as FDA's finding for the reference product, looking at extrapolating from that information to other indicators previously approved for the reference product, considering again those factors that I outlined in the previous slide.

Biosimilar extrapolation is based on all the

available data that is in the 351(k) BLA; all of that comparative data comparing the proposed product and the reference product; and FDA's finding for the reference product from the clinical safety and efficacy studies that were shown above; and again, FDA's finding that the reference product is safe, pure, and potent.

Extrapolation is not from the indications studied in a 351(k) application for the biosimilar to non-studied indications. It is really looking at, again, that totality of the evidence, all of that comparative data, as well as FDA's previous findings regarding the reference product, and that is what supports extrapolation in addition to the justification.

In summary, the development of a biosimilar product is different from a stand-alone product. Again, the goal is to demonstrate biosimilarity, which is that the products are highly similar with no clinically meaningful differences. The goal of that program is not to reestablish safety and effectiveness in de novo.

The analytical comparisons are the foundation for determining whether the products are highly similar, which again is that first prong of biosimilarity. Clinical PK and/or PD data is generally considered the most sensitive endpoint for detecting differences between the products, and assessment of immunogenicity is also needed. Then a comparative clinical study may be needed if questions remain or there is lingering uncertainties regarding whether there is clinically meaningful differences between the products.

Approval of the proposed biosimilar product is based on the integration of various information and its totality of the evidence approach, again, with that stepwise evidence development, each building on the next. This is evidence that is generated by the biosimilar applicant to provide the overall assessment of biosimilarity.

Again, FDA's high standard for approval of biosimilar and interchangeable products at the end of the day, again, it is not an abbreviated approval standard; it is an abbreviated licensure

pathway. And so that means when FDA licenses a product, folks can be confident that the safety and effectiveness of the approved product, the biosimilar or the interchangeable product, they can rely on that just as they would the reference product.

With that, we have some time for any clarifying questions about the regulatory pathway in terminology, expectations, again, not product-related questions, but just general questions.

Clarifying Questions to the Presenter

DR. RINI: Thanks. Dr. Lewis?

DR. LEWIS: On page 42 of the sponsor's thing, they quote you or your documents saying that "if the reference product has a long relatively safe marketing history and there have been multiple versions of the reference product on the market with no apparent differences in safety and effectiveness, this would be an appropriate drug to approach biosimilar."

Despite the data with -- and I am going to slaughter this name because I never say it

right -- peginesatide, did you guys determine that -- because you don't comment on it. Did you determine that that was true?

DR. CHRISTL: The biosimilar pathway is open to any biological products, and then it would be the reference product here is licensed by FDA. It has its own safety and effectiveness profile that is there, and so they're demonstrating biosimilarity to that product.

It is not to say that any product that FDA licenses doesn't have safety issues. Every approval that we make is a risk-benefit decision where the decision is made that the benefit outweighs the risk.

So yes, any of these products, there may be associated safety issues, but it is not to say that is not appropriate to develop as a biosimilar product.

DR. LEWIS: I think my question was slightly different. I think it says here that if there are multiple versions of the existing product on the market and they don't all have the same safety

profile, perhaps that is not appropriate for a biosimilar, or did I misinterpret that statement?

DR. RINI: Angelo?

DR. de CLARO: This is Angelo de Claro with FDA. The statement there are multiple versions of a product, peginesatide, we would not consider that as a different version of this product. We consider each -- that would be its own reference product.

For this one, the reference product is defined as US-licensed Epogen/Procrit. That's what we're relying on for this particular application.

DR. LEWIS: Okay. So because of the different amino acid composition, et cetera, you thought that was sufficiently different to not be considered?

DR. de CLARO: Yes. We can certainly consider if it is within the class of erythropoiesis-stimulating agents regarding safety and efficacy profiles based on understanding, but within the context of biosimilarity, it is always pegged to one specific product.

DR. LEWIS: Thank you.

DR. RINI: Thank you. Oh, you have another one? Sure, go ahead.

DR. LEWIS: Also, in the sponsor's material, they share with us information about the worldwide use of this product, which is quite extensive, and I didn't notice anywhere -- and you don't refer to it in your documents. I didn't notice anywhere where you comment on that.

Are we not to consider that information?

DR. de CLARO: Angelo de Claro again. I think that question, if you could pose that later during the FDA and sponsor presentations, we could provide a better context to answer that question. Thank you.

DR. LEWIS: Thank you.

DR. RINI: I just had a quick question, and I know it's not relevant to this application, but the difference between interchangeability and biosimilarity?

DR. CHRISTL: Again, the biosimilarity standard is that the products are highly similar

with no clinically meaningful differences. For interchangeability, there are additional statutory standards that need to be met in terms of a showing. So not only do the products need to demonstrate that they are biosimilar, so meet that highly similar with no clinically meaningful differences standard, but also support a showing in their application that it can be expected to produce the same clinical result in any given patient and that the impact of switching or alternating between the products as compared to just staying on the reference product is evaluated and supported.

Again, the Act goes on to state that an interchangeable product may be substituted for the reference product without the intervention of the prescriber.

DR. RINI: Any there other questions from the committee for Dr. Christl?

(No response.)

DR. RINI: Thank you.

We will now proceed with additional FDA

opening remarks from Dr. de Claro.

Opening Remarks - Angelo de Claro

DR. de CLARO: Good morning. We are here today to discuss an application for Epoetin Hospira, a proposed biosimilar to US-licensed Epogen/Procrit. During my presentation, I will use the term US-Epogen to describe US-licensed Epogen/Procrit.

This application is being presented at today's advisory committee meeting because this represents the first FDA application for a proposed biosimilar to US-Epogen. The proposed indications for Epoetin Hospira are the same as for US-Epogen. The approved indications for US-Epogen and the year of FDA approval are shown on the table.

The initial approval for US-Epogen occurred in 1989. The indications listed on the table reflect the current wording of the approved indications. The wording of the indications have changed, specifically indication 1 and 3, due to revisions based on efficacy and safety results from multiple clinical trials.

FDA has identified four key topics for the advisory committee to consider for today's meeting. The first topic is to discuss whether Epoetin Hospira is highly similar to US-Epogen, notwithstanding minor differences in clinically inactive components, based on evidence from analytical studies.

FDA notes that the applicant used multiple orthogonal physicochemical, and functional methods to characterize the primary, secondary, and tertiary structure; post-translational modification; biological activity; and stability profiles.

The second topic to consider would be to discuss whether there are no clinically meaningful differences between Epoetin Hospira and US-Epogen in terms of safety, purity, and potency based on the results from the clinical studies. The applicant conducted comparative clinical studies in healthy subjects and in patients with chronic kidney disease and evaluated the following parameters: pharmacokinetics, pharmacodynamics,

efficacy, safety, and immunogenicity.

The comparative clinical studies are summarized in this table. Details on the study design, route of administration, study population, endpoints, and results will be discussed by both the applicant and the FDA.

Because the applicant conducted the clinical studies in healthy subjects and patients with chronic kidney disease, FDA requests discussion whether there is adequate scientific justification to support licensure for all of the proposed indications. The applicant provided scientific justification, which includes discussion of the mechanism of action and similarity with regards to product quality attributes, pharmacokinetics, pharmacodynamics, immunogenicity, efficacy, and safety.

Finally, FDA requests the committee to vote whether the totality of evidence supports licensure of Epoetin Hospira as a biosimilar product to US-licensed Epogen/Procrit for the indications for which US-licensed Epogen/Procrit is currently

licensed and for which the applicant is seeking licensure.

Thank you for your participation today. FDA looks forward to hearing the committee's feedback and insights regarding the Epoetin Hospira application.

DR. RINI: Thank you.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including sponsor's nonemployee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest and those based on the outcome of this meeting.

Likewise, FDA encourages you at the

beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the applicant's presentation.

Applicant Presentation - Sumant Ramachandra

DR. RAMACHANDRA: Good morning, Dr. Rini, members of today's advisory committee, and members of the FDA. I am Sumant Ramachandra, senior vice president at Pfizer.

We are pleased to be here to present our proposed epoetin alfa biosimilar, which we will refer to Epoetin Hospira. We are seeking approval of Epoetin Hospira as a biosimilar to the U.S. reference product Epogen and Procrit, first approved by the FDA nearly 30 years ago.

Please note that we are currently not seeking an interchangeability designation. We are seeking approval of Epoetin Hospira for all four

Epogen/Procrit indications. Three indications are to treat anemia. The final indication is to reduce the need for red blood cell transfusion.

The development and manufacturing of Epoetin Hospira was based on our highly related epoetin product in Europe called Retacrit. This was approved as a biosimilar in December of 2007 and has been in the market for over 9 years with more than 363,000 patient-years of treatment administered.

The drug substance, also known as the active ingredient for Epoetin Hospira, originated from the development of our biosimilar approved in Europe, which we will refer to as EU Retacrit, and utilizes the same cell line, growth medium, and purification manufacturing processes.

The BLA for Epoetin Hospira is for a US-only program licensure and is not reliant on a bridge to EU Retacrit. The development of Epoetin Hospira follows the same stepwise approach outlined in FDA guidance to establish biosimilarity. FDA input was sought and incorporated across the development

program.

The Epoetin Hospira data package is foundationally based on a comprehensive characterization of the protein structure, physical chemical properties, and biological function. Two 13-week repeat-dose comparative toxicity studies were conducted in rats and dogs using subcutaneous and intravenous routes of administration, respectively.

The Epoetin Hospira data package also includes two comparative pharmacokinetic and pharmacodynamic studies with subcutaneous administration, 1 with single dose, and the other with multiple dose. Two double-blind randomized controlled studies comparing Epoetin Hospira to Epogen were conducted using subcutaneous or intravenous administration in patients with chronic kidney disease on dialysis.

FDA guidance outlines the specific scientific considerations that should be addressed to support extrapolation. This justification is based on the historical studies and extensive

knowledge of Epogen/Procrit as well as the totality of evidence demonstrating biosimilarity.

As we will review in today's presentation, the totality of evidence in the Epoetin Hospira development program demonstrates biosimilarity and supports extrapolation to all Epogen/Procrit indications.

For our agenda this morning, Dr. Vanden Boom will review the analytical biosimilarity assessment, then Dr. Martin will describe the results of our comparative nonclinical, clinical pharmacology, and clinical studies. Finally, I will conclude with a scientific justification supporting biosimilarity and extrapolation across all indications.

We also have some external responders with us here today to help answer questions. All external experts have been compensated for their time and travel.

I will now invite Dr. Vanden Boom to the podium to present the analytical biosimilarity assessment.

Applicant Presentation - Thomas Vanden Boom

DR. VANDEN BOOM: Thank you. I'm Tom Vanden Boom, vice president of biosimilars, pharmaceutical sciences for Pfizer. As highlighted by Dr. Ramachandra, analytical studies provide the foundation for the biosimilarity assessment.

The analytical studies evaluated the similarity of physical chemical structure and function between Epoetin Hospira and the Epogen/Procrit reference product as part of the overall assessment of biosimilarity.

Specifically, what I would like to briefly cover is a summary of the Epoetin Hospira and reference product lots included in this assessment; an overview of the analytical methods used in the Epoetin Hospira biosimilarity assessment; and results from the biosimilarity assessment, including the results from bioassays used to evaluate the bioactivity or functional activity of the Epoetin Hospira product.

Let me start with a brief overview of the lots used in the biosimilarity assessment. The

biosimilarity assessment included testing of a significant number of Epoetin Hospira and reference product lots, as shown in this table. Thirty-three state-of-the-art analytical methods, listed here by category, were developed to comparatively examine product attributes related to primary structure, secondary, and tertiary structure, post-translational modification, product-related substances and impurities, drug product characteristics, and the functional activity of the epoetin protein present in the two products.

Wherever possible, complementary orthogonal methods were developed and used to provide a more comprehensive comparison of product attributes in the analytical biosimilarity assessment. The breadth of the analytical methods used, along with the significant number of lots included in the biosimilarity assessment, enabled a comprehensive understanding of the analytical similarity between Epoetin Hospira and the reference product.

The key molecular features of epoetin examined in the comparative analytical studies

include the primary structure, secondary structure, tertiary structure, and post-translational modifications of the protein. As part of the overall requirements for biosimilars, primary structure is expected to be the same as the reference product.

Epoetin Hospira was demonstrated to have an identical primary structure or amino acid backbone, as shown in this slide, to the reference product. Structurally, the disulfide linkages that contribute to the proper folding of the epoetin protein in Epoetin Hospira, highlighted in yellow in this slide, were also demonstrated to be identical to the reference product.

Finally, the sites of N and O-linked glycosylation, specifically 3 asparagine amino acid residues and 1 serine amino acid residue, again highlighted in yellow, are also identical between Epoetin Hospira and the reference product.

Turning now to the comparative analysis of higher-order structure, which includes secondary and tertiary structure, secondary and tertiary

structural elements of the epoetin protein were examined using a complementary set of spectral methods that together support the highly similar structure of Epoetin Hospira to the Epogen/Procrit reference product. These methods measure various spectral signatures sensitive to changes in higher-order structure.

I will briefly review the results from the subset of spectral methods shown here. The results from additional spectral methods are included in the briefing book. Let's begin with the methods used to examine secondary structure.

This slide shows the comparative FAR-UV circular dichroism traces of Epoetin Hospira and Epogen/Procrit. Using this method, alpha helix, beta sheet, and random coil protein secondary structures each give rise to a characteristic shape and magnitude of circular dichroism spectrum. The spectra for both products are consistent with the expected 4-helix bundled structure of epoetin.

Fourier-transform infrared spectroscopy also demonstrates similarity of secondary structure.

The FTIR measures the absorption of radiation in the infrared region of the spectrum. Each protein has a characteristic set of absorption bands in its infrared spectrum. The comparative FTIR traces provide a complementary demonstration that these structural elements are similar between the two products.

Moving to the comparison of the tertiary structure, which also shows a high degree of similarity between Epoetin Hospira and the reference product, the overlapping spectra and characteristic maxima, corresponding to the near UV signals for the tryptophan, tyrosine, and phenylalanine amino acid residues, provides a measure of the similarity in the microenvironments of these amino acid residues in the folded epoetin protein present in the two products.

Taken together, the results from the complementary spectral methods used in the analytical biosimilarity assessment demonstrate that the higher-order structure of the epoetin protein present in Epoetin Hospira is similar to

that of the reference product.

Another important physical chemical feature examined in the analytical biosimilarity assessment is N-linked glycosylation. Glycosylation involves the covalent addition of carbohydrates to the protein and represents an important structural feature of the epoetin protein.

A key glycosylation attribute examined in the analytical biosimilarity assessment was total sialic acid. Increased sialylation is known to reduce in vivo clearance of epoetin, resulting in a longer half-life.

The measured total sialic acid content for lots of Epoetin Hospira and Epogen/Procrit are shown in this figure. The dashed horizontal lines represent the mean of the reference product plus or minus 3 standard deviations. These data demonstrate that total sialic acid is similar between the two products.

Let me now turn to a comparison of high molecular weight species, a key product attribute. It is important to note that the Epoetin Hospira

manufacturing process was designed to tightly control high molecular weight species. This attribute is important due to the potential for product aggregates and other high molecular weight species to be immunogenic.

In order to support the analytical biosimilarity assessment, a quantitative Western blot method was developed to measure epoetin-related high-molecular weight species. The Western blot figures in this slide show the relative levels of epoetin monomer and high molecular weight species in representative lots of Epoetin Hospira and Epogen. The percentage of epoetin-related high molecular weight species in each lot is determined using densitometry.

The measured levels of high molecular weight species in Epoetin Hospira are similar to or lower than those of the Epogen/Procrit reference product, as shown in the table at the bottom of this slide.

Another important product attribute is epoetin protein content, which also shows high similarity to the reference product. The epoetin

content target for Epoetin Hospira was defined and specifications established based on the epoetin content results observed for the Epogen/Procrit reference product.

The epoetin protein content for the Epoetin Hospira drug product lots produced using the proposed commercial manufacturing process are shown here along with the Epogen/Procrit reference product results. The results for all of the Epoetin Hospira lots produced using the commercial manufacturing process are within the observed range of the reference product.

It is important to note that this method is capable of detecting very minor differences in protein content that are not biologically relevant.

As shown in the right panel, which provides the in vivo bioassay results for the same set of Epoetin Hospira and reference product lots, these minor differences in protein content do not result in meaningful differences in in vivo biopotency.

Turning now to the evaluation of the functional attributes of Epoetin Hospira, the

functional activity of Epoetin Hospira was evaluated in the analytical biosimilarity assessment using multiple complementary bioassay methods. These include in vivo biopotency, in vitro biopotency, and receptor binding. In addition, the kinetics of epoetin binding to the epoetin receptor was determined using surface plasma and resonance.

The most clinically relevant analytical functional measure of the epoetin protein is the in vivo biopotency assay. The graphic here shows the epoetin stimulation of the red blood cell maturation process beginning with pluripotent stem cells and ending with red blood cells.

The in vivo biopotency method measures the pharmacodynamic response of a epoetin in normocythemic mice at the point in the red blood cell maturation pathway highlighted by the yellow arrow. Specifically, the number of reticulocytes in peripheral blood is measured in the bioassay. This is the same measure used to support clinical studies.

Statistical testing showed equivalence in in vivo biopotency between Epoetin Hospira and the reference product. Analytical equivalence for the in vivo biopotency attribute was demonstrated based on the constructed 90 percent confidence interval around the mean difference, shown by the red interval, falling within the equivalence margins established at plus or minus 1.5 times the standard deviation of the reference product, shown by the vertical dashed lines. The dataset used in this analysis is shown in the right panel for reference.

Importantly, this result demonstrates that the physical chemical similarity between Epoetin Hospira and the reference product results in similar biological activity.

We also looked at cell proliferation. The in vitro cell-based assay measures the epoetin dependent proliferation of the human UT-7 cell line resulting from epoetin receptor-binding and signal transduction, analogous to the epoetin-dependent initiation step of the red blood cell maturation cascade, shown by the yellow arrow. This attribute

is normalized and expressed as specific activity, which provides the inherent biological activity of the molecule.

Statistical equivalence testing was performed as described previously. Again, the dataset used in this analysis is shown in the right panel for your reference.

These results demonstrate that the physical chemical similarity observed between the two products also results in similar in vitro cell-based functional activity of the epoetin protein present in Epoetin Hospira.

Moving to receptor binding, receptor binding of the epoetin protein present in Epoetin Hospira was also demonstrated to be similar to the reference product. This was evaluated using a competitive receptor-binding method. This method measures the competitive binding of the epoetin protein present in either Epoetin Hospira or the reference product to an immobilized epoetin receptor. Relative potency is determined by comparing the dose response for the test sample to

the dose response of a well-characterized biological reference standard.

The close overlay of the dose-response curves for Epoetin Hospira and the reference product in the receptor-binding assay provides another indication that the epoetin protein present in these two products is similar.

Finally, the receptor-binding kinetics of the epoetin protein present in Epoetin Hospira and the reference product were examined using a Surface Plasmon Resonance or SPR method. This method permits the determination of the receptor-binding on and off rates for the two products. The results demonstrate that the receptor-binding kinetics are similar between Epoetin Hospira and the reference product.

These results provide further evidence that the higher-order structure required for receptor-binding and functional activity is similar between the two products.

In summary, based on the comprehensive analytical biosimilarity assessment completed,

Epoetin Hospira was demonstrated to be analytically highly similar to the Epogen/Procrit reference product. As expected, the similar physical chemical and higher-order structural features of Epoetin Hospira resulted in highly similar functional, biological activity, receptor-binding, and specific activity of the epoetin protein present in Epoetin Hospira.

I will now turn it over to Dr. Martin to review the Epoetin Hospira nonclinical and clinical studies.

Applicant Presentation - Nancy Martin

DR. MARTIN: Good morning. I'm Dr. Nancy Martin, consultant to Pfizer, previously vice president of clinical development biosimilars at Hospira, a Pfizer company.

Our nonclinical evaluation included two 13-week comparative toxicity studies in rats and dogs. We've examined toxicology, immunogenicity, toxicokinetics, and pharmacodynamics in both species. The key toxicology findings demonstrate similar gross and microscopic pathology between the

two treatment groups in both species, consistent with epoetins.

In rat, under sub-Q conditions, the comparative immunogenicity was influenced by human serum albumin as an excipient in the reference product formulation. The immunogenic response in rat is higher with the reference product. As such, the toxicokinetics and pharmacodynamic data are confounded by the differential immunogenic response in the rat.

This was not seen in the dog in the IV study, which demonstrated consistent immunogenicity, toxicokinetics, and pharmacodynamics. Importantly, any nonclinical differences noted in the rat did not translate to humans in PK/PD or immunogenicity.

The clinical studies provide more suitable conditions than nonclinical models to assess the comparative PK, PD, and immunogenicity. As you will see, the clinical pharmacology studies show PK/PD equivalence in humans.

Let's now look at the comparative

pharmacology data. The PK/PD studies are the most discerning clinical studies to detect in vivo performance differences in the drug products should they exist. We conducted two clinical pharmacology studies to demonstrate pharmacokinetic and pharmacodynamic equivalence as shown here.

Both studies evaluated subcutaneous administration as a sensitive route to assess differences in pharmacokinetics, pharmacodynamics, and immunogenicity. Let's first look at the single-dose crossover study.

This study randomized 81 healthy male subjects to receive either a single 100-unit per kilo dose of Epoetin Hospira or Epogen in a crossover fashion. When the single-dose concentration time profiles are displayed for Epoetin Hospira and Epogen, we see similar mean concentration time profiles.

As highlighted in yellow, the 90 percent confidence intervals of the geometric mean ratios for both AUC and Cmax were completed contained within the prespecified acceptance limits of 80 to

125 percent, consistent with FDA guidance for industry regarding clinical pharmacology data for biosimilars. Based on these data, PK equivalence was established under single-dose conditions.

In addition, the reticulocyte count profiles following single-dose administration also showed similar profiles. Reticulocyte count is a well-known marker directly reflective of the mechanism of action of epoetin and is measurable after single-dose administration.

The 90 percent confidence intervals of the geometric mean ratio for reticulocyte count for area under the effect curve and Emax, again, highlighted in yellow, are completely contained within the prespecified acceptance limits, demonstrating single-dose pharmacodynamic equivalents of Epoetin Hospira and Epogen.

Let's move to the multiple-dose PK/PD study. This study was an open label randomized parallel group design that evaluated pharmacokinetic and pharmacodynamic equivalence under multiple-dose conditions. 129 healthy males were randomized to

receive 12 doses of 100 units per kilo of study drug over 4 weeks. The epoetin concentration time profiles are similar between Epoetin Hospira and Epogen following multiple-dose administration.

Pharmacokinetic equivalence was established when the 90 percent confidence intervals for the geometric mean ratios for AUC and Cmax were both entirely contained within the predefined 80 to 125 percent equivalence margin.

As highlighted in yellow, these data are within the prespecified acceptance limits. This establishes multiple-dose PK equivalence of Epoetin Hospira and Epogen under multiple fixed-dose conditions. In addition, examination of the hemoglobin concentration time profiles after multiple-dose administration demonstrate similar profiles for Epoetin Hospira and Epogen.

Hemoglobin is an established marker that reflects the known mechanism of action of epoetin on erythropoietic response and is used clinically to titrate dose to therapeutic effect.

The pharmacodynamic equivalence margin was

predefined per protocol as the area under the effect curve for hemoglobin of 96.5 to 103.5 percent. The acceptance limits were informed by entry criteria hemoglobin values of approximately 14.2 grams per deciliter and a clinically relevant change in hemoglobin of a half gram per deciliter for pharmacodynamic equivalence.

Highlighted in yellow, the 90 percent confidence intervals for area under the effect curve for hemoglobin were completely contained within the acceptance limits, demonstrating pharmacodynamic equivalence under multiple-dose conditions.

Let's now turn to the mechanism of action of epoetin, which is conserved across all conditions of use. Erythropoietin synthesized and released from the kidney regulates red blood cell mass in response to tissue hypoxia as found in anemia. Per reference product labeling, epoetin stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. This is independent of whether the epoetin deficiency is relative or absolute across

indications.

Fortunately, there are direct measures of erythropoiesis, specifically reticulocyte count and hemoglobin, that are clinically available in widespread use. Importantly, Epoetin Hospira has demonstrated pharmacokinetic and pharmacodynamic equivalence to the reference product using these measures under strict discerning conditions in healthy subjects, which is foundational across all conditions of use.

Let me now review the comparative clinical study data, which further support biosimilarity. I will first discuss the efficacy data.

Two double-blind randomized controlled clinical studies were conducted in the United States to demonstrate equivalence of Epoetin Hospira to Epogen in a patient population with chronic kidney disease on hemodialysis.

The primary study was a comparative sub-Q efficacy and safety study. The additional supportive study was a comparative IV study. Both studies included an option for patients who

completed study to enroll into long-term open label studies where subjects received Epoetin Hospira treatment.

The eligibility criteria aligned with epoetin guidelines, clinical trial precedent for epoetins, and labeling for appropriate patient selection. Key criteria are shown. In order to be randomized in these hemoglobin maintenance trials, patients needed stable hemoglobin levels using stable Epogen doses.

Let me first begin by describing the sub-Q study. A dose stabilization period was built into the sub-Q design for patients previously receiving IV epoetin to establish a stable baseline. Patients already stable on sub-Q dosing of Epogen could be directly randomized into the 16-week maintenance period.

The study results were derived from the final 4 weeks of each patient's maintenance period, which included hemoglobin level and study drug dose as the co-primary endpoints. Many key elements of the clinical trial design were consistent between

the sub-Q and the IV studies.

Let me now review the IV study. The IV study consisted of a maintenance period, again shown by the red box, as no dose stabilization was needed. This study used the same co-primary endpoints as the sub-cutaneous study. Both studies assessed efficacy equivalents based on the co-primary endpoints of mean weekly hemoglobin levels and mean weekly study drug dose during the last 4 weeks of each patient's maintenance phase.

A determination of similar efficacy was made if the 95 percent confidence intervals for both co-primary endpoints were entirely contained within the protocol-defined prespecified equivalence margins.

In 2017, during the BLA review, FDA requested the 90 percent confidence intervals. I will present the 90 percent confidence intervals here. Both sets of results can be found in the briefing book.

The equivalence margins were based on published hemoglobin data and treatment targets, as

well as published epoetin dosing data in patients with chronic kidney disease on hemodialysis. Specifically, the prespecified hemoglobin equivalence margin was plus or minus 0.5 grams per deciliter, and the prespecified dose equivalence margin was plus or minus 45 units per kilo per week.

An ANCOVA model with appropriate baseline values as covariates was used to calculate the confidence intervals for the least squares means of the differences between Epoetin Hospira and Epogen for the two co-primary efficacy endpoints.

The study disposition was similar between treatment groups in the comparative sub-Q efficacy and safety study. A similar proportion of patients discontinued study. The disposition of patients in the IV study was also similar.

The demographics of patients with CKD were similar between treatment groups within each study and between the two studies. The demographics of the studies are representative of the chronic kidney disease on hemodialysis population in the

United States.

We also see consistency in baseline hemoglobin, epoetin dose, and adequate IM stores between the treatment groups in each study, as well as other common baseline characteristics. In at least 80 percent of the patients, the etiology of renal failure was secondary to hypertension or diabetes. Overall, the demographics and baseline characteristics align with those seen among patients with chronic kidney disease on hemodialysis.

Let's look at the primary efficacy results for the intent-to-treat population. In the subcutaneous study, the 90 percent confidence interval for the difference in hemoglobin was minus 0.13 to plus 0.21 grams per deciliter, and for dose was minus 12.54 to plus 7.85 units per kilo per week, as highlighted in yellow on the slide.

Both 90 percent confidence intervals for the co-primary endpoints were entirely contained within the prespecified equivalence limits. These results indicate that there are no clinically meaningful

differences in efficacy between Epoetin Hospira and Epogen when administered subcutaneously, further supporting similarity.

We see consistency of results with the co-primary endpoint analysis for the IV study. The 90 percent confidence intervals are entirely contained within the prespecified equivalence limits, indicating there is no clinically meaningful differences in efficacy between Epoetin Hospira and Epogen, again supporting similarity. Both 95 percent and 90 percent confidence intervals met the acceptance criteria for efficacy results in these studies.

A series of sensitivity analyses were performed across various analysis populations to assess the robustness of the primary analysis conclusions. The results for the subcutaneous study are shown here. Similar findings are observed in the intravenous study. Overall, the sensitivity analyses are concordant with and support the primary intend to treat analysis conclusions for efficacy.

In addition, secondary endpoints support the findings from the co-primary endpoints. Two prespecified key secondary endpoints are shown. A consistent percentage of patients had hemoglobin targets within 9 to 11 grams per deciliter between treatments. In the subcutaneous study, 4 percent of patients required blood transfusions, and in the IV study, 6 percent of patients required blood transfusions in each treatment group.

I'll now turn to clinical safety. The primary evidence of safety comes from pooled data from the two randomized controlled studies. Overall, incidence of reported events in the combined randomized controlled studies were consistent between treatment groups across all categories.

In both treatment groups, approximately 75 percent of patients experienced at least one adverse event. A similar percentage of patients across both treatment groups experienced at least one serious adverse event, and deaths occurred in approximately 2 percent of patients in each

treatment group.

Adverse events greater than 5 percent incidence in either treatment group are summarized here. The most common were nausea, AV fistula site complication, vomiting, and muscle spasms. The nature of these events are as expected in the chronic kidney disease with hemodialysis population.

With regard to serious adverse events, the incidence of serious adverse events was consistent between Epoetin Hospira and Epogen between treatment groups. Again, the SAEs reported are consistent with what would be expected in this population.

Now turning to events of interest, events of interest were prespecified and informed by the U.S. package insert for Epogen/Procrit. Starting with thromboembolic events, 39 events were reported in 33 patients treated with Epoetin Hospira and 36 events in 26 patients treated with Epogen. Overall, there was a similar frequency of serious, severe, and treatment-related thromboembolic events

between the treatment groups.

For hypertension events, 33 events were reported in 28 patients treated with Epoetin Hospira and 32 events in 21 patients treated with Epogen. The majority of these events were reported as non-serious and non-severe.

Concomitant antihypertensive medication use was consistent between treatment groups, and evaluation of objective blood pressure data showed consistency between treatment groups with regard to central tendency and extreme values. Other events of interest were comparable between treatment groups. In the clinical program, there were no reported events of pure red cell aplasia.

Immunogenicity assessments were conducted with validated methods, including radioimmunoprecipitation for the detection of anti-epoetin antibodies, and if positive, testing using a cellular-based assay for neutralizing properties. Serum samples were collected throughout the studies.

Let's look at the immunogenicity results.

There was a similar number of patients with detectable ADA results between Epoetin Hospira and Epogen. The low number is in line with published data for epoetins. Most of these patients were ADA positive at baseline. In all cases, patients remained clinically stable throughout treatment. No neutralizing antibodies were detected in any patient, and no cases of PRCA were reported.

In total, a program-wide systematic assessment supports a consistent immunogenicity profile of Epoetin Hospira and Epogen.

In summary, the clinical program supports the demonstration of biosimilarity between Epoetin Hospira and Epogen. PK/PD equivalence was established under single- and multiple-dose conditions as foundational across all conditions of use.

The comparative efficacy data demonstrated similar efficacy under sub-Q and IV conditions in a sensitive population of patients with anemia. The clinical data also support consistent and well-characterized safety and immunogenicity

profiles between the two products. Overall, the clinical program demonstrated no clinically meaningful differences between Epoetin Hospira and Epogen.

Thank you. Dr. Ramachandra will now conclude our presentation.

Applicant Presentation - Sumant Ramachandra

DR. RAMACHANDRA: The Epoetin Hospira development program used the defined stepwise approach to demonstrate biosimilarity to the Epogen/Procrit reference product. The comprehensive analytical studies using state-of-the-art methods demonstrated physical chemical structure and biological function of Epoetin Hospira is highly similar to Epogen/Procrit.

The comparative clinical development program further supports the conclusion that Epoetin Hospira is highly similar with no clinically meaningful differences to the reference product. PK and PD equivalence was established. Additionally, two well-controlled comparative efficacy and safety studies demonstrated

equivalence in efficacy response. Finally, the safety profile, including immunogenicity, is consistent between Epoetin Hospira and Epogen.

The demonstration of biosimilarity coupled with the well-characterized nature of the reference product together support extrapolation across all conditions of use for the reference product. The central therapeutic effect across all indications is mediated by the interaction of epoetin with the EPO receptor and its downstream cascade leading to erythropoiesis.

Additionally, comparative in vitro, in vivo, and clinical PD data demonstrate that the mechanism of action across all indications of Epoetin Hospira and the reference product is the same. The PK/PD of Epogen/Procrit has been well characterized. Importantly, the PK and PD equivalence between Epoetin Hospira and Epogen was established under both single-dose and multiple-dose conditions.

Epogen/Procrit has a well-characterized immunogenicity profile across the patient groups treated for each indication as reflected in its

product labeling. Our data demonstrate a consistent immunogenicity profile to Epogen.

Epogen/Procrit has a well-known safety profile. A program-wide systematic evaluation of safety was conducted and demonstrated consistent safety between Epoetin Hospira and Epogen.

Finally, the potential impact of administration was considered. In the comparative clinical efficacy and safety studies, equivalence was established for efficacy with both subcutaneous and IV routes of administration.

In summary, the consistent MoA and PK, as well as the well-established safety and immunogenicity profile of the reference product, Epogen/Procrit, for all approved indications combined with the totality of data supporting biosimilarity, justifies extrapolation across all indications.

In conclusion, the totally of evidence across comparative, analytical, nonclinical, and clinical studies provide the necessary data to demonstrate Epoetin Hospira is biosimilar to

Epogen/Procrit across all indications.

Finally, approval of Epoetin Hospira will expand options available to patients and the healthcare system. Thank you very much.

DR. RINI: Thank you for that presentation. We will now proceed with presentations from FDA.

FDA Presentation - Frances Namuswe

DR. NAMUSWE: Good morning. In the next 45 minutes, the presenters listed here will present FDA's assessment of the applicant's data submitted to support Epoetin Hospira as a biosimilar to US-licensed Epogen/Procrit, which we will also refer to as US-Epogen or US-Epogen/Procrit.

I am Frances Namuswe, and I will present FDA's analysis and conclusions from the analytical similarity data. My colleague, Dr. Chao Wang, will present the results from FDA's statistical analysis used to support our conclusions.

I will start by summarizing EPO's mechanism of action. Endogenous EPO is produced primarily in the kidney and stimulates production of red blood cells. This process begins with binding of EPO to

the EPO receptor on erythroid progenitor cells primarily found in the bone marrow. This binding initiates signal transduction that leads to the survival, proliferation, and differentiation of erythroid progenitor cells into mature red blood cells.

The pharmacodynamic markers commonly used to assess erythropoiesis or production of red blood cells are reticulocyte count and hemoglobin levels. Both markers are upregulated by binding to the EPO receptor and subsequent signal transduction. Recombinant EPO has the same mechanism of action as endogenous epo.

Before I present the conclusions from our assessment, I want to highlight or reiterate some of the key features that are important for EPO's biological activity. Epo is a glycosylated protein, and glycosylation is important for its in vivo biological activity because it impacts the half-life of circulating epo.

The EPO model in the upper left corner presents the glycans as the protruding structures

on the folded protein. These glycans make up approximately 40 percent of the molecular weight of the protein. Epo glycans are heterogenous, and some of this heterogeneity is shown in the figure on the right.

For example, they can contain a variable number of branched chains, chemical modifications on the individual monosaccharides such as the O-acetylation shown on all the individual cartoons; multiple repeating units per chain as shown in the fourth cartoon; different numbers of terminal sialic acids per glycan represented by the purple diamonds; and in recombinant product, you may find human and nonhuman mononsaccharide species.

The role of the various glycans in biological activity continues to be studied. However, there's a consensus that terminal sialic acid residues on the glycans are important for EPO clearance.

This slide shows the applicant's studies that the agency reviewed. The studies reviewed to support clinical immunogenicity assessment are

indicated by the asterisks. In all studies, US-Epogen/Procrit was used as the active comparator.

This slide shows the product quality attributes assessed by the applicant to support analytical similarity. The attributes can be groups into six categories, including structure, glycosylation, product-related species, biological activity, drug product attributes, and the stability profiles of the products.

The applicant used multiple orthogonal methods to assess these attributes. It is important to point out that the formulation of US-Epogen/Procrit contains human serum albumin, or HSA, that interferes with several analytical methods. The applicant provided data to support that removal of HSA did not impact most quality attributes of US-Epogen/Procrit. In cases where its removal impacted the quality attribute, the applicant developed and qualified alternative methods that did not require HSA removal to assess the attribute.

To assess analytical similarity, the sponsor used a total of 35 lots of Epoetin Hospira drug product, 9 lots of Epoetin Hospira drug substance, and 54 lots of US-Epogen/Procrit. The lots used in clinical studies and the proposed commercial process were included in the analytical similarity assessment, and all drug products' strength for which the applicant is requesting approval were represented.

The number of lots for each attribute was justified by the applicant. Prior to data analysis, the applicant conducted a risk assessment of each quality attribute to determine the criticality or importance of that various attribute with respect to biological activity; PK/PD; efficacy; and safety, including immunogenicity.

For comparative data analysis, the applicant assigned each attribute to one of three tiers of statistical analysis based on their criticality and other considerations. As shown in the table on the right, tier 1 uses equivalence testing, tier 2 uses quality ranges such as mean plus or minus 3

standard deviations, and tier 3 uses graphical comparisons. This approach is in agreement with the agency expectations.

FDA's assessment also included independent statistical analysis of the applicant's data. This is a summary of our analytical similarity assessment based on the data provided by the applicant. The totality of the analytical similarity data support a conclusion that Epoetin Hospira is highly similar to US-licensed Epogen/Procrit notwithstanding minor differences in clinically inactive components.

Based on the analytical similarity data and publicly available information, Epoetin Hospira has the same primary structure as US-licensed Epogen/Procrit. In addition, high order structure and biological activity data support the protein folding, biological activity, and the intrinsic properties of EPO as similar between the two products.

Similar levels of most product-related species and similar stability profiles were also

observed between the two products, as shown in the table on the right side. Similar product-related species means same type and similar amounts of species of interest.

Differences were observed in the levels of some glycosylation species and one trisulfide species. As I will elaborate in the next slides, these differences did not preclude a conclusion that the two products are highly similar.

To elaborate on the differences in glycosylation, the figure on this slide shows a chromatography profile of all the N-glycans in Epoetin Hospira in the top panel and US-Epogen/Procrit in the two bottom panels. The peaks in the chromatogram represent the different N-glycan species separate by this method. Data from these and several other methods were used to identify and quantitate the different glycan species.

These data show that Epoetin Hospira and US-Epogen/Procrit have the same glycosylation profiles, same glycosylation site, similar site

occupancy, the same glycan species, and similar levels of several glycans. Importantly, no new glycan species are seen in Epoetin Hospira. However, there are some differences between the profiles of the products due to minor differences in the amounts of some glycan species. Some of these differences are marked in the figure.

Examples of glycan species that correspond to these differences include the relative amounts of the branch chains, repeating units per chain, O-acetylation of the terminal sialic acids, sialic acid distribution, and the amounts of nonhuman sialic acid species.

As I mentioned earlier, EPO glycosylation impacts in vivo biological activity. The overall impact of the differences in glycosylation on biological activity was evaluated by a mouse-based assay that measures the increase in reticulocyte count following a given dose of epo. This assay was demonstrated through studies conducted by the applicant to be sensitive to these differences.

Biological activity was also assessed using

in vitro cell-based and receptor-binding assays. These assays are more precise and support the results obtained using the mouse-based assay.

The results of these studies show that the observed differences in glycosylation do not result in an observable effect on biological activity or the intrinsic properties of the molecule. To illustrate this, we will show analysis of in vivo biological activity and in vitro specific activity.

These attributes were selected for tier 1 equivalence testing because in vivo biological activity represents EPO's mechanism of action and is the most clinically relevant assay. In vitro specific activity provides the information regarding the intrinsic properties of epo.

Dr. Wang will now present the results from this statistical equivalence analysis of these two attributes.

FDA Presentation - Chao Wang

DR. WANG: Good morning. I'm Chao Wang, the CMC statistical reviewer for the application. I will present the statistical equivalence analysis

of the two quality attributes for biological activity.

First, let's talk about the statistical equivalence test. For quality attributes, the equivalence test is used to determine whether the mean difference between the test and reference products is within equivalence margins. Let sigma R be the standard deviation of reference product, which is estimated from the reference data generated by the applicant. Then the null hypothesis is that the mean difference is either less than or equal to minus 1.5 sigma R or greater than or equal to 1.5 sigma R. The alternative is that the mean difference falls within the range from minus 1.5 sigma R to plus 1.5 sigma R.

Test and reference pass the equivalence tests if the equivalence test plots, the 90 percent confidence interval for a mean difference, shown as blue segments, falls within the equivalence margins marked by two vertical lines.

Here we present the test results for the quality attributes in vivo biological activity.

The data used in equivalence tests are shown in the scatter plots where the sample for Epoetin Hospira are marked by red circles and US-Epogen/Procrit by blue diamonds.

Note that the data for the Epoetin Hospira lots were obtained after adjustment of EPO contents. The equivalence test plot shows that the 90 percent confidence interval of the mean difference is within the equivalence margins. The detailed test results are shown in the table. Thus, in vivo biological activity passed the equivalence test.

The results for in vitro specific activity is shown similarly. From the equivalence test plot, we can see that the 90 percent confidence interval of the mean difference is within the equivalence margins. So in vitro specific activity passed the equivalence test as well.

Dr. Namuswe will now resume with the CMC discussion.

FDA Presentation - Frances Namuswe

DR. NAMUSWE: Based on in vivo and in vitro

biological activity data, receptor-binding, and our statistical analysis, we do not expect the minor differences in glycosylation to have an impact on efficacy and safety.

The other difference observed between Epoetin Hospira and US-Epogen/Procrit was the amount of a trisulfide species present on average at 4.5 percent levels higher in Epoetin Hospira. Trisulfide species are formed by insertion of an extra sulfur atom into the disulfide bonds, and they are reported to form during manufacturing processes.

The difference in the amount of these trisulfide species is not expected to have clinical impact because these differences did not result in differences in biological activity of Epoetin Hospira and US-licensed Epogen/Procrit.

In addition, trisulfide species were reported in even higher levels in an earlier version of Epoetin Hospira, and they did not result in differences in in vitro or in vivo specific activity compared to the clinical and commercial

Epoetin Hospira product. These data suggest that these species do not impact the intrinsic properties of the EPO molecule.

In addition, the literature of other recombinant products indicates that trisulfide species rapidly convert to disulfide species in vivo. Based on the biological activity data and the literature, we do not expect the differences in trisulfide species to have an impact on efficacy and safety.

In conclusion, the totality of the analytical similarity data supports a conclusion that Epoetin Hospira is highly similar to US-Epogen/Procrit notwithstanding minor differences in clinically inactive components.

That concludes the CMC presentation. Our next topic will be pharmacology and toxicology.

FDA Presentation - Natalie Simpson

DR. SIMPSON: Good morning. I am Natalie Simpson, the pharmacology toxicology reviewer for this application. This is a quick overview of the current nonclinical approach for biosimilar's

review and the comparative animal studies submitted for Epoetin Hospira and US-Epogen/Procrit.

Comparative animal studies may support the similarity of a proposed product to a reference product. However, if comparative structural and functional data using the proposed product provides strong support for analytical similarity to a reference product, a more tailored approach to the amount and type of animal data needed to support a demonstration of biosimilarity can be taken.

The applicant submitted two comparative animal studies that are presented for completeness but were not designed to support a demonstration of biosimilarity. They were a 13-week subcutaneous or SC repeat-dose toxicity, and pharmacokinetic or PK study in Sprague-Dawley rats, and a 13-week intravenous or IV repeat-dose toxicity and PK study in beagle dogs.

The rat and dog were selected as the species for comparative toxicology studies, which is appropriate based on the mechanism of action of epo. However, immunogenicity has been associated

with long-term repeat SC dosing of human EPO in rats.

This table summarizes the conclusions in bold drawn by the FDA from the two comparative animal studies. Additionally, the route of administration and the species are bolded in the study title column to ease in the interpretation of the differences between the two studies.

In both studies, animals were administered Epoetin Hospira or US-Epogen/Procrit 3 times per week at the same doses of 150, 450, and 1500 reduced to 900, due to mortality, international units per kilogram or IU per kg.

For rats administered Epoetin Hospira or US-Epogen/Procrit subcutaneously, we could not make meaningful comparisons for the pharmacodynamic, or PD, and PK endpoints because there was decreased PD activity and exposure that correlated with a high level of antidrug antibody or ADA development for the US-Epogen-treated rats.

Dogs administered either product intravenously displayed increases in PD activity.

However, there were differences up to 40 percent in PK parameters in dogs mainly for exposures and clearance rates, but there was a large amount of individual animal variability indicated by the asterisk.

In both the rat and dog comparative toxicology studies, PD activity plateaued at the lowest dose tested, and there were no major differences in toxicity between the two treatment arms.

In summary, in stepwise evidence development, the PK and PD differences in animals observed from the perspective of pharmacology toxicology would be addressed by subsequent clinical studies. The differences in exposures and PD activity in rats could be related to immunogenicity. For example, there was more antidrug antibody development in US-Epogen-treated groups, which had immunogenic human serum albumin in the formulation, than in groups treated with Epoetin Hospira.

It is important to keep in mind that

immunogenicity in animals is not predictive of immunogenicity in humans. In general, there were no major differences in the toxicity profile between Epoetin Hospira and US-Epogen/Procrit.

This concludes the pharmacology toxicology presentation. Our next topic will be clinical immunogenicity.

FDA Presentation - Steven Bowen

DR. BOWEN: Thank you. Good morning. I'm Steve Bowen from the Office of Biotechnology Products, and I reviewed the clinical immunogenicity assessment for this application.

For all therapeutic proteins, there is potential for the therapy to induce an unwanted immune response, usually in the form of antidrug antibodies, or ADA, that can impact the safety and efficacy of the drug. For ESA therapy, immunogenicity is of particular concern because the endogenous counterpart of epoetin alfa is erythropoietin, a critical nonredundant growth factor that is required for the development of red blood cells.

We know from experience with other ESAs that changes in certain product quality attributes can cause the development of neutralizing ADA in patients receiving the therapy. When neutralizing ADA cross-react with endogenous erythropoietin, a life-threatening form of anemia known as pure red cell aplasia can occur.

Due to the immunogenicity risks associated with ESA products, a comparative assessment of the ADA response to Epoetin Hospira and Epogen was critical for this application. Therefore, in our review, we sought to address the question of whether Epoetin Hospira was similar to Epogen with respect to immunogenicity, particularly for the development of neutralizing antibodies, and whether the data supported demonstration of no clinically meaningful differences between the two products.

The applicant performed one single-dose crossover study in healthy subjects, and three multiple-dose parallel arm studies in healthy subjects and in patients with chronic kidney disease, or CKD, which are framed in red.

Immunogenicity was monitored in all clinical studies. However, the parallel arm study design was ideal to compare immunogenicity of Epoetin Hospira and US-Epogen because it allowed ADA to be attributed to one product versus the other. Therefore, the assessment of immunogenicity between Epoetin Hospira and US-Epogen was based primarily on data derived from these studies.

Serum samples were collected from subjects at time points before and after exposure that were appropriate to capture the development of ADA. Samples were tested for binding and neutralizing ADA using validated assays that were carefully reviewed by the agency and determined to be consistent with FDA recommendations for ADA assays.

These tables indicate the percentage of patients in each study that were positive for ADA at baseline prior to first exposure to the study drug and patients with treatment-induced ADA who were negative at baseline but became positive after exposure. The percentage of patients with neutralizing antibodies, or Nabs, is also indicated

in the far right column.

For each of the three clinical studies, the rate of ADA development were similar between the Epoetin Hospira and US-Epogen arms. No patients developed neutralizing antibodies to either drug in any of the clinical studies.

To summarize, the immunogenicity of Epoetin Hospira and US-licensed Epogen was compared in three multiple-dose parallel arm studies in 849 patients with CKD and 129 healthy subjects. The assays used to test serum samples from subjects enrolled in these studies were reviewed by the FDA and found to be properly validated. The rates of binding ADA were similar between Epoetin Hospira and US-Epogen arms, and no neutralizing ADA were observed in any of the clinical studies.

In conclusion, the clinical immunogenicity assessment demonstrates no increase in immunogenicity risk for Epoetin Hospira as compared to US-licensed Epogen and supports a demonstration of no clinically meaningful differences between the two products.

This concludes the clinical immunogenicity presentation. Our next topic will be clinical pharmacology.

FDA Presentation - Vicky Hsu

DR. HSU: Good morning. I am Vicky Hsu, the clinical pharmacology reviewer for the application. The goal of the clinical pharmacology program is to evaluate the PK and PD similarity between Epoetin Hospira and US-licensed Epogen. This included evaluation of single-dose PK and PD similarity between Epoetin Hospira and US-licensed Epogen.

The single-dose PD marker is reticulocyte count. It also included an evaluation of multiple-dose PD similarity between Epoetin Hospira and US-licensed Epogen. The multiple-dose PD marker is hemoglobin level.

During our review, we aimed to answer the question do the clinical pharmacology data submitted under this BLA support a demonstration of no clinically meaningful differences between Epoetin Hospira and US-licensed Epogen?

As indicated in the red box, the applicant

conducted two studies to evaluate the PK and PD similarity between their product Epoetin Hospira and US-licensed Epogen. Study 12-02 was the single-dose study that provided the pivotal PK similarity evaluation. It used a crossover design in 81 healthy subjects randomized 1 to 1 into either crossover sequence group.

A subcutaneous dose of 100 units per kilogram was administered in each period with a washout time of 28 days between periods. The primary endpoints included PK and PD similarity assessments.

Study 14-01 was the multiple-dose study. It was a parallel design in 121 healthy subjects randomized 1 to 1 into either the Epoetin Hospira arm or the US-licensed Epogen arm. Subcutaneous doses of 100 units per kilogram were administered 3 times a week for 4 weeks for a total of 12 doses.

The agency considers hemoglobin level as the primary PD endpoint for this study. Multiple-dose PK was also characterized in this study, but this data is considered supportive in a PK similarity

assessment.

For the single-dose study 12-02, the PK profile for baseline-adjusted EPO concentration is shown in the left panel. The gold line represents Epoetin Hospira, and the blue line represents US-licensed Epogen. A baseline adjustment was applied to the EPO concentrations in order to correct for endogenous erythropoietin concentrations, which is analytically indistinguishable from exogenous erythropoietin.

Following a single subcutaneous dose of 100 units per kilogram, maximum EPO concentrations are reached at around 12 to 15 hours post-dose. The right panel depicts the single-dose reticulocyte count profile expressed as a percentage of erythrocytes. Maximum reticulocyte count is achieved at around 120 hours or 5 days post-dose.

The geometric mean ratios and their corresponding 90 percent confidence intervals for the single-dose PK and PD endpoints are shown in this plot against an axis depicting the

prespecified similarity margin of 80 to 125 percent. As you can see, in the single-dose study 12-02, all the PK endpoints of Cmax and AUC and reticulocyte count PD endpoints of percent reticulocyte Emax and AUEC met the prespecified criteria for determining similarity.

Similar to the previous plot, the geometric mean ratios and their corresponding 90 percent confidence intervals for multiple-dose PK and PD endpoints are shown against an axis depicting the prespecified similarity margin of 80 to 125 percent.

As you can see, in the multiple-dose PK endpoints of Cmax and AUC fell within the 80 to 125 percent margin. As previously stated, the multiple-dose PK data are considered supportive PK in the overall clinical pharmacology similarity assessment.

Regarding the multiple-dose PD endpoints, the agency considers hemoglobin Emax and AUEC as co-primary PD endpoints. As shown in this plot, these PD endpoints also met the prespecified

criteria for demonstrating similarity.

In summary, the PK and PD study results support the demonstration of no clinically meaningful differences between Epoetin Hospira and US-licensed Epogen. These results add to the totality of the evidence to support a demonstration of biosimilarity of Epoetin Hospira and US-licensed Epogen.

This concludes the clinical pharmacology presentation. Our next topic will be clinical efficacy.

FDA Presentation - Lola Luo

DR. LUO: Good morning. My name is Lola Luo, the clinical statistical reviewer for the application. I will present the comparative clinical study results.

The applicant conducted two studies to evaluate the efficacy and the safety of Epoetin Hospira and the US-licensed Epogen/Procrit in patients with chronic kidney disease on hemodialysis. This data support the demonstration of no clinically meaningful differences between

Epoetin Hospira and US-licensed Epogen/Procrit.

Study 10-13 was a randomized double-blinded parallel group study of subcutaneous administration of Epoetin Hospira or US-licensed Epogen/Procrit with a titration period and a 16-week maintenance period.

Study 10-01 was a randomized double-blinded parallel group study of intravenous administration of Epoetin Hospira or US-licensed Epogen/Procrit with a 24-week treatment period.

The applicant disclosed the multiple sites in both studies were good clinical practice noncompliant. In study 10-13, three sites were closed during the conduct of the study, which impacted 10 percent of enrolled subjects and 8 percent of the subjects in the intent-to-treat population. In study 10-01, a total of 9 sites were excluded, which represented 14 percent of subjects enrolled and 11 percent of subjects in the ITT population. The agency conducted sensitivity analyses for both efficacy and safety endpoints, excluding the GCP noncompliant sites to confirm the

integrity of the initial analysis.

There are two primary endpoints for study 10-13 and study 10-01, the mean weekly hemoglobin level during the last 4 weeks of the treatment period and the mean weekly dosage per kilogram body weight during the last 4 weeks of the treatment period.

The equivalence margin proposed by the applicant for the hemoglobin is plus/minus 0.5 gram per deciliter. This margin was based on the observed within subject variability of approximately plus/minus 1 gram per deciliter obtained from published literature. Half of this observed within subject variability was deemed to be not clinically meaningful.

The equivalence margin proposed by the applicant for the dose is plus/minus 45 units per kilogram per week. This margin was also based on published literature. Changes of equal or less than 45 units per kilogram per week provided no effect on hemoglobin level, and higher dose increments were needed to provide a consistent

dose-dependent increase in hemoglobin. The agency has no objection on either of the two equivalence margins proposed.

Randomization is 1 to 1 double blinded. Study 10-13 used the titration period study drug dose low, medium, high as the stratification factor. Study 10-01 had no stratification factors.

288 and 564 subjects were planned for sub-Q and IV studies, respectively. To achieve 90 percent of power was the given equivalence margin and the parameter assumptions. Intent-to-treat analysis population is defined as all randomized subjects. A total of 246 subjects were randomized into the ITT subpopulation in the sub-Q study, and 612 subjects were randomized in the IV study.

Good clinical practice analysis population is defined as the ITT population excluding subjects from the closed sites. There were 226 subjects in the GCP population in the sub-Q study and 547 subjects in the IV study.

For the primary analyses, a hierarchical testing procedure is used to adjust for

multiplicity. First, the difference in mean weekly hemoglobin level was tested. If the 90 percent confidence intervals of the difference were within the equivalence margin, the difference in mean weekly dose would then be tested. Analysis of covariance model was used to analyze the primary endpoints.

Approximately 89 percent of patients completed both studies. Missing data appeared to be balanced across study arms. Results from sensitivity analyses were consistent with the results from the primary analysis.

For the mean weekly hemoglobin level in both sub-Q and IV studies, the 90 percent confidence intervals for the differences are within the equivalence margin for both analysis populations.

For the mean weekly dose in both sub-Q and IV studies, the 90 percent confidence intervals for the differences are also within the equivalence margin for both analysis populations.

In summary, the 90 percent confidence intervals for the differences between Epoetin

Hospira and US-licensed Epogen/Procrit in both primary endpoints are within the equivalence margins in both sub-Q and IV studies. These results are consistent among different sensitivity analyses and subgroups. Data support a demonstration of no clinically meaningful differences between Epoetin Hospira and US-licensed Epogen/Procrit.

This concludes the clinical efficacy presentation. Our next topic will be on clinical safety.

FDA Presentation - Lori Ehrlich

DR. EHRLICH: Good morning. I'm Lori Ehrlich, the clinical reviewer for the application. I will review the analysis of safety for the clinical studies.

This is a high-level overview of the safety analysis in study 10-13 during the randomized maintenance period with subcutaneous treatment, shown as the original analysis population on the left and analysis after removal of the non-GCP compliant sites on the right.

There were no significant differences in the rates of treatment-emergent adverse events between patients with Epoetin Hospira and US-licensed Epogen/Procrit. Removal of the sites closed for GCP compliance issues did not change the overall safety analysis.

This is a similar high-level overview of the treatment-emergent adverse events in study 10-01 within intravenous treatment shown as the original analysis population on the left and the analysis after removal of the non-GCP compliant sites on the right.

There were no significant differences in the rates of treatment-emergent adverse events between the patients treated with Epoetin Hospira and US-licensed Epogen/Procrit. Removal of the sites with GCP compliance issues did not change the overall safety analysis.

Finally, a review of the major labeled safety events for erythropoietin-stimulating agents, specifically, myocardial infarction, stroke, and thromboembolism, showed these events

occurred in both arms with no imbalances and at rates consistent with the prescribing information for the approved drug. There were no cases of pure red cell aplasia in these studies.

In summary, from two randomized clinical studies using subcutaneous and intravenous epoetin, shown here, and a review of two open-label long-term safety studies, the safety monitoring and the clinical studies was adequate. Overall, there were no imbalances in safety events between patients who received Epoetin Hospira versus US-licensed Epogen/Procrit.

A sensitivity analysis excluding non-GCP compliant sites did not change the overall analysis.

The applicant is seeking indications that are the same as US-licensed Epogen/Procrit, namely, for the treatment of anemia due to chronic kidney disease both on dialysis and not on dialysis, anemia due to zidovudine treatment, chemotherapy-induced anemia, and the reduction in allogenic transfusions for patients undergoing surgery.

The clinical studies conducted by the applicant were in healthy subjects and in patients with chronic kidney disease on hemodialysis, so extrapolation must be used for other indications.

In support of extrapolation to other indications, the agency notes that the mechanism of action of epoetin alfa is the same across all indications. The applicant has demonstrated similarity of their product with respect to analytical attributes, PK/PD effects, immunogenicity, efficacy, and safety of both the IV and subcutaneous routes of administration. Therefore, the agency considers extrapolation across all indications to be scientifically justified.

I will now review the overall summary of the FDA findings. This provides a reminder of the description of biosimilarity, which includes two components. To be a biosimilar, the product must be highly similar to the reference product notwithstanding minor differences in clinically inactive components, and the product must have no

clinically meaningful differences in safety, purity, and potency. The concept of potency has long been interpreted to include effectiveness.

The FDA finds that the totality of the analytical data supports a demonstration of highly similar notwithstanding minor differences in clinically inactive components. The clinical data, which includes pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity, supports the finding of no clinically meaningful differences.

Residual uncertainties were identified during the product review, including differences in glycosylation and trisulfide species. These residual uncertainties were adequately addressed by other data, including clinical data.

In conclusion, the totality of the evidence supports biosimilarity of Epoetin Hospira and US-licensed Epogen/Procrit. Extrapolation to all indications of use for US-licensed Epogen/Procrit is supported by the understanding of the mechanism of action across indications and demonstration of biosimilarity.

DR. RINI: Thank you for those presentations. Given the length of the presentations, we're going to do a 15-minute break now, and then afterward, we'll have time for clarifying questions to the presenter and the public section.

Remind the committee members there should be no discussion of the topic at hand amongst yourselves or with anybody during the break, and we will resume at 10:25. Thank you.

(Whereupon, at 10:11 a.m., a recess was taken.)

Clarifying Questions to the Presenters

DR. RINI: We're going to go ahead and get started if people can take their seats. So we now have time for clarifying questions from the committee to any of the presenters, and I believe Dr. Hancock is going to lead us off with some questions.

DR. HANCOCK: Thank you for the very interesting presentations. I just wanted to ask some analytical questions. My first question was

that the company presented the 100 percent sequence coverage.

Did you achieve this coverage just using enzyme trypsin, or did you use other proteolytic enzymes?

DR. RAMACHANDRA: Sumant Ramachandra for the sponsor. The coverage was done by three peptide maps, trypsin, lysine-C, and Glu-C to the identical coverage.

DR. HANCOCK: Fine, because trypsin just gives you an amino acid and a dipeptide. Okay.

DR. RAMACHANDRA: That's right. So we used three. Thank you.

DR. HANCOCK: Good. So moving on, the trisulfide stability, when you designed an accelerated stability program, did the level of the trisulfide variant stay constant, go up or down? What happened?

DR. RAMACHANDRA: I'll ask Dr. Vanden Boom to discuss the trisulfide and how it expressed.

Dr. Vanden Boom?

DR. VANDEN BOOM: The trisulfide species,

which is likely formed in cell culture, is stable under both normal conditions, stability condition, the storage condition, and under stress conditions.

DR. HANCOCK: That's important because if the trisulfide is not stable, you could get disulfide scrambling with concerns here.

Then moving on to another variant, the degree of sialylation in the different branch structures, di, tri, and tetra and ternary, did you look at the distribution of sialic acid in these different branch forms?

DR. RAMACHANDRA: Total sialylation was the same. I'll ask Dr. Cathy Srebalus-Barnes to address the variants that were there.

DR. SREBALUS-BARNES: Hi. Catherine Srebalus-Barnes. I head up the biosimilars analytical R&D group at Pfizer. We did look at sialic acid distribution across the glycans. Although there were minor differences noted in the relative abundance, the total sialic acid is consistent because there are partially sialylated structures in both products.

DR. HANCOCK: Did you do this with LCMS of an enzyme map with things like ETD and CID disassociation?

DR. SREBALUS-BARNES: Yes. So in our core presentation, we listed a number of the methods. At a high level, our strategy is that we have multiple glycosylation methods. We use native glycan analysis, which is what you saw in the FDA presentation, and then we use a series of X-O glycosylase enzymes to trim down the glycans. To simplify them, we analyzed them, and we also used mass spec identification.

DR. HANCOCK: And you found the distribution of sialic acid in the branch forms similar between your drug and the original one?

DR. SREBALUS-BARNES: There were minor differences.

DR. HANCOCK: No, I understand.

DR. SREBALUS-BARNES: Minor differences, but as you look at the total sialic acid, it was consistent.

DR. RINI: Thank you. I forgot to mention

to the committee if you want to ask a question, just raise your hand, and Lauren will put you on the list and call you in sequence. And Dr. Karara had a question.

DR. KARARA: My question relates to the number of subjects that were excluded from the PK analysis in the pivotal PK study, the single-dose study, presumably relating to antidrug antibody. But you started with 81 enrolled, 81 subjects in the PK analysis on table 20, the summary PK data from 61 subjects, so about 25 percent of the enrolled subjects were excluded.

DR. RAMACHANDRA: I'll ask Dr. Martin to discuss the disposition of the patients in the sub-Q study, clin pharm study.

DR. MARTIN: Dr. Nancy Martin. Dr. Karara, the single-dose PK study had 81 subjects that were enrolled. With regard to the subjects that were removed from the pharmacokinetic analysis, the pro-specified statistical analysis plan indicated there were several reasons why. You had to meet the certain criteria for the pharmacokinetic

population.

You had to have adequate measurable concentrations to actually calculate the area under the curve, and in the event there were positive antidrug antibodies, patients were excluded. Patients who only participated in one of the two periods were also excluded.

So these were the three primary reasons why those subjects of 10 out of the 81 were removed from the pharmacokinetic analysis.

DR. KARARA: Do you have a breakdown of the subjects that were removed due to antidrug antibodies, and if it showed up in period 1, by which treatment? Do you have a breakdown of those, how many of the 20? There are 20 subjects.

DR. MARTIN: Yes. Slide up, please.

The information that we're looking at here is from the single-dose PK/PD study 12-02. In the pharmacodynamic population, 6 subjects received only period treatment 1; 1 subject had positive anti-EPO antibody at pre-dose; and 1 subject received both treatments but dropped from study

after the 6-hour sample in period 2. There were an incremental 2 subjects that had insufficient data to calculate the primary PK parameters.

So in total, 10 of the 81 were removed from the primary pharmacokinetic population. Importantly, this primary PK population demonstrated PK and PD equivalence, and we provided additional sensitivity analyses in our briefing book, including all 81, the safety population, that support the primary analysis conclusion. Thank you.

DR. KARARA: Thank you.

DR. RAMACHANDRA: Thank you, Dr. Martin.

DR. RINI: Thank you. Dr. Cramer.

DR. CRAMER: Steve Cramer, RPI. I have a clarifying question. You state that minor adjustments were made to the proposed DP commercial process after completion of the clinical studies to support similar EPO content, and then these changes were evaluated and determined to not have an impact on the conclusions from the analytical similarity and clinical studies.

I guess you can't really talk about what the changes are in the process, or maybe you can. But my question is, when you made those changes, what does it mean, EPO content? Was it the quality of the content? Was it the concentration? Did the product-related variant profile change, and were the conclusions that you made from all the studies done on the original proposed process? You state that it's still the same conclusions, but I'm just curious. We didn't see any data on that.

DR. RAMACHANDRA: This is a drug substance of epoetin. It was the same before the change and after the change. It's literally the drug product and the actual content of epoetin within that drug product.

DR. CRAMER: You mean the concentration?

DR. RAMACHANDRA: Concentration, yes.

DR. CRAMER: Everything else was the same?

DR. RAMACHANDRA: Yes.

DR. CRAMER: Thank you.

DR. RINI: Dr. Waldman?

DR. WALDMAN: My clarifying has to do with

immunogenicity. I apologize for my back. My understanding of the studies are that they demonstrated no neutralizing antibody and no episodes of pure red cell aplasia for either of the drugs that were tested.

Because I don't know this off the top of my head, I presume that the incidence of neutralizing antibodies and pure red cell aplasia, it's a low incidence of patients that are on epo.

DR. RAMACHANDRA: It's a rare event, yes.

DR. WALDMAN: This is for discussion. My question really had to do with making the statement of biosimilarity or equivalence between these two drugs when the populations that were tested were not suitably large enough to see any incidence at all of an event which is a rare event.

DR. RAMACHANDRA: Yes.

DR. WALDMAN: Really what my question had to do with.

DR. RAMACHANDRA: There's a baseline rate of PRCA based on the experience with epoetin over the history that the product has been on the market.

It's between 1.4 to 3.6 cases per about 10,000 patient-years with subcutaneous uses and primarily in the population of chronic disease rather than oncology.

To put that into context, I'd like to ask Dr. MacDougall, who has extensive experience in this area, to address the question.

DR. MacDOUGALL: Thank you for the question. I'm a nephrologist in London, and I've been involved in working groups for clinical anemia practice guidelines internationally.

I think we're in a very fortunate position in 2017 in that we understand a lot more about this issue of antibody mediated pure red cell aplasia than we did when biosimilars were introduced in Europe 10 years go. We have 10 years' experience with biosimilar recombinant erythropoietin. We know a lot about the incidence of this product, as we've just heard, and we know about the mechanism of why this problem occurs.

Originally, the problem, we know it was due to an interaction between polysorbate 80 and rubber

leachates. With a subsequent root cause analysis with another product, we knew it was due to tungsten contamination of a syringe.

So we learned a lot about what induced these pure red cell aplasia, and I think we can be somewhat reassured that with the manufacturing processes that we're using nowadays and were used for this product, that we would not be expecting what we had 10 years ago with the originator and previous products.

DR. RAMACHANDRA: Thank you, Dr. MacDougall.

DR. WALDMAN: So essentially what I'm hearing is there's a really, really low incidence and a really, really low risk --

DR. RAMACHANDRA: Yes.

DR. WALDMAN: -- beyond what could be tested in this program.

DR. RAMACHANDRA: Yes.

DR. WALDMAN: I understand that. So the follow-on question to that is how will you go forward and monitor in the future to make -- because lots of patients are going to get

this in the future, and the population will ultimately become big enough to surface these episodes.

How will you monitor? What programs do you have to monitor in the future to make sure that there are no differences?

DR. RAMACHANDRA: Yes. So we have actually intensified pharmacovigilance monitoring process as part of this particular product category. It includes data capture aids to facilitate collection of details related to NAbs or PRCA.

The other one is a proactive request for ADA testing to be conducted at a central laboratory to aid diagnosis and guide patient treatment. We want to ensure that this rare event is captured, and based on our extensive experience in Europe, we recognize that the rates do occur at a baseline rate. But we want to ensure that it is captured if any cases do arise.

DR. WALDMAN: Was the rate the same in Europe with the biosimilar and the innovator?

DR. RAMACHANDRA: We have about 363,000

patient-years of experience in Europe with EU Retacrit. I do want to point out that the EU program is considered distinct from this program even though it's a highly related. I want to be respectful to that. But the EU program, there were two confirmed cases out of that 363,000.

So how we read it, again based on the baseline of either 1.4 or 3.6, it's at consistent or lower than what is the baseline rate that was seen previously. Thank you.

DR. RINI: Thank you. Dr. Uldrick?

DR. ULDRICK: Thanks. I have a few questions, mainly about extrapolation, but first one quick follow-up. For the two observed pure red cell aplasia cases, what were the underlying patient population?

DR. RAMACHANDRA: I'll ask Dr. Nancy Martin to go over those two particular cases.

DR. MARTIN: The two cases occurred in the chronic kidney disease population. One was pre-dialysis, and the other case was peritoneal dialysis.

DR. ULDRICK: Thank you.

My first question regarding extrapolation is actually to the FDA, and I'm looking at indication number 2, which is treatment of anemia due to zidovudine administration in HIV-infected patients with an EPO level less than 500. To a certain extent, this is a 26-year-old indication that is no longer relevant.

In thinking about extrapolation to this indication, I was wondering what the considerations are and how we should think about inclusion of outdated and potentially outdated indications.

DR. MARTIN: Consider the indication as current even though it is acknowledged by the agency that it is probably no longer significantly used. We have not taken the steps nor discussed with the innovator whether or not that indication was irrelevant and needed to be removed. So I think at this time, it remains part of the consideration.

DR. ULDRICK: The second question, I guess is for both the sponsor and the FDA, is related to

whether or not the indications for 2 and 3, the patient populations are similar enough to the patient populations were evaluated, the chronic kidney patients.

Specifically, although the mechanism of action of the drug is the same, the mechanism of anemia is different in these patient populations, and the immunogenicity is potentially different in these patient populations.

Is there any data on the comparability of immunogenicity of Procrit and Epogen in cancer and HIV patients compared to the chronic renal insufficiency patients that we could use to help make this decision?

DR. de CLARO: Angelo de Claro with FDA. Our thinking with regards to granting licensure for all indications, it's not directly extrapolating the characteristics of one population to the other and comparing that. It's based on a higher level of the totality of evidence of what your understanding is of the molecule with regards to you consider other attributes other than the

clinical properties.

If you have to start matching patient population characteristics, I think that would be very difficult to do across -- especially if you're dealing with very different indications. So our thinking is really more in line with regards to use all the available data that you have. That's why we're framing it just not based on the mechanism of action but also on product attributes, PK/PD, safety, and immunogenicity.

DR. ULDRICK: Thank you.

DR. RINI: Thank you. Dr. Mager?

DR. MAGER: Thank you. Don Mager from Buffalo.

This question is for the FDA, and I think it was partially answered with the last follow-up question from Dr. Waldman. But essentially, I had expected to see information and data coming from the European product since it's been available for over 10 years, and I was surprised not to see it. And I recognize that this is separate and not being considered as part of any bridging or anything in

this particular application, but I was wondering if the FDA was aware of any new safety or efficacy concerns from the European product.

DR. de CLARO: Angelo de Claro with FDA. The review approach FDA took for this product, as the sponsor had acknowledged, was that the European product is a related product. It's not the same as the proposed biosimilar product.

Dr. Christl's initial presentation on the overview -- actually, this allows the FDA to rely on use of non-U.S. comparators in our assessment. In this case, FDA does not have the complete scientific bridge in order to rely on the European data. The scientific bridge, as Dr. Christl mentioned, would have consisted of not just analytical but also consisted of clinical pharmacology and clinical data to establish that the relationship between the European product, the proposed biosimilar, and the U.S. reference product.

That was the approach that we -- that was the issue that we were faced with. We did not have

that complete scientific bridge to the EU product to allow us to bridge all of the clinical information for that.

DR. RINI: Dr. Lewis?

DR. LEWIS: Can I understand what you're saying? Are you saying that the chemical nature like the glycosylation of the European product is different than the one we're reviewing, or are you saying that for some reason the company just didn't give you the data that you wanted and needed? I'm confused.

DR. de CLARO: With regards to discussing proprietary information regarding a product characteristic, FDA cannot comment on that. But what we can say is because we did not have that complete scientific bridge is the reason why we couldn't rely on that data.

DR. RAMACHANDRA: The sponsor can comment.

DR. de CLARO: The sponsor can comment. FDA can't.

DR. LEWIS: But what you're saying, though, is that -- this comes to my question at the

beginning. Of course, it would be just wonderfully reassuring to look at all that European data and say nobody had a hypersensitivity reaction, they've given it to lots of people, it's all just great. But there is some reason why you're not having us extrapolate to that. And maybe the sponsor can clarify what that reason is.

DR. RAMACHANDRA: Let me, please, in three parts. So first of all, historically, we tech-transferred the same cell line, manufacturing processes, purification processes to a much higher scale in the United States for this particular program. We also adjusted the protein content to more match the US-reference product, Epogen/Procrit.

Dr. Vanden Boom can go over the comparability assessment that was done as part of that transfer and pre and post. And then I'd like to ask Dr. Paul Cornes to just go over the European experience from his perspective. He's a European physician, knows this area quite well, and he can talk about it. But from a perspective, we regard

this particular program as a U.S. application for the U.S. versus we actually did not perform a formal bridge from Europe to the U.S.

I'll ask Dr. Vanden Boom first to go up because of those changes that I mentioned, and then Dr. Cornes.

DR. VANDEN BOOM: Tom Vanden Boom, head of biosimilars pharmaceutical sciences for Pfizer. As Dr. Christl and Dr. de Claro noted, we did not do a three-way bridge, but what we did do, which I can briefly summarize for you, is a comparability study between the EU Retacrit product and our Epoetin Hospira product.

Slide up, please. That's summarized here. So over a wide range of attributes covering a structure and biological activity, comparability between these two versions of the product were confirmed. There were minor differences noted in this T5 trisulfide species described earlier. They weren't biologically significant.

DR. LEWIS: And the glycan product?

DR. VANDEN BOOM: The glycosylation, as you

would expect from using a same cell line and same manufacturing process, is very comparable between the two products.

DR. CORNES: Thank you. I'm Dr. Paul Cornes. I'm an oncologist from Bristol at England. We've used these products extensively for the last 10 years, and I built the economic model for NISAR, our national health technology assessment group, to look at epoetins in cancer.

The bottom line really is that we have several epoetin biosimilars in Europe, and all of them have extrapolated successfully to the oncology indication. So I could show you for several meds, but let's just take the European Retacrit.

If I could bring up slide 29 for you, and show you here that with more than 4,700 patents in the cancer label in Europe, across four studies, you see that our effectiveness is as expected, 7 to 9 out of every 10 patients will respond hematologically. Serious complication rate, our venous thrombotic episode rate, is in the 1 to 4 percent range, which exactly matches the label.

If you're looking for even larger populations and smaller databases, then I'm going to take you to a population study in northern Italy where a population of 6 million, we link the diagnosis database and the prescribing database and the outcomes database, looking for even rarer events.

So if I can bring up the slide for that and show you the Trotta study, which is slide 28, if I can have slide 28 there. Slide 28 tracks a population of 6 million patients and looks at patients exclusively treated either by biosimilars or by originator drugs.

Looking at the outcomes of death, of needs for transfusion, for major cardiac acute events, and blood dyscrasias to pick up pure red cell aplasia, you'll see with that size database, the hazard ratios all are across normal, which reassures us that the process of delivering biosimilars actually works for cancer patients, too.

DR. RAMACHANDRA: Thank you, Dr. Cornes.

DR. RINI: Thank you.

Dr. Lewis, I had you in my list for another question. Did you get all your questions answered?

DR. LEWIS: (Inaudible -- off mic.)

DR. RINI: Turn your microphone on.

DR. LEWIS: I have a question, if you could comment on not just the red blood cell aplasia but the hypersensitivity reactions that can occur as an immunological response and what is the relationship between the presence of the antidrug antibodies and those hypersensitivity reactions historically with EPO products specifically.

I know that glycosylation, for example in the renal world in IgA nephropathy, changes in that can certainly lead to immunologic responses. So I'm concerned about not just the presence of the antidrug antibodies or whether they're still bioactive despite them but also hypersensitivity.

DR. RAMACHANDRA: Yes. Dr. MacDougall is an immunology expert in this particular area. He'd probably be best to give you the overview for epoetins and hypersensitivity.

DR. MacDOUGALL: Hi. Ian MacDougall again. Thanks, Dr. Lewis, for your question. You're absolutely right. I think glycosylation does influence immunogenicity. But I think if you look at it specifically in relation to the epoetin products, the classical or perhaps paradigm would be taking darbepoetin alfa, which is super glycosylated, is a modified increased immunogenicity with darbepoetin versus epoetin, and there's not.

We have experience from the PREMs registry, which I was the lead investigator on, which showed that in thousands of patients, over 15,000 patients, there was no change in the rate of immunogenicity versus darbepoetin versus epoetin.

We also have, if we can call up slide -- we have 10 years' experience of European Union regulatory pathway. If we can call up the slide KR-33?

This paper was published in by Paul Chamberlain, and it basically shows that there are no observed differences in clinically relevant

immunogenicity between approved biosimilar and originator products since the EMA authorized these products 10 years ago.

So I think we're in a very fortunate position. We have 10 years' experience of comparison of products. I don't think glycosylation impacts hugely on the likelihood of immunogenicity.

DR. RAMACHANDRA: Thank you, Dr. MacDougall.

DR. RINI: Thank you. Dr. Cole, did you have a question?

DR. COLE: I wanted to ask about the two studies that are efficacy and safety studies. Looking at the hemoglobin levels, I was just wondering if you had any summaries of how the hemoglobins looked over time during those studies.

DR. RAMACHANDRA: I'd like to ask Dr. Martin to address that question.

DR. MARTIN: During the course of the studies, we actually examined hemoglobin levels on a weekly basis. We have this in the briefing book, and I'll show it here in figure 40 that actually

provides both for the sub-Q on the left and the IV study on the right.

The Epoetin Hospira is in blue. The Epogen reference product is in red. I've given you an assessment of repeated measures throughout the course of the studies. These data are consistent between the two treatment products. Thank you.

DR. COLE: One last question. For the dropouts that occurred in those studies, was the timing of the dropouts roughly similar between --

DR. RAMACHANDRA: I'll ask Dr. Martin to address that in terms of the dropout timing.

DR. MARTIN: Yes. We examined the timing of dropout between the two treatment groups, and there was no statistically significant difference in the timing of discontinuation between patients on Epoetin Hospira and Epogen arms in either the sub-Q study or the IV studies, as shown here.

DR. COLE: Thank you.

DR. RINI: Dr. Cramer?

DR. CRAMER: I have one last question about scale. We have these different lots of material,

and again, sorry for my back, too. And the question is, some were at 400 liter scale; some were at 20,000 liter scale. And I'm wondering about the different lots.

Do we have a flavor for which ones came from which scale, and would that have had an impact?

DR. RAMACHANDRA: With clarification, the commercial scale is 20,000 liters. But I'll ask Dr. Vanden Boom to talk about the data in terms of scale. Dr. Vanden Boom?

DR. VANDEN BOOM: So for the biosimilarity assessment, 100 percent of the lots used in that formal assessment are from the proposed commercial manufacturing scale, which is 20,000 liter scale. You may have noted in the briefing book references to smaller scale. That's typically done, as I know you're aware, in tech-transfers. So before you leap to 20,000 liters, you confirm that you're seeing what you're expecting to see at 400 liters. But in summary, all of the biosimilarity assessment was done with materials produced at the proposed commercial scale.

DR. CRAMER: The reason I asked the question is because if you look at the text here, it says that the lot for the drug product for both the 13-week comparative toxicology studies was from the 400 liter scale. Is that incorrect?

DR. VANDEN BOOM: I'll briefly comment, and Dr. Ramachandra can comment. So for the analytical biosimilarity assessment, which is what I was speaking to, we used exclusively the commercial scale.

DR. CRAMER: But for this one, not.

DR. RAMACHANDRA: For this one specifically, it was an early study and was not done -- as the FDA mentioned, for the totality of biosimilarity assessment but as part of the entry to inhuman study, the two species were done.

DR. CRAMER: Thank you.

DR. RINI: Are there any other questions, clarifying questions for the sponsor?

(No response.)

Open Public Hearing

DR. RINI: If not, we'll start the open

public hearing.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue at the beginning of your statement, it will

not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

I'll ask speaker number 1 to step up to the podium and introduce yourself and any organization you're representing.

MS. CARDEN: Good morning. My name is Mary Jo Carden, and I represent the Academy of Managed Care Pharmacy, and I have no conflicts to report today.

The focus of my discussion will be on the

biosimilar's pathway implementation and the policy issues from AMCP's perspective and not on the specific product itself.

I'd like to thank you for the opportunity to present AMCP's perspective on the biosimilar pathway. AMCP is the leading professional organization dedicated to increasing patient access to affordable medicines, improving health outcomes, and ensuring the wise use of health dollars.

Through evidence and value-based strategies and practices, the academy's 8,000 pharmacists, physicians, nurses, and other practitioners manage medication therapies for the 270 million Americans served by health plans, pharmacy benefit management firms, and emerging care models and the government.

AMCP supports the implementation of a robust biosimilars pathway to ensure that Americans continue to receive access to safe, effective, and affordable biologics and biosimilars. AMCP has been working extensively with FDA and other stakeholders on federal and state legislation and regulations that impact the biosimilars pathway.

Recently, AMCP had made biosimilars education for healthcare providers a key priority.

AMCP applauds the FDA for releasing draft guidance on interchangeability and finalizing guidance on naming and labeling. While we continue to have concerns with some provisions in the draft and final guidance documents, AMCP is generally pleased that the FDA has provided additional clarity on the implementation of the pathway.

In regard to interchangeability, AMCP generally supports the flexible stepwise and totality of evidence approach to demonstrating interchangeability. AMCP also commends the FDA for not being too prescriptive and recognizing that a one-size-fits-all approach is not feasible, given the complexity of the biologic and biosimilar products.

In comments, AMCP noted several factors that should be considered by FDA before finalizing the guidance. AMCP supports the ability of applicants seeking interchangeable designation to use switching studies for non-US-licensed reference

products. There is no scientifically justifiable distinction between reference products acquired in the United States and those licensed in other comparable markets.

AMCP encourages FDA to align the final interchangeability guidance with existing requirements for reference products, which permit the use of non-US-licensed reference products when a bridging study to the U.S. exists.

AMCP also encourages FDA to consider the following issues as it finalizes the guidance: whether new or expanded indications for a reference product would also be considered interchangeable, including the manner in which the labels will be harmonized; naming of interchangeable biologic products; possibility of interchangeability from biosimilar to biosimilar in the future; and whether follow-on products approved under the 505 pathway will be considered interchangeable or biosimilars when incorporated into the 351(k) pathway.

AMCP is pleased that the draft interchangeability guidance includes the

possibility of using postmarketing surveillance and pharmacovigilance for purposes of making interchangeability determinations.

AMCP has taken a proactive approach to pharmacovigilance. For example, the AMCP biologics and biosimilars collective intelligence consortium, BBCIC, proactively monitors both biologics and biosimilars using data from distributive research networks for millions of de-identified patients.

BBCIC research protocols are currently in progress and initial research findings are anticipated to be presented in the fall of 2017. BBCIC will serve as a valuable resource to address important questions about the use, impact, safety, and clinical effectiveness of biologics and biosimilars on human health.

In regard to the final guidance document for naming and labeling that have helped provided clarity on the requirements of the biosimilar pathway, AMCP remains concerned about the final naming guidances use of a randomized 4-letter suffix for all biologics and biosimilars. AMCP

does support the use of a shared non-proprietary name for biosimilars, reference products, and interchangeable products, as well as a requirement to use the NDC code on all claims to identify product, lot number, and package size.

AMCP believes that the use of the random 4-letter suffix does not ensure easy product identification. Rather, the suffix adds an additional unnecessary data element that, A, may result in medication errors because of transcription errors in databases associated with the additional characters added by the suffix; and B, may lead to disincentives to the use of biosimilars for the reference product because they appear unrelated to each other.

Last but not least, AMCP has made a significant commitment to educating healthcare providers, including pharmacists, physicians, and nurses. In 2016, we launched the Biosimilars Resource Center, www.biosimilarsresourcecenter.org, to provide an unbiased, policy-neutral repository of educational resources and information on

biosimilars.

AMCP is joined in these efforts by the American Association of Colleges of Pharmacy, America's health insurance plans, the American Pharmacists Association, the American Society of Consultant Pharmacists, the Hematology and Oncology Pharmacists Association, the National Alliance of State Pharmacy Associations, and the National Community Pharmacists Associations.

AMCP believes that in addition to a robust pathway to facilitate adoption of biosimilars in the United States, education of healthcare providers and consumers is equally as important. AMCP also supports FDA's initiatives on biosimilars education.

To wrap up, thank you again for this opportunity, and AMCP looks forward to continuing its work with FDA and other stakeholders on implementing the biosimilars pathway and providing education.

DR. RINI: Thank you. Speaker number 2?

MS. ARNSTEN: Good morning. My name is

Kathleen Arnsten. I have nothing to disclose. I'm here representing LADA, PBSA, and ASBM. Thank you for the opportunity to provide my unique perspective.

Biosimilar drugs hold tremendous promise and therapeutic advantage for people like me just as biologic medicines have for millions of Americans. Like many others who suffer from lupus, I have several other autoimmune disorders, including anemia and kidney disease. I currently take 42 medications a day and have unique allergies and sensitivities to both active and inactive ingredients in drugs.

Please understand no one-size-fits-all products exist for complex patients like me. Our immune response to treatments is unique, contrary, and at times, adverse. Due to the heterogenous nature of autoimmune diseases, no two cases are alike, and treatment is highly individualized.

At this initial juncture of biosimilar development, we believe that it is critical for both patients and physicians to be confident that

these drugs are safe and as effective as the original innovator. In order to be designated as interchangeable, biosimilars must produce the same clinical result in any given patient in each condition for which the biologic reference product was approved. Therefore, we support a policy requiring rigorous criteria that includes nonclinical and clinical data.

Any product that is named interchangeable must be shown to be safe and effective for patients in a future marketplace that could have multiple biosimilars and interchangeable products for one originator biologic, which would likely lead to patients being switched multiple times over the course of their treatment.

Given that the FDA has not yet finalized guidance on interchangeability, please keep in mind complex autoimmune patients who do not fit the norm as you review the application with regards to patient safety.

We applaud the FDA for establishing guidance for distinguishable suffixes and support the

establishment of a biosimilars policy that includes unique nonproprietary names with meaningful suffixes for future interchangeable biosimilars in order to ensure patient safety; provide vital transparency and aid in accurate product identification during the prescribing, dispensing, and pharmacovigilance processes; and promote compliance and ensure timeliness in addressing adverse events.

Utilizing discernible names is critically important in identifying exactly which medicine was received if an adverse event does occur since in reality, biologics or biosimilars will be administered to individuals like me suffering from serious life-threatening diseases who are usually taking multiple concomitant medications.

The FDA review and approval process must also properly evaluate the biosimilar through postmarketing surveillance in order to not diminish product efficacy and be detrimental to patient safety. Pre-approval, nonclinical and clinical testing will establish that there are no meaningful

differences in safety, efficacy, or mechanism of action comparability. However, only routine life experience will show this in distinct subpopulations. Therefore, accurate post-approval tracking is absolutely crucial.

Pharmacovigilance is essential for all biological medicines because these treatments may produce idiosyncratic or immunogenic reactions in patients like me who may also be hypersensitive to changes in production methods or impurities.

Adverse effects are difficult to predict and may only occur after many years of treatment. Because biosimilars go through an abbreviated review process, the FDA must do more to implement comprehensive postmarket tracking and reporting to detect safety problems with these treatments. As a matter of fact, the biologic originator of the product being considered by the FDA this week has a black box warning on its label due to its connection with a rare serious adverse reaction. This exceptional but potentially fatal event shows the need for an aggressive postmarketing tracking

system.

As an individual who was harmed by an egregious payer utilization management practice and am now blind in my right eye, I am extremely concerned that patients who are stable on a biologic will be switched for nonmedical reasons to a biosimilar that has not been determined to be interchangeable by the FDA.

We realize the FDA does not have any jurisdiction over insurance companies or PBMs, but we anticipate that payers will promote use of biosimilars. And therefore, we urge you to provide robust safeguards to protect patients such as applying strong scientific safety standards and publishing an official statement that switching a stable patient to a non-interchangeable biosimilar is perilous.

In conclusion, I ask you to develop a comprehensive education program for all stakeholders, including prescribers, pharmacists, patients, and public officials, in order for these drugs to advance. And I thank you again for the

opportunity to share my perspective as you evaluate this BLA and applaud the FDA for continually recognizing the importance of the patient voice during the drug review process.

DR. RINI: Thank you. Speaker number 3?

MR. La MOTTE: Hello. My name is Larry La Motte. I'm speaking here on behalf of Patients for Biologics Safety and Access, better known as PBSA, and I have nothing to disclose or report.

PBSA is a coalition of more than 20 patient organizations representing millions of Americans who suffer from serious life-threatening diseases that are difficult to diagnose and treat. Our members typically experience a healthcare system that takes years to identify appropriate providers, produce an accurate diagnosis, and discover the best course of treatment to bring greater stability for more optimal health outcomes. As patient advocates, our goal is to ensure that patient safety is paramount as the FDA implements the BCPIA.

My statement today focuses primarily on the

broader issues relating to the biosimilars' pathway. First off, FDA should promptly, as soon as possible, finalize their interchangeability guidance, taking patient concerns into account, and should do so before any biologic is ever designated as interchangeable.

The reason why this is important, and Kathleen touched on this, is that we find that the urgency, given the recent steps by major insurers and pharmacy benefit managers in the absence of such guidance -- while none of the four biosimilars were approved to be interchangeable, payers are moving through the use of formularies and taking reference products off their formularies and instead putting biosimilars, forcing nonmedical switching of patients who are stable. This is unconscionable, and it goes against the law.

We need to protect stabilized patient from nonmedical switching, and we call on the FDA in its guidance to develop policies relating to that to discourage that kind of effort.

We have submitted details comments on other

aspects of the draft interchangeability guidance, but there are two things that I'd like to touch on. The final guidance should appropriately reflect the clearly different and higher standard for interchangeability provided by Congress to protect patient safety, including substantial clinical testing beyond that required for filing a product biosimilar, and it should also require interchangeable biosimilars to have distinct nonproprietary names with meaningful suffixes.

Since biosimilars go through an abbreviated review process and are regularly approved to treat conditions, FDA must require aggressive postmarket tracking and reporting to detect safety problems. That does not exist at this time, and we hope that that will come about very soon.

As indicated today with this particular product and the black box warning on its labeling, we see it's even more important to get that underway as soon as possible. And we also recognize that FDA must have also the adequate staffing and resources to carry out that.

Again, with respect to some of the things that Kathleen said, we also are very interested in making sure that the FDA consider the creation of a patient engagement advisory committee for biosimilars. We note that the FDA is looking to increase its amount of patient engagement with the possible creation of an office of patient engagement, and we wholeheartedly support that in hope that there will be a specific type of advisory committee for the pathway for biosimilars.

I thank you very much for considering our views on these very important issues because we are very concerned about the safety of patients, that they have confidence that the drugs that are coming before them are safe and efficacious. I don't have anything more to say. Thank you very much.

DR. RINI: Thank you. Speaker number 4?

MR. PHILLIPS: Good morning. My name is Thair Phillips. I'm the president of RetireSafe, a nationwide nonprofit advocacy organization for older Americans. I have nothing to declare.

I'm here today representing our 200,000

supporters and activists and to give a voice to many of those who are patients receiving the new life-extending and life-enhancing medicines. RetireSafe wants both biosimilars and interchangeable products to be successful. That success in a large part depends on the confidence that doctors, pharmacists, and patients have that these products are safe, effective, and accessible.

In past surveys, our people overwhelmingly confirmed that seniors want clear labeling, distinct names, and effective communication between the pharmacist and the doctor. We will continue to focus on safety, effectiveness, and accessibility.

We are encouraged by the number of drug manufacturers who have created biologics that have also entered the biosimilar marketplace. This is evident in the biosimilar being discussed today.

As we have stated in the past, we feel it would be prudent for the FDA, as they finalize regulations on biosimilars and interchangeability, to listen closely to these manufacturers' recommendations. They have an important and

balanced perspective.

The biosimilar being discussed today continues the emergence of this important area of medicine. We hope that this trend will continue but see complications arising that will require detailed guidance to address situations like if a biosimilar already exists for a reference product, will the second biosimilar need to be tested against the existing biosimilar?

Will a biosimilar be allowed to be approved for a subset of the reference product's indications? Will the label clearly identify the product as a biosimilar or as an interchangeable? These are important considerations that RetireSafe feels should be addressed by the FDA.

RetireSafe was also encouraged by the draft guidance dealing with interchangeable products that was recently released. The FDA draft guidance deals directly with how substitution will be regulated at the pharmacy, including adherence to the doctor's prescription and adherence to the drug's label. Many states have laws concerning

interchangeable products that outline required communication between the pharmacist and the doctor.

What is missing in the recent draft guidance is guidance concerning substitution that occurs outside of the pharmacy. When the rules on interchangeability are finalized, we are confident that the FDA will aggressively enforce these rules to maintain the safety of the patient. RetireSafe thinks that the FDA cannot continue to maintain this safety without extending their final guidance to include the entire supply line.

Today, the FDA monitors closely the manufacturing and shipping of pharmaceuticals to ensure that the product that was approved by the FDA is delivered to the patient. They ensure that no ingredient was substituted, no inferior manufacturing methods were used, and that shipping requirements were adhered to. If a biosimilar was substituted for a reference product during shipping, the FDA would immediately take action.

RetireSafe thinks that a similar type of

unauthorized substitution is already taking place when a PBM or insurance company removes a reference product from its formulary. This creates a barrier to access for the patient, and in many cases, forces a substitution, a substitution that would not be tolerated at a pharmacy.

We think that the recent change to the Purple Book concerning substitution reveals the intent of the FDA to limit unauthorized substitution, but it focused on the pharmacy rather than on the entire supply line, and therefore would not limit this outside the pharmacy type of unauthorized substitution. If this practice is allowed to continue, not only will the safety of the patient be threatened, but manufacturers will have no incentive to apply for the interchangeable designation.

We believe that, whether through final guidance or through recommendations to HHS or Congress, the FDA needs to aggressively protect the patient's safety by eliminating this type of unauthorized substitution.

RetireSafe recognizes the difficult task that FDA has ensuring the safety of patients. Biologics are a wonderful but complicated medicine. We want the increased access that biosimilars and interchangeables offer. We think that ensuring patient safety at the beginning will earn the confidence of the patient, the doctor, and the pharmacist and will allow us to realize these promised savings. Thank you.

DR. RINI: Thank you. Speaker 5?

DR. CRYER: Good morning. My name is Dr. Dennis Cryer, and I am the lead co-convener physician of the Biologics Prescribers Collaborative or BPC. We are a project of the Alliance for Patient Access or AfPA, and we work together on a lot of issues. I want to comment that our organization is very much aligned with the comments of the three speakers that immediately preceded me.

Basically, today I have four points that I want to make. Our full comment has been submitted to the docket and is available for your reading

pleasure at your leisure, and I do know that actually the FDA people do read those. So I'm confident that it will be carefully considered.

The four points I want to make today are the following. First, for biosimilar product labeling, they must contain all the needed data for physicians to make the appropriate prescribing decisions for their patients. Label is a critical tool for physicians to make prescribing decisions and to manage potential adverse events. As such, it is of the utmost importance that any drug label be complete and accurate.

A biosimilar label identical to that of its reference product omits readily available product-specific and often important data, which may by its absence imply that the biosimilar is interchangeable with the reference product and approved for all of the same indications when in fact it may not be.

A biosimilar, unlike a generic small molecule, has its own clinical data. Thus, there will be likely specific information from the data

package that will help physicians. Most importantly, it would be the provision of information on immunogenicity, which can vary from the reference product biologic. Greater inclusion of data will increase physician confidence, protect patients and lead to greater and more informed utilization.

The second point is simply that the FDA should proceed with caution when considering biosimilar application requests for indication extrapolation. I won't go into this because I think it was nicely discussed and thoroughly discussed this morning by the FDA.

The third point that I want to make is that FDA should provide clear and concise guidance to industry surrounding interchangeability, particularly the interchangeability among biosimilars and their reference products. Again, this has been discussed a fair bit today. The draft guidance was recently closed to comments, and we look forward to a final guidance being developed.

We favor a more rigorous approach to demonstrating interchangeability rather than a less rigorous one, and I think the scientists and clinicians among us would all agree.

With an increasing number of biosimilars in the developmental pipeline, BPC expects some will be put forward with the interchangeable status. As FDA works to finalize their draft guidance, it is critical that sponsors are provided sound direction that ensures transparency, patient safety, and physician confidence.

To provide clarity for physicians and their patients, labeling for interchangeable biosimilars should include a statement of whether the biosimilar is interchangeable with the reference product and/or other biosimilars on the market, and for which specific indications interchangeability was demonstrated.

Fourth, each biological product needs a distinguishable nonproprietary name. This guidance is out. While we had hoped for meaningful naming, we do appreciate FDA's careful consideration of

this important issue and the requirement at least for distinct names. As we gain real-world experience using these new medicines, we look forward to working with the agency to amend policies where we can achieve greater patient benefit and safety, including potentially evolving to a meaningful suffix.

The last thing I wanted to mention today, which was not one of my original four bullet points, was my concern about the observation of GCP noncompliance in the application. I think this is always a concern in the development of small drug molecules. In the biologics, I think it becomes an even more important one.

I was encouraged by the sponsor's mention of the process of tech-transfer to the United States to scale up for production, and I hope that under Pfizer's guidance, GCP will not continue to be an issue. But I think for all of the biosimilars, particularly those that have been developed by smaller less well-known and less sophisticated, perhaps, companies, I think it's a concern that we

need to be mindful of.

I thank you for this opportunity today for me to speak on behalf of Biologics Prescribers Collaborative and wish you well in your deliberations. Thank you.

Questions to the Committee and Discussion

DR. RINI: Thank you. The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will turn its attention to the task at hand, the careful consideration of the data as well as consideration of the public comments.

We'll now proceed with the question to the committee and the panel discussion. I'd like to remind public observers that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

If I could have the question up. The way this is going to work is that there are three discussion points and then there's one voting

question. We'll go through in turn each of the three discussion points, ask for comments from the committee, and then we'll turn to the final voting question.

The first discussion point is please discuss whether evidence from analytical studies supports a demonstration that Epoetin Hospira is highly similar to US-licensed Epogen/Procrit notwithstanding minor differences in clinically inactive components.

I'll ask our panel members to weigh in specifically. There are analytical experts to discuss their views on this. Dr. Hancock?

DR. HANCOCK: In listening to the presentations and reviewing the documents, and also having the company responses to some detailed questions, I feel that the analytical comparability has been established.

DR. RINI: Thank you.

Are there other comments from an analytical perspective on this discussion point? Dr. Cramer?

DR. CRAMER: I agree.

DR. RINI: Thank you.

Anybody else? Any other points on this discussion?

(No response.)

DR. RINI: We'll turn our attention to discussion point number 2. Please discuss whether there are no clinically meaningful differences between Epoetin Hospira and US-licensed Epogen/Procrit based on the results from the clinical studies.

Comments from the committee about this discussion point? Dr. Waldman?

DR. WALDMAN: I think from the data that was presented, it's a fair statement to make to say that they are comparable in the things that could be measured.

DR. RINI: Thank you. I agree.

Other discussion points about whether there are clinically meaningful differences from the data presented between these two products?

Dr. Nowakowski.

DR. NOWAKOWSKI: I agree. I think presented

studies were convincing in this regard.

DR. RINI: So in summary, the committee agrees that there are no clinically meaningful differences between these products based on the data presented.

Discussion point number 3, please discuss whether there is adequate scientific justification to support licensure for all of the proposed indications for the product at hand. Dr. Uldrick.

DR. ULDRICK: I agree that the mechanism of action and similarity of quality attributes and PK and PD are similar. I, however, have residual concerns about immunogenicity and efficacy and safety in patients with HIV and patients with cancer. The concerns about patients with cancer are somewhat answered by looking at the postmarketing data from Europe, but we were instructed not to look at that data in reviewing the product today.

DR. RINI: Thank you.

Are there other comments about this discussion point? Dr. Lewis?

DR. LEWIS: I would say the hemodialysis patients, the population it was tested in, are patients who are immunocompromised and might have a reduced immunologic response. And the hypersensitivity/antigenicity issue I think is one that remains, that's a consideration.

DR. RINI: I agree. It'd be nice to see more data across the proposed indications within the limitations of the regulatory pathway.

Other committee member discussion points or contributions to this discussion point?

(No response.)

DR. RINI: It sounds like there are some concerns about the applicability of the data across indications, maybe mostly related to immunogenicity.

Now we will turn our attention to the vote. This is the question for the vote. I will read it to you.

Does the totality of evidence support licensure of Epoetin Hospira as a biosimilar product to US-licensed Epogen/Procrit for the

following indications for which US-licensed Epogen/Procrit is currently licensed and for which the applicant is seeking licensure?

Does anybody have any questions about the question, any points of clarification needed for what we're asking here?

(No response.)

DR. RINI: If there's no further clarification questions, we'll now begin the voting process. We'll be using an electronic voting system. Once we begin the vote, buttons will start flashing and continue to flash even after you have entered your vote. Press the button firmly that corresponds to your vote. If you're unsure of your vote or wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. Lauren will then read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and what they voted

into the record. You can also state the reason why you voted as you did, if you wish to.

Please now press the button on your microphone that corresponds to your vote. You have approximately 20 seconds to vote. Press the button firmly. After you have made your selection, again, the light will continue to flash, and if you need to change your vote, please press the corresponding button before the vote is closed.

(Vote taken.)

DR. TESH: The voting result for the record is 14 yes, 1 no, 0 abstentions, 0 non-voting.

DR. RINI: We'll now go around the room and ask people to state what they voted and add why they voted that way. We'll start with Dr. Gordon, who is a non-voting member, but just wanted to ask if there's anything you wanted to add in terms of a discussion around the vote.

DR. GORDON: I would just comment that I think the issues around the immunogenicity are a legitimate question, and it's unfortunate that there couldn't be more integration, if you will, or

understanding of the data from Europe.

DR. RINI: Thank you. Dr. Mager?

DR. MAGER: Don Mager. I voted yes to the question. I think the totality of the evidence supports the conclusion that the biological product is biosimilar to the reference product.

There were minor differences, I think, in the analytical assessment such as the glycosylation pattern as well as differences in preclinical studies in terms of exposure and response. So this does raise some residual uncertainties, but the clinical studies -- those minor differences were shown not to be clinically meaningful in the clinical studies.

It supports similar safety and efficacy, and then also, based on determination of a biosimilar product and a clear understanding of the mechanism of action of epo, I think there's a very strong scientific basis for extrapolation to all the approved indications of the reference product.

DR. RINI: Thank you. Dr. Estrella?

DR. ESTRELLA: I voted yes as well, and I

have no additional explanations to the comprehensive one that Dr. Mager mentioned.

DR. RINI: Thank you. Dr. Cramer?

DR. CRAMER: I voted yes, and Dr. Mager exactly stated what I was going to state.

DR. RINI: Thank you. Dr. Karara?

DR. KARARA: Yes, I voted yes because the PK and PD similarity has been established in the two well-designed PK and PD studies that support the demonstration of no clinically meaningful differences between PK and PD between the two products.

DR. RINI: Thank you. Dr. Lewis?

DR. LEWIS: I voted yes because I think it met the regulatory guidelines that the FDA set out. I have to say that I have residual deep concerns about the fact that this drug itself, the original epo, is associated with increased cardiovascular risk in CKD patients, red blood cell aplasia, and a drug, which I unfortunately sat on the panel and approved, peginesatide, resulted in many deaths from hypersensitivity.

I think that the innovator drug or the original drug in some of the subsequent things are truly problematic. The way this will get rolled out, if it's rolled out in dialysis patients, will be massively all at once in these large dialysis organizations.

So I'm hoping that the changes in glycosylation and sialylation, that I realize are quantitative and to some extent actually chemical, are not going to lead to immunogenicity. But it did meet the regs.

DR. RINI: Thank you. Dr. Waldman?

DR. WALDMAN: I voted yes because I thought there was no substantial differences analytically, biologically, or clinically in what was tested. I think the residual uncertainty of immunogenicity and hypersensitivity, and the extrapolation across different patient populations will emerge in postmarketing surveillance. I think that's when we'll get the clearest picture of whether there really is any uncertainty in how these drugs perform.

DR. RINI: Thank you. Dr. Arscott?

DR. ARSCOTT: I voted yes. I came in with concerns about the patient populations for the HIV and the oncology patients. However, I do believe that after sitting here today and hearing the justification, it meets the regulation, so I voted yes. I would like to see extensive follow-up in these two population groups, though. Thank you.

DR. RINI: Thank you. Ms. Preusse?

MS. PREUSSE: Courtney Preusse, consumer representative. I voted yes but with some hesitation. Although I see the cost effectiveness benefit among the patient population in providing a biosimilar to the market, I'm still concerned, still uneasy with the fact that the patient population in which this drug was tested is very small in the U.S. And I was really hoping to hear from the audience patient experiences with this particular application of this drug.

I know that from personal experience that these agents are not easy to metabolize, that there are side effects, significant side effects. And

although similar to the existing drug on the market, it would have been nice to hear from other patients. So yes but with hesitation.

DR. RINI: Thank you. Dr. Uldrick?

DR. ULDRICK: I voted no. The analytical, preclinical, and clinical data support biosimilarity, and I strongly support approval for indications 1 and 4 based on the clinical data. As previously stated, I have residual concerns about lack of data of immunogenicity and basic safety data in patients with HIV and cancer, and for that reason, voted no for broader indication.

DR. RINI: Thank you. Dr. Cole?

DR. COLE: Bernard Cole, I voted yes largely for the reasons that have already been stated. I share Dr. Uldrick's concern a bit and hope that additional safety can be checked with patients, especially cancer patients and HIV patients.

DR. RINI: Thank you.

I'll go last so I can summarize.

Dr. Nowakowski?

DR. NOWAKOWSKI: I voted yes. I believe

that the analytical studies and preclinical and clinical data supported biosimilarity data assessment.

DR. RINI: Thank you. Dr. Riely?

DR. RIELY: I voted yes. I found the data compelling. I understand the concerns around immunogenicity for HIV and cancer patients. I was somewhat reassured by the nonclinical data showing an absence of increased immunogenicity for this biosimilar.

DR. RINI: Thank you. Dr. Klepin?

DR. KLEPIN: I voted yes for the reasons that were already mentioned. The main point of discussion I thought, as others, was the extrapolation to the populations that weren't studied. I think the scientific rationale for that is reasonable. And in thinking about how we would answer some of the questions, as Dr. Waldman stated, really you're going to need large sample sizes in postmarketing surveillance. So I can't see a way to get around that, and I don't see that that necessarily should otherwise hold up the data

that we've seen.

DR. RINI: Thank you. Dr. Hancock?

DR. HANCOCK: I voted yes based on the analytical similarity, the clinical data, and mechanism of action. It meets biosimilarity. Obviously, patient populations will change on marketing, and it will need to be followed up on, but I voted yes.

Adjournment

DR. RINI: Thank you. Brian Rini, I also voted yes. If I could just maybe summarize what the panel has said, I think from an analytical perspective, it didn't seem like there were any major issues. Some minor issues that the experts were comfortable weren't significant.

I think probably the biggest concerns were around some of the indications, which are either no longer relevant or for which there were not adequate data, i.e., the HIV and oncology populations. And I think the lack of data is mostly related to a safety issue, i.e., immunogenicity.

I thought Dr. Lewis made a great point that if it's approved and rolled out, it gets rolled out massively, kind of all at once, which is maybe different than some other drugs that we usually deal with on this committee. So the need for vigilance, I think, is exceedingly important, not only for this drug but for all the drugs in this circumstance.

I also heard from the public comments a lot about a distinct naming system. That's important to avoid errors, especially in patients with allergies as noted, and then also a big concern about switching, nonmedical switching I think somebody termed it, where it's a formulary issue; and patients are switched from the reference product to a biosimilar when that may not be appropriate for that individual patient.

But overall, I think it met the regulatory requirements, as you've heard, and that's why I voted yes.

If there's no further FDA or other comments, we'll now adjourn the meeting. Panel members,

leave your badge here so they can be recycled and take all your belongings with you. Thank you-all for your participation.

(Whereupon, at 11:39 a.m., the meeting was adjourned.)